NOVARTIS

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457F2366 / NCT02745080

A randomized, double-blind, active control, multicenter study to evaluate the efficacy at week 52 of subcutaneously administered secukinumab monotherapy compared with subcutaneously administered adalimumab monotherapy in patients with active psoriatic arthritis

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List of abbreviations

ACR	American College of Rheumatology
[redacted]	[redacted]
AE	Adverse Event
ALT/SGPT	Alanine aminotransferase / serum glutaminc pyruvic transaminase
ANA	antinuclear antibody
anti-CCP	anti-cyclic citrullinated peptide
anti-dsDNA	anti-double stranded DNA antibodies
AST/SGOT	Aspartate aminotransferase / serum glutamic oxaloacetic transaminase
BSA	body surface area
BSL	baseline
CASPAR	Classification criteria for Psoriatic Arthritis
CCP	cyclic citrullinated peptide
cDMARD	conventional Disease modifying anti-rheumatic drugs (also known as non-biologic DMARDs)
CFR	Code of Federal Regulations (U.S.)
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTC	Common Toxicity Criteria
CV	Cardiovascular
[redacted]	[redacted]
[redacted]	[redacted]
DMARD(s)	disease-modifying antirheumatic drug(s)
[redacted]	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA/EMEA	European Medicines Agency
[redacted]	[redacted]
ESR	erythrocyte sedimentation rate
EU	European Union

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
FAS	full analysis set
FDA	(U.S.) Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAQ-DI	Health Assessment Questionnaire – Disability Index
hCG	human chorionic gonadotropin
HDL	high density lipoprotein
HIV	human immunodeficiency virus
[redacted]	[redacted]
hsCRP	high sensitivity C-Reactive Protein
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL	interleukin
IL-17	Interleukin 17
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
IVR	Interactive Voice Response
[redacted]	[redacted]
LDL	low density lipoprotein
[redacted]	[redacted]
LFT	Liver function test
LLN	Lower limit of normal
LLOQ	lower limit of quantification
MAR	missing at random assumption
[redacted]	[redacted]

[redacted]

[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
mmHg	millimeter of mercury
MMRM	mixed-effects repeated measures model
MRI	magnetic resonance imaging
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
OC/RDC	Oracle Clinical/Remote Data Capture
[redacted]	[redacted]
PASI	Psoriasis Area and Severity Index
[redacted]	[redacted]
PFS	prefilled syringe
[redacted]	[redacted]
[redacted]	[redacted]
PoC	proof of concept
PPD	purified protein derivative
PRN	as required
PRO	Patient Reported Outcome
PsA	psoriatic arthritis
[redacted]	[redacted]
PSO	psoriasis
PUVA	psoralen ultraviolet light A
QTcF	Fridericia QT correction formula
RBC	red blood cell
RF	rheumatoid factor
SAE	Serious Adverse Event
s.c.	subcutaneous(ly)
[redacted]	[redacted]
SJC	swollen joint count
SmPC	Summary of Product Characteristics
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reactions

[redacted]

t.i.d.	three times daily
TJC	tender joint count
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
UV	ultraviolet
UVA	Ultraviolet light A
UVB	Ultraviolet light B
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization
[redacted]	[redacted]

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch Replaces the term "Period" previously used for NOVDD studies	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent

[redacted]

Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

[redacted]

Amendment 02

Amendment rationale The estimands described in Section 9.4.3 have been clarified to align with the study objectives, which are comparing efficacy of secukinumab monotherapy with adalimumab monotherapy.

In Section 9.4.4, the non-parametric regression (Koch 1998) model is not essential to the final analysis but may be performed.

In Section 9.4.4, as it is expected to have few patients who discontinue treatment but remain in the clinical trial without rescue medication, it may not be necessary to examine the effect of them on the primary endpoint by using sensitivity analysis. Sensitivity analyses will be conducted to examine the effect of taking concomitant treatment of MTX and/or other cDMARDs along with study drug.

Changes to the protocol

In Section 9.4.3, the latter part of the first sentence, regardless of adherence to randomized treatment" has been deleted. Additional changes to the sentence have been made to clarify the estimand and the definition of monotherapy response has been added.

In the second paragraph of Section 9.4.4, "ACR20 response at Week 52 will also be evaluated" has been changed to "ACR20 response at Week 52 may also be evaluated".

In the last paragraph of Section 9.4.4, "and the effect of treatment discontinuation without rescue medication" has been changed to "and/or the effect of treatment discontinuation without rescue medication".

Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities

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 are non-substantial and do not require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the trial specific model ICF.

[redacted]

Amendment 01

Amendment rationale

At the time of this amendment no subjects have been randomized in the study. No change to the study population is proposed by this amendment.

This protocol amendment is primarily issued for the following reasons:

1. The half-life of adalimumab is reported to be approximately 2 weeks, therefore in the original protocol the safety follow-up was planned to cover 5 x the half-life or approximately 10 weeks. Consequently, the safety follow-up visit was scheduled for 10 weeks after last dose of adalimumab. Some Health Authorities have mandated that the safety follow-up for adalimumab be extended to 4 months after last dose of adalimumab, to be consistent with the Humira® SmPC 2016.
2. Exclusion Criteria 2 provided guidelines and examples where local label requirements for contraception use, after the last dose of study treatment, should be followed by women of childbearing potential. Health Authority requests have been received that the protocol should specify contraception use for five months after last dose of adalimumab (see Humira® SmPC 2016).

Changes to the protocol

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

The wording of "Visit Schedule and assessments" (Section 6), "Study Design" (Section 3.1) and the "Study Design" section in the "Protocol Summary" have been amended to extend the follow-up period. Table 6-1 "Assessment schedule", [redacted]

The wording of Exclusion Criteria 2 (Section 4.2) and "Informed consent procedures" (Section 10.2) has been updated with guidelines for contraception use after the last dose of study treatment, for women of childbearing potential.

The wording of "Permitted dose adjustments and interruptions of study treatment" (Section 5.5.5) and "Prohibited medication" (Section 5.5.8) have been updated to extend the interruption requirement if the patient receives a live vaccine. "Study completion and post study treatment" (Section 5.5.13) has been updated to extend the recommended time before starting a new biologic. These changes were made because elimination of adalimumab may take up to 4 months.

The wording in the following Sections, "Purpose and timing of interim analyses/design adaptations" (Section 3.5), "Prohibited medication" (Section 5.5.8), [redacted], "Interim analysis" (Section 9.6) and "References" (Section 12) have been amended.

[redacted]

Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities

A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities.

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

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

[redacted]

Protocol summary

Protocol number	CAIN457F2366
Title	A randomized, double-blind, active control, multicenter study to evaluate the efficacy at week 52 of subcutaneously administered secukinumab monotherapy compared with subcutaneously administered adalimumab monotherapy in patients with active psoriatic arthritis
Brief title	Study of the efficacy of secukinumab monotherapy compared with adalimumab monotherapy in subjects with active psoriatic arthritis
Sponsor and Clinical Phase	Novartis Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to compare the safety and efficacy of secukinumab monotherapy and adalimumab monotherapy in patients with active psoriatic arthritis (PsA) who are naïve to biologic therapy for PsA or PsO and are intolerant or having inadequate response to conventional disease-modifying antirheumatic drug (cDMARDs). Efficacy will be evaluated based on multiple indices of improvement in signs and symptoms, physical function, quality of life and patient reported outcomes. In PsA, more than half of the patients take biological DMARDs as a monotherapy with very good control of their disease. Similar outcome in response has been demonstrated with or without use of cDMARDs (including methotrexate). Thus no biologics have shown positive synergistic effects on any clinical outcomes and this is reflected in all their labels. Treatment with biologic monotherapy in PsA is therefore clinically justifiable and avoids unwarranted exposure to the potential toxicity of cDMARDs. The randomized, double-blind, active control, multicenter, parallel-group design used in this study is in alignment with phase III trials of other biologics in this disease area and also in compliance with the European Medicines Agency (EMA) guidelines on PsA trials.
Primary Objective(s)	To demonstrate that the efficacy of secukinumab monotherapy 300 mg s.c.at Week 52 is superior to adalimumab monotherapy (40 mg s.c.) based on the proportion of subjects achieving an American College of Rheumatology 20 (ACR20) response.
Secondary Objectives	To demonstrate that:

[redacted]

	1. Secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, based on the proportion of subjects achieving PASI90 response. 2. Secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, based on the proportion of subjects achieving an ACR50 response. 3. The improvement (change) from baseline on secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, for the Health Assessment Questionnaire – Disability Index (HAQ-DI©) score. 4. Secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, based on the proportion of subjects achieving the resolution of enthesitis. An additional secondary objective is to evaluate the safety and tolerability of secukinumab monotherapy (300 mg s.c.) compared with adalimumab monotherapy (40 mg s.c.) as assessed by vital signs, clinical laboratory values, and adverse events monitoring.
Study design	This is a randomized, double-blind, active control, multicenter, parallel-group trial evaluating secukinumab monotherapy and adalimumab monotherapy in approximately 850 subjects with active PsA. A screening period of up to 8 weeks before randomization will assess subject eligibility. Efficacy assessments will occur through Study Week 52. Two follow-up visits at Week 60 and 68 will occur thereafter. Total maximum study duration, including screening period, is up to 76 weeks. At Baseline, subjects whose eligibility is confirmed will be randomized to either Group 1 (secukinumab 300 mg as 2 x 150 mg s.c. injections), or Group 2 (adalimumab 40 mg as 1 s.c. injection) with approximately 425 subjects/group. In order to maintain the blind, both groups will receive 1 or 2 placebo s.c. injections to keep consistency in the number of injections at each dosing visit. Secukinumab is available in 150 mg/1.0 mL pre-filled syringes (PFS) and adalimumab is available in 0.4 mL PFS. Placebo (1.0 and 0.5 mL, PFS) is also available. Group 1 - Secukinumab 300 mg s.c. Secukinumab 300 mg (2 x 1 mL PFS) will be administered at Baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks until Week 48. In addition, all Group 1 subjects will receive placebo (1 x 1mL PFS) at given visits in order to maintain the blind. Group 2 - Adalimumab 40 mg s.c. Adalimumab 40 mg (1 x 0.4 mL PFS) will be administered at Baseline followed by dosing every 2 weeks until Week 50. In

[redacted]

	addition, all Group 2 subjects will receive placebo (1 x 0.5mL or 2 x 0.5mL PFS) at given visits in order to maintain the blind
Population	The study population will consist of a representative group of male or female subjects at least 18 years of age, fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR), and PsA for at least 6 months and have active PsA disease defined as >3 swollen and tender joints in spite of treatment with NSAIDs and/or cDMARDs. Subjects will be eligible to enter the study if they have not previously been treated with biologic DMARDs (e.g., TNFα inhibitors), or cell-depleting therapies and either have previously been treated with cDMARD, including but not limited to MTX, with an inadequate response on therapy or have stopped treatment due to safety/tolerability problems after at least one administration of a cDMARD.
Key Inclusion criteria	1. Informed consent must be obtained before any assessment is performed. 2. Male or non-pregnant, non-lactating female subjects at least 18 years of age. 3. Diagnosis of PsA as classified by CASPAR criteria and with symptoms for at least 6 months and with active PsA at baseline defined as ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each). 4. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies negative at screening. 5. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥2 cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis. 6. Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs. 7. Subjects who are regularly receiving 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 52. 8. Subjects receiving corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 52. 9. Subjects must have previously been treated with a cDMARD, including but not limited to MTX, with an inadequate response to therapy, or must have stopped treatment due to safety/tolerability problems after at least one administration of the cDMARD.

[redacted]

	Subjects who are receiving a cDMARD will be allowed to enter the study only after cDMARD discontinuation and appropriate wash-out e.g. 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine wash-out has been performed.
Key Exclusion criteria	1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test. 2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 5 months for adalimumab in the EU). 3. Chest X-ray or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified physician. 4. Previous exposure to any biologic drugs for PsA and PSO, including but not limited to TNFα inhibitors, secukinumab, or other biologic drugs targeting IL-17 or IL-17 receptor. 5. Subjects receiving high potency opioid analgesics including but not limited to methadone, hydromorphone, and morphine. 6. Ongoing use of prohibited psoriasis treatments/medications (e.g., topical corticosteroids or ultraviolet therapy at randomization). 7. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 or investigational agents.
Investigational and reference therapy	Investigational treatment: Secukinumab 150 mg, liquid formulation in a PFS (2 x 1 mL PFS for 300 mg dose) Reference treatment: • Adalimumab 40 mg, liquid formulation in a 0.4 mL PFS • Placebo, liquid formulation in a 1 and 0.5 mL PFS
Efficacy assessments	• American College of Rheumatology (ACR) 20, 50 [redacted] responses [redacted]

[redacted]

	[redacted] • Psoriasis Area and Severity Index (PASI) [redacted]
Key safety assessments	• Evaluation of adverse events/serious adverse events • Physical examination • Vital signs • Height and weight • QuantiFERON TB-Gold test or PPD skin test • Electrocardiogram • Local tolerability (injection site reactions) • Laboratory evaluations (hematology, clinical chemistry, lipids) • Pregnancy and assessment of fertility • Tolerability of study treatment [redacted]
Other assessments	• Quality of Life questionnaires/ Patient reported outcomes (PROs) [redacted]
Data analysis	The primary endpoint in the study is the proportion of subjects who achieve an ACR20 response at Week 52. The statistical hypothesis for ACR20 being tested is that there is no difference in the proportion of subjects fulfilling the ACR20 criteria at Week 52 in the secukinumab 300 mg group vs. adalimumab. Let pj denote the proportion of ACR20 responders at Week 52 for treatment regimens j, j=0, 1 where --0 corresponds to adalimumab, --1 corresponds to secukinumab In statistical terms, H1: p1 = p0, HA1: p1 $\neq$ p0, i.e. H1: secukinumab is not different to adalimumab regimen for signs and symptoms (ACR20 response) at Week 52 The primary endpoint of ACR20 at Week 52 in the FAS will be evaluated using a logistic regression with treatment as a factor and weight as a covariate. Odds ratios will be computed for comparisons

[redacted]

	of secukinumab 300 mg vs. adalimumab regimen utilizing the logistic regression model fitted. Safety analyses will include summaries of AEs, laboratory measurements, and vital signs.
Key words	psoriatic arthritis, secukinumab, adalimumab, monoclonal antibody, CASPAR

[redacted]

1 Introduction

1.1 Background

Psoriatic arthritis (PsA), a chronic inflammatory disease that can affect peripheral and axial joints, entheses and the skin, is associated with impaired physical function and poor quality of life (Gladman 2005; Rosen 2012). Pathogenesis-based interventions, particularly therapies targeting tumour necrosis factor (TNF), have improved outcomes in patients with PsA. Recently, the interleukin 12/23 inhibitor ustekinumab has also shown some clinical benefit but inhibition of radiographic progression mainly in anti-TNF naïve patients (McInnes 2013; Kavanaugh 2014). Despite this progress, not all patients respond to or tolerate therapy, and clinical needs are largely unmet.

Interleukin (IL) 17A and its receptor are expressed in synovial tissues and as such the IL-17 pathway is proposed to contribute to the pathogenesis of PsA. IL-17A can mediate a variety of effector biological functions that can result in skin, enthesial joint inflammation, bone damage and tissue remodelling (FitzGerald 2014).

Secukinumab, a human monoclonal antibody that inhibits the effector function of IL-17A, has been previously shown to be better than placebo, etanercept and ustekinumab in improving the signs and symptoms of psoriasis (Langley 2014; Thaci 2015). In the phase III, FUTURE 1 and FUTURE 2 studies, of 1003 patients with PsA, secukinumab significantly improved key clinical domains of disease versus placebo, including signs and symptoms, radiographic disease progression, physical functioning and quality of life (Mease 2015; McInnes 2015).

Most anti-TNF inhibitors including adalimumab (Humira® package insert; Humira® SmPC 2016), as well as secukinumab, an IL-17A inhibitor (Cosentyx® package insert; Cosentyx® SmPC 2016), are approved for treatment of patients with active PsA with or without methotrexate (MTX). Results on signs and symptoms with both adalimumab and secukinumab have demonstrated good response with or without MTX. This suggests that both treatments are effective without the need of unwarranted exposure to MTX and its well-recognized toxic effect. In fact up to 40% of patients treated with the most commonly used disease-modifying anti-rheumatic drug (DMARD), MTX, discontinue or are noncompliant with MTX because of toxic effects (Nikiphorou 2014). In addition, data from registries of biological drugs and a US claims database suggest that up to a third of patients take TNF inhibitors as monotherapy (Behrens 2015; Bonafede 2013).

It is noteworthy that the current selection of biological DMARDs to manage PsA is empirical (Gossec 2016). As such, a need exists for comparative studies to assess new treatments. This study compares adalimumab and secukinumab as monotherapy, in keeping with approved labels, and will provide critical scientific evidence that will improve evidence-based decision making in the treatment of patients with PsA. This study addresses the current data gap between clinical research and day-to-day clinical practice on the therapeutic utility of biologic monotherapy in patients with active PsA.

1.2 Purpose

The purpose of this study is to compare the safety and efficacy of secukinumab monotherapy and adalimumab monotherapy in patients with active psoriatic arthritis who are naïve to

[redacted]

biologic therapy for PsA or PSO and are intolerant or having inadequate response to cDMARDs (e.g. MTX). Efficacy will be evaluated based on multiple indices of improvement in signs and symptoms, physical function, quality of life and patient reported outcomes.

2 Study objectives and endpoints

2.1 Primary objective

To demonstrate that the efficacy of secukinumab monotherapy (300 mg s.c.) at Week 52 is superior to adalimumab monotherapy (40 mg s.c.), based on the proportion of subjects achieving an American College of Rheumatology 20 (ACR20) response.

2.2 Secondary objectives

To demonstrate that:

Secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, based on the proportion of subjects achieving PASI90 response.

Secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, based on the proportion of subjects achieving an ACR50 response.

The improvement (change) from baseline on secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, for the Health Assessment Questionnaire – Disability Index (HAQ-DI©) score.

Secukinumab monotherapy (300 mg s.c.) is superior to adalimumab monotherapy (40 mg s.c.) at Week 52, based on the proportion of subjects achieving the resolution of enthesitis.

An additional secondary objective is to evaluate the safety and tolerability of secukinumab monotherapy (300 mg s.c.) compared with adalimumab monotherapy (40 mg s.c.) as assessed by vital signs, clinical laboratory values, and adverse events monitoring.

[redacted]

3 Investigational plan

3.1 Study design

This is a randomized, double-blind, active control, multicenter, parallel-group trial evaluating secukinumab monotherapy and adalimumab monotherapy in approximately 850 subjects with active PsA. A screening period of up to 8 weeks before randomization will assess subject eligibility (see Figure 3-1). Efficacy assessments will occur through Study Week 52. Two follow-up visits at Week 60 and 68 will occur thereafter. Total maximum study duration, including screening period, is up to 76 weeks.

At Baseline (BSL), subjects whose eligibility is confirmed will be randomized to one of two groups (1:1): Group 1 (secukinumab 300 mg) with approximately 425 subjects or Group 2 (adalimumab 40 mg) with approximately 425 subjects. In order to maintain the blind, both groups will receive 1 or 2 placebo s.c. injections to keep consistency in the number of injections at each dosing visit. Secukinumab (300 mg) is available in 2 x 1.0 mL pre-filled syringes (PFS) and adalimumab is available in 1 x 0.4 mL PFS. Placebo (1.0 and 0.5 mL PFS) is also available.

Group 1 - Secukinumab 300 mg s.c.

Secukinumab 300 mg (2 x 1 mL PFS) will be administered at Baseline, Weeks 1, 2, 3 and 4, followed by dosing every 4 weeks until Week 48.

In addition, all Group 1 subjects will receive placebo (1 x 1mL PFS) at given visits in order to maintain the blind (see Figure 3-1; Table 5-1).

Group 2 - Adalimumab 40 mg s.c.

Adalimumab 40 mg (1 x 0.4mL PFS) will be administered at Baseline followed by dosing every 2 weeks until Week 50.

In addition, all Group 2 subjects will receive placebo (1 x 0.5mL or 2 x 0.5mL PFS) at given visits in order to maintain the blind (see Figure 3-1; Table 5-1).

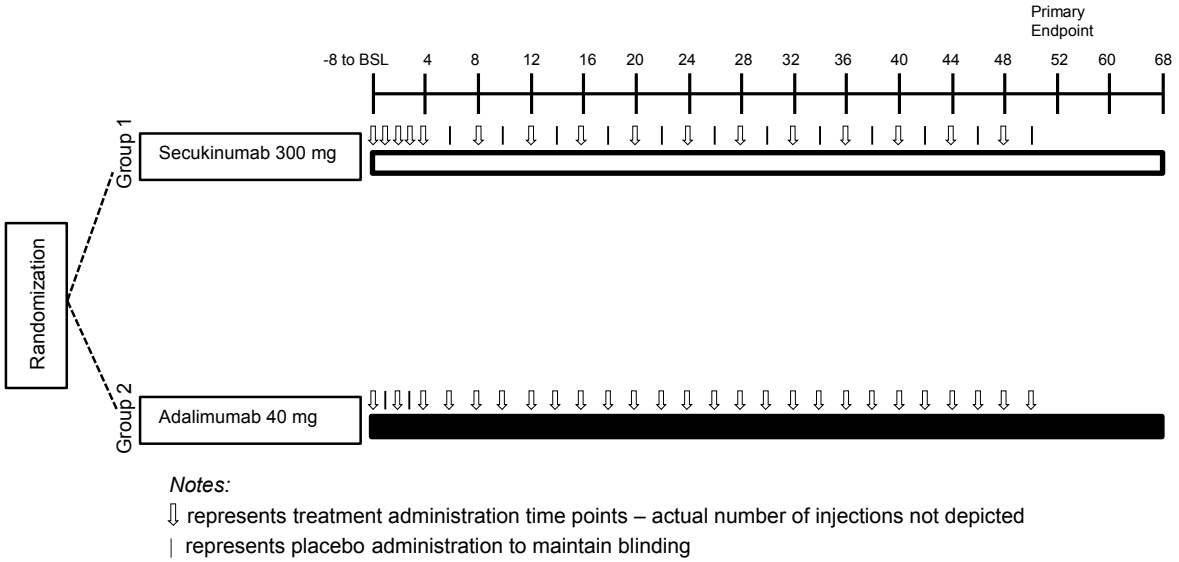
Study staff involved in drug handling and administration (e.g., investigational treatment receipt, inventory, storage, administration, and accountability) and IRT processes, will be unblinded and must not be the investigator or study staff involved in safety and efficacy assessments or eCRF completion. In addition, investigational treatment administered by the designated study staff member who is unblinded to treatment assignment must be done in a manner that maintains subject blinding as described in the Study Reference Manual. All other subject-related activities will be managed by blinded site personnel throughout the study.

Rescue medication, defined as any other therapeutic intervention for PsA should be avoided before completion of Week 52 assessments (see Section 5.5.6). Although no subject will be restricted from receiving necessary intervention for lack of benefit or worsening of disease,

[redacted]

subjects will be discontinued from the investigational treatment if rescued with prohibited medications (as described in Section 5.5.8). Subjects who take rescue medication in the study can continue to attend all subsequent scheduled visit assessments unless informed consent is withdrawn.

Figure 3-1 Study design



3.2 Rationale for study design

In PsA, more than half of the patients take biological DMARDs as a monotherapy with very good control of their disease (Nikiphorou 2014; Behrens 2015). Similar outcome in response has been demonstrated with or without use of the cDMARDs (including MTX). Thus no biologics have shown positive synergistic effects on any clinical outcomes and this is reflected in all their labels. A strategy of treatment with biologic monotherapy in PsA is therefore clinically justifiable and avoids unwarranted exposure to the potential toxicity of cDMARDs.

The randomized, double-blind, active control, multicenter, parallel-group design used in this study is in alignment with phase III trials of other biologics in this disease area and also in compliance with the European Medicines Agency (EMA) guidelines on PsA trials (EMA 2005).

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

The dosing regimens in this study rely upon dose-efficacy relationships observed in a PoC trial (CAIN457A2206) and two phase III trials (CAIN457F2306, CAIN457F2312) in PsA, as described below. The 24-week placebo-controlled PoC trial in 42 patients with PsA (CAIN457A2206) showed that two i.v. secukinumab doses of 10 mg/kg given 3 weeks apart were well-tolerated. ACR response endpoints consistently showed numerically greater responses for secukinumab compared with placebo, up to and including week 24. Post hoc and

subgroup analyses showed differences in signs and symptoms at 6 weeks in TNF-naïve subjects (ACR20 response achieved in 62% of subjects receiving secukinumab vs. 20% receiving placebo). Posthoc analysis showed that secukinumab, compared with placebo, resulted in significant improvement in acute-phase parameters (CRP, ESR) from baseline to Week 6 (McInnes 2014).

A placebo-controlled, double-blinded phase III study (FUTURE 1, CAIN457F2306) involving 606 patients with active moderate-to-severe PsA used an i.v. loading regimen (3 x 10 mg/kg) of secukinumab every 2 weeks followed by secukinumab s.c. 75 mg or 150 mg administered every 4 weeks. Secukinumab was well tolerated and produced rapid, clinically significant and sustained improvements in signs and symptoms (i.e. ACR20/50, PASI75/90), resolution of dactylitis and enthesitis and inhibition of joint structural (radiologic) damage at Week 24 in PsA patients with or without concomitant MTX (Mease 2015). In a subsequent phase III study (FUTURE 2, CAIN457F2312; N=397), secukinumab also resulted in significant improvement (compared with placebo) at Week 24 in signs and symptoms of patients with PsA with or without concomitant MTX (McInnes 2015).

In the PsA phase III studies, secukinumab administered at 300 mg s.c. suggested a potential for additional improvement compared to 150 mg in some TNF naïve patients. In accordance with the US prescribing information, if patients continue to have active PsA, a dosage of 300 mg s.c. should be considered (Cosentyx® package insert). This study will evaluate secukinumab (300 mg) for the treatment of adults with active PsA compared with adalimumab (Humira; 40mg s.c.).

Adalimumab is approved for the treatment of PsA at a recommended dose of 40 mg administered every other week, and this is the regimen patients randomized to the adalimumab group will receive. For secukinumab, the approved PsA treatments include both the 150 mg and 300 mg dose regimens (at Weeks 0, 1, 2, 3, and 4 followed by every 4 weeks).

In summary, the secukinumab maintenance regimen in this study is based on data suggesting optimal efficacy and safety in PsA; the dose for the adalimumab active control is based on an approved dose from data showing optimal efficacy and safety in patients with PsA.

Formulation to be used

This study will use secukinumab 150mg/1mL and placebo liquid, in single-use PFS. Adalimumab will be administered in the formulation approved for PsA (40 mg/0.4 mL) in a single-use PFS.

3.4 Rationale for choice of comparator

An active comparator group is necessary to evaluate whether secukinumab is superior to an approved therapy in PsA. The parallel-group controlled design is the most appropriate method to compare the two therapies and is consistent with the study of other biologics in the treatment of PsA.

In order to demonstrate superiority of secukinumab 300 mg to the standard of care treatment in PsA, adalimumab was chosen, being the commonly accepted reference therapy.

3.5 Purpose and timing of interim analyses/design adaptations

The primary analysis may be conducted when all patients complete the Week 52 visit. In the case this analysis is conducted, all patients will have final data pertaining to the Week 52 endpoints, thus no adjustment to the type I error will be made and the final analysis after the last visit (Week 68) will include the data collected from the post-treatment follow-up period.

3.6 Risks and benefits

Secukinumab has shown efficacy in several inflammatory diseases, including PsA, AS, and psoriasis. The large safety dataset of secukinumab across indications involving over 8,200 patients did not show unexpected safety issues relative to the known mode of action. In general, secukinumab is safe and well-tolerated and has demonstrated a similar safety profile to etanercept and ustekinumab in two head-to-head comparison studies over one-year in psoriasis (Langley 2014; Thaci 2015). The most frequently reported AEs are non-serious mild to moderate infections, mainly upper respiratory tract infections. In addition, there is an increase in superficial candidiasis, mainly oral candidiasis, with secukinumab compared with placebo, but the cases were generally mild or moderate in severity, non-serious and responsive to standard treatment. There is also a small increase in neutropenia cases with secukinumab compared with placebo. Common Toxicity Criteria (CTC) AE grade 3 neutropenia (<1.0-0.5 x 10^9/L) was uncommonly observed with secukinumab, and most cases were mild to moderate, transient and reversible and without a temporal relationship to serious infections. Hypersensitivity reactions include urticaria. Rare events of anaphylactic reaction to secukinumab have also been observed in clinical studies.

With adalimumab (Humira®), the most common adverse reactions (incidence >10%) across indications are infections (e.g. upper respiratory, sinusitis), injection site reactions, headache and rash (Humira® package insert; Humira® SmPC 2016). The most serious adverse reactions were serious infections including hepatitis B virus reactivation, neurologic or hematological reactions, autoimmune disorders and malignancies. In clinical trials of Humira®, allergic reactions overall (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) were observed in approximately 1% of patients.

The immunogenicity potential, i.e. of eliciting anti-drug antibodies (ADA), is higher for adalimumab (up to 26%) than for secukinumab (<1%) (Humira® package insert; Cosentyx® package insert). However, the presence of ADAs does not appear to be associated with development of adverse reactions or lack of efficacy for both secukinumab and adalimumab.

[redacted]

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from its mechanism of action is anticipated to be similar or improved compared to the other approved inflammatory cytokine-targeting therapies. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and extensive guidance to the investigators provided by Novartis and in the current version of the Investigator Brochure for secukinumab. Based on the overall favorable risk-benefit assessment, the current trial with secukinumab (and the comparator adalimumab) is justified.

4 Population

The study population will consist of a representative group of male or female subjects at least 18 years of age, fulfilling the Classification criteria for Psoriatic Arthritis (CASPAR) criteria (see Appendix 1) and PsA for at least 6 months and have active PsA disease defined as >3 swollen and tender joints in spite of treatment with NSAIDs and/or cDMARDs. The goal is to randomize approximately 850 subjects. Subjects will be eligible to enter the study if they have not previously been treated with biologic DMARDs for PsA or PSO (e.g., TNFα inhibitor), or cell-depleting therapies and either, have previously been treated with cDMARD, including but not limited to MTX, with an inadequate response on therapy or have stopped treatment due to safety/tolerability problems after at least one administration of a cDMARD.

The study population will be comprised of the subjects who have passed screening assessments and who comply with eligibility criteria. Subjects can be re-screened only once, and no study related re-screening procedures should be performed before re-consent by the subject. Mis-randomized subjects will not be re-screened.

4.1 Inclusion criteria

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

1. Informed consent must be obtained before any assessment is performed.
2. Male or non-pregnant, non-lactating female subjects at least 18 years of age.
3. Diagnosis of PsA as classified by CASPAR criteria (see Appendix 1) and with symptoms for at least 6 months and with active PsA at baseline defined as ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit, counts as one joint each).
4. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (CCP) antibodies negative at screening.
5. Diagnosis of active plaque psoriasis, with at least one psoriatic plaque of ≥2 cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis.
6. Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs.
7. Subjects who are regularly receiving 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 52.
8. Subjects receiving corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 52.

[redacted]

9. Subjects must have previously been treated with a cDMARD, including but not limited to MTX, with an inadequate response to therapy, or must have stopped treatment due to safety/tolerability problems after at least one administration of the cDMARD.

Subjects who are receiving a cDMARD will be allowed to enter the study only after cDMARD discontinuation and appropriate wash-out e.g. 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine wash-out has been performed.

4.2 Exclusion criteria

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

1. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
2. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it after the last dose (e.g. 20 weeks for secukinumab, 5 months for adalimumab in EU). Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository.
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

In case local regulations deviate from the methods listed, local regulations apply and will be described in the ICF.

Women are considered post-menopausal and not of child bearing potential if they have had at least 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g.

[redacted]

age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

3. Chest X-ray or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified physician.
4. Previous exposure to any biologic drugs for PsA and PSO, including but not limited to TNFα inhibitors, secukinumab or other biologic drugs targeting IL-17 or IL-17 receptor.
5. Subjects receiving high-potency opioid analgesics, including but not limited to, methadone, hydromorphone, and morphine.
6. Ongoing use of prohibited psoriasis treatments/medications (e.g., topical corticosteroids or ultraviolet (UV) therapy at randomization). The following wash out periods need to be observed:
   - Oral or topical retinoids: 4 weeks.
   - Photochemotherapy (e.g., PUVA): 4 weeks.
   - Phototherapy (UVA or UVB): 2 weeks.
   - Topical skin treatments (except in face, eyes, scalp and genital area during screening; only corticosteroids with mild to moderate potency): 2 weeks.
7. Previous treatment with any cell-depleting therapies, including but not limited to anti-CD20 or investigational agents (e.g., alemtuzumab (Campath®), anti-CD4, anti-CD5, anti-CD3, and anti-CD19).
8. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days until the expected pharmacodynamic effect has returned to baseline, whichever is longer.
9. History of hypersensitivity to any of the study drugs or excipients or to drugs of similar chemical classes.
10. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization.
11. Any therapy by intra-articular injections (e.g., corticosteroid) within 4 weeks before randomization.
12. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy.
13. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy.
14. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure (New York Heart Association status of class III or IV) and uncontrolled diabetes.
15. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFTs) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic

[redacted]

transaminase (ALT/SGPT), alkaline phosphatase or serum bilirubin. The investigator should be guided by the following criteria:

a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible and in all cases, at least prior to enrollment/randomization, to rule out any possible 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.

16. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L).
17. Screening total white blood cell (WBC) count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85 g/L).
18. Active systemic infections during the last two weeks (exception: common cold) prior to randomization.
19. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive purified protein derivative (PPD) skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines), or a positive QuantiFERON TB-Gold test. 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 prior to enrollment.
20. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization.
21. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
22. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial.
23. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
24. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
25. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
26. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.
27. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.

[redacted]

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

Novartis will supply the following study drugs:

Investigational treatment

-- Secukinumab 150 mg, liquid formulation in 1 mL PFS (2 x 1 mL PFS for 300 mg dose)

Reference treatment

--Placebo, liquid formulation in a 1 and 0.5 mL PFS

--Adalimumab 40 mg, liquid formulation in a 0.4 mL PFS

The study drugs will be administered by a designated study staff member at the site, who will be unblinded to treatment assignment (secukinumab vs. adalimumab), in a manner that maintains subject blinding and as described in the Study Reference Manual. The individual administering the investigational treatment must not be the investigator or study staff involved in safety and efficacy assessments or eCRF completion. The injections through Week 50 will be performed at the study site. Site staff and patient may agree on home administration at some visits as per Table 6-1 (Assessment schedule).

Secukinumab 150mg PFS and placebo 1 mL PFS will be provided in a double blind fashion and have identical appearance.

Adalimumab 40mg PFS and placebo 0.5 mL PFS will be provided as open label supplies. They have different appearance from each other and from secukinumab 150mg/placebo 1mL.

All study drugs will be labeled accordingly.

For detailed instructions on storage of the study drugs, please refer to Section 5.5.3.

5.1.2 Additional treatment

No additional treatment beyond investigational and reference treatments are included in this trial.

5.2 Treatment arms

Subjects will be randomly assigned to one of two treatment Groups in a 1:1 ratio, with approximately 425 subjects planned for each group. Subjects in Group 1 will receive secukinumab 300 mg, subjects in Group 2 will receive adalimumab 40 mg.

- Group 1:
  --secukinumab 300 mg s.c.: 2 x 1.0 mL PFS (150 mg)
- Group 2:
  --adalimumab 40 mg s.c.: 0.4 mL PFS (40 mg)

In order to maintain the blind, both groups will receive the same number of s.c. injections of active and/or placebo at each dosing visit throughout the study, as follows:

[redacted]

If the subject is allocated to Group 1, they will receive secukinumab 300 mg as two PFS, or one placebo 1mL PFS at specified visits as shown in Table 5-1 below.

If the subject is allocated to Group 2, they will receive adalimumab 40 mg as one PFS, or one adalimumab PFS and one placebo 0.5mL PFS, or two placebo 0.5mL PFS at specified visits as shown in Table 5-1 below.

Table 5-1 Blinding scheme

Treatment assignment/ study drug administration		Study dosing visits (in weeks, from randomization)																											
		0	1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	50	52
Group 1 secukinumab 300mg	secukinumab 300mg 1ml PFS	2	2	2	2	2		2		2		2		2		2		2		2		2		2		2		2	
	Placebo 1ml PFS						1		1		1		1		1		1		1		1		1		1		1		
Group 2 adalimumab 40mg	adalimumab 40mg 0.4ml PFS	1		1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
	Placebo 0.5ml PFS	1	2	1	2	1		1		1		1		1		1		1		1		1		1		1			

Site staff and patient may agree on home administration at some visits as per Table 6-1 (Assessment schedule).

5.3 Treatment assignment and randomization

At baseline, all eligible subjects will be randomized via IRT to one of the two treatment groups (secukinumab 300 mg s.c. or adalimumab 40 mg s.c.) as described in Section 5.2. A designated site staff member other than the investigator or study staff involved in safety and efficacy assessments or eCRF completion will contact IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to the investigator or study site staff involved in the conduct of efficacy assessments.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and study staff (except for those involved in drug handling, drug administration, and IRT processes): 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 random assignment of medication numbers to packs containing the study drug(s).

[redacted]

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

5.4 Treatment blinding

This is a double-blind randomized treatment trial.

Subjects, investigators, site personnel, and persons performing the assessments (except for those described below) will remain blinded to treatment assignment from the time of randomization until the database lock and analyses are completed, using the following methods:

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.

Investigational treatment will be dispensed by an unblinded pharmacist (or other unblinded qualified site personnel) who is independent of those involved in the assessment of study subjects. In addition the unblinded pharmacist (or other unblinded qualified site personnel) will store study medication and keep medication records containing unblinded information in a separate area to which blinded staff do not have access.

Study treatments will be administered by "independent study drug administrator"- an unblinded suitably qualified individual (nurse, physician, or other unblinded qualified site personnel) who is not responsible for any aspect of subject assessment or follow-up. "Independent study drug administrator" could be the same person dispensing the drug if suitably qualified to perform both activities.

Prior to the administration, the unblinded site personnel will put in place suitable methods, e.g physical barriers such as curtains, blindfolds, or similar as agreed with the subject and available to prevent subject seeing the appearance of their study treatment and keep the blind. The procedural details relating to treatment blinding and blinded drug administration will be described in the Study Reference Manual which will be provided separately.

The individual administering study treatment and all study subjects will be advised to refrain from making any comments to study staff or to other subjects regarding the appearance of study treatments

Unblinding will occur in the case of subject emergencies (see Section 5.5.12) and at the conclusion of the study. The appropriate study site and Novartis personnel will assess whether the study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

[redacted]

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

[redacted]

5.5 Treating the subject

5.5.1 Subject numbering

Each subject is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next sequential number by the investigator. Study personnel other than the investigator or study staff involved in safety and efficacy assessments will contact the IRT and provide the requested identifying information for the subject to register them in the IRT. The site should select the electronic case report form (eCRF) book with the matching Subject Number from the electronic data capture (EDC) system to enter data.

If the subject fails to be treated for any reason, the IRT must be notified within 2 days that the subject was not treated. The reason for not being treated will be entered on the Screening Study Disposition CRF.

Subjects may 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 investigational treatment

Each study site will be supplied by Novartis with secukinumab 150mg/1 mL PFS and 1 mL placebo PFS in packaging of identical appearance. Novartis will also supply adalimumab 40mg /0.4 mL PFS and 0.5 mL placebo PFS as open label supplies.

The investigational treatment packaging has a 2-part label. A unique medication number is printed on each part of this label which corresponds to placebo or active treatment. The unblinded pharmacist (or other unblinded qualified site personnel) will identify the investigational treatment package(s) to dispense to the "independent study drug administrator"- by contacting the IRT and obtaining the medication number(s)-. Immediately before dispensing the package to the "independent study drug administrator", the unblinded pharmacist will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Study Investigational treatment must be received by a designated unblinded site staff member at the study site, handled and stored safely and properly, and kept in a secured location to which only the unblinded site personnel have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization Quality Assurance (CPO QA).

[redacted]

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

Single PFS will be packaged in individual boxes. The PFS sealed in its outer box must be stored in an access controlled/locked refrigerator. They must be carefully controlled in accordance with applicable regulations governing investigational medicinal products and the active reference therapy (adalimumab).

The pharmacist or other qualified site personnel must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log which will be kept in a Pharmacy File in a secured location to which no blinded site staff would have access to. Monitoring of drug accountability will be performed by an unblinded field monitor (who is not the monitor accountable for other portions of the study) 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 investigator will return all partly used and unused investigational treatment, packaging, drug labels and a copy of the completed drug accountability log to Novartis as instructed.

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

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Study treatments (secukinumab 300 mg, adalimumab 40 mg and placebo) will be administered by s.c. PFS throughout the study. Administration of study treatment must occur only after the study assessments for the visit have been completed.

Administration of study treatment will occur at the study site through Week 50. Site staff and patient may agree on home administration by designated site staff at some visits as per Table 6-1 (Assessment Schedule), in which case the applicable study assessments can be made by phone before study treatment administration.

The first study treatment administration will occur at the baseline/randomization visit only after eligibility criteria have been confirmed, all study baseline assessments have been performed and the scheduled blood samples have been drawn. At each subsequent visit, all study assessments (as applicable per Table 6-1), should be completed prior to the injection of study treatment. [redacted]

All investigational treatment kits assigned by the IRT will be recorded in the IRT. The investigator should promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled.

[redacted]

5.5.4.1 Subcutaneous administration with PFSs

Secukinumab solution for s.c. injection (150 mg in 1.0 mL active/placebo), adalimumab solution for s.c. injection (40 mg in 0.4 mL) and placebo (0.5 mL), will be provided in PFS. The study treatment solution must be injected into non-affected areas of the skin.

The injections will be administered into the appropriate site of the body (thighs, arms, abdomen) and each injection should be given at a different injection site to reduce the risk of reaction. Each new injection should be given at least one inch from the previously used site. If the abdomen is chosen, a 2-inch area around the navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red or hard, or where the subject has scars or stretch marks.

Single PFS will be packaged in individual boxes for secukinumab, placebo and adalimumab. Prior to administration the boxes containing the PFS with study treatment solution should be allowed to come to room temperature **unopened** for 15 to 30 minutes prior to injection. Used PFS should be disposed immediately after use in a sharps container OR according to local regulations.

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

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments are not permitted. For subjects who are unable to tolerate the protocol-specified dosing scheme (including subjects who in the opinion of the investigator are at significant safety risk unless dosing is temporarily interrupted), investigational treatment interruption is permitted in order to keep the subject on study drug. In such cases, investigational treatment should be interrupted only during the time that a risk is present and ongoing. Investigational treatment can be restarted at the next scheduled visit after resolution of the safety risk.

The effect of secukinumab or adalimumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. The elimination of adalimumab may take up to four months (Humira® SmPC 2016); in case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for four months.

Any investigational treatment interruption must be recorded on the corresponding eCRF.

[redacted]

5.5.6 Rescue medication

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

Rescue medication must not be used before completion of Week 52 assessments (see Section 3.1). Please see Section 5.5.7 and Section 5.5.8 for details. Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, subjects will be discontinued from investigational treatment if treated with prohibited medications (as described in Section 5.5.8). Subjects who discontinue investigational treatment can continue to attend all subsequent scheduled visit assessments unless informed consent is withdrawn. If study investigational treatment is discontinued, subjects may take study prohibited medication under the investigator's guidance and per locally approved prescribing information.

Efficacy and safety will be assessed in detail at every study visit and subjects who are deemed by the investigator not to be benefiting from study treatment, or for any reason on the subject's own accord, will be free to discontinue study participation at any time.

Use of rescue medication must be recorded on the corresponding eCRF.

5.5.7 Concomitant medication

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

Guidelines for the use of specific medications are provided below.

Leflunomide wash-out with cholestyramine

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

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomization. The subject should remain on a stable dose until Week 52.

[redacted]

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 52, only due to adverse events.

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

Intra-articular corticosteroids are not permitted within 4 weeks prior to baseline and up to week 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 corticosteroids is not permitted within 8 weeks prior to Week 52. The joints injected with intra-articular corticosteroids will be assessed as both swollen and tender in the SJC and TJC, from injection time onwards.

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

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

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.

After Week 52, a change in the NSAIDs, low strength opioids or paracetamol/acetaminophen treatment regimen is permitted.

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

5.5.8 Prohibited medication

Use of the treatments displayed in Table 5-2 is NOT allowed after the start of the washout period unless specified otherwise below or in Section 5.5.9.

Live vaccines should not be given until 4 months after last study treatment administration (see Section 5.5.5).

Table 5-2 Prohibited medication

Medication	Action (after randomization)	Washout period (before randomization)
Any biologic drugs, including but not limited to TNFα inhibitors, secukinumab, or other biologic drugs targeting IL-17 or IL-17 receptor	Discontinue investigational treatment	Biologics for PsA and PSO: never Biologics for other indications: 16 weeks
Any cell-depleting therapies including but not limited to anti-CD20 or investigational agents [e.g.,	Discontinue investigational treatment	Never

Medication	Action (after randomization)	Washout period (before randomization)
alemtuzumab (Campath), anti-CD4, anti-CD5, anti-CD3, and anti-CD19]		
cDMARDs (e.g. MTX) including apremilast	Discontinue investigational treatment	4 weeks
Leflunomide	Discontinue investigational treatment	8 weeks
Leflunomide with cholestyramine washout	Discontinue investigational treatment	4 weeks
Any investigational treatment or participation in any interventional trial	Discontinue investigational treatment	4 weeks or 5 half-lives (whichever is longer)
Unstable dose of NSAIDs (selective COX-2 inhibitors)	Discontinuation of investigational treatment may be required on a case by case basis. (Dose adjustments allowed after week 52)	2 weeks
Analgesics other than NSAIDs, paracetamol/acetaminophen, and low strength opioids PRN	Discontinue investigational treatment	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent (until Week 52)*	If administered due to a medical urgency unrelated to the patient's arthritis, study treatment should be interrupted until the steroid is discontinued. If administered not for a medical urgency or related to the patient's arthritis, then discontinuation of investigational treatment may be required on a case by case basis	2 weeks

[redacted]

Medication	Action (after randomization)	Washout period (before randomization)
Unstable dose of systemic corticosteroids ≤ 10 mg prednisone equivalent (until Week 52)*	Discontinuation of investigational treatment may be required on a case by case basis. (Dose adjustments allowed after week 52)	2 weeks
Intra-articular corticosteroids injections, (until Week 52)*	Discontinue investigational treatment, (see Section 5.5.7)	4 weeks
Intramuscular or intravenous corticosteroid treatment	Discontinuation of investigational treatment may be required on a case by case basis	4 weeks
Live vaccinations	If administered due to a medical urgency, study treatment should be interrupted for 4 months. If administered not for a medical urgency then discontinue investigational treatment	6 weeks
Oral or topical retinoids	Discontinue investigational treatment	4 weeks
Photochemotherapy (e.g. PUVA)	Discontinue investigational treatment	4 weeks
Phototherapy (UVA or UVB)	Discontinue investigational treatment	2 weeks
Topical skin treatments (except in face, eyes, scalp and genital area; only corticosteroids with mild to moderate potency)	Discontinue investigational treatment	2 weeks

[redacted]

Medication	Action (after randomization)	Washout period (before randomization)
* see details about corticosteroid management in Section 5.5.7		

5.5.9 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment or the study for any reason at any time. The investigator should discontinue study treatment for a subject if, on balance, he/she believes that continuation would be detrimental to that subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent
- Subject's request to terminate treatment
- Emergence of the following AEs:

1. Any severe or serious AE that requires treatment with an unacceptable co-medication
2. Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratosis, treated in situ carcinoma of the cervix, or non-invasive malignant colon polyps which are being or have been removed
3. Life-threatening infection

- Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (a general guidance on clinically notable laboratory values is provided in Appendix 7)
- Pregnancy
- Use of prohibited treatment as per Table 5-2 and in particular addition of concomitant cDMARD (e.g. MTX). Subjects who discontinue study treatment but continue to attend scheduled visits may use prohibited medications under the guidance of the study Investigator.
- Any other protocol deviation that results in a significant risk to the subject's safety

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if there is a lack of improvement or worsening of their symptoms, or if on balance, the investigator believes 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.

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.

Subjects who discontinue **study treatment** should NOT be considered withdrawn from the study and can continue to attend all subsequent scheduled visit assessments, except if informed consent is withdrawn.

[redacted]

5.5.10 Withdrawal of consent

Subjects may be considered discontinued if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature discontinuation occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature discontinuation from the study and record this information on the appropriate Study Phase Completion eCRF. Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

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

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information in the Withdrawal of Consent eCRF. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up. The data collected on the subject to the point of withdrawal remains part of the study database and may not be removed.

5.5.11 Loss to follow-up

For 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 contacting the subject, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled End-of-Study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

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

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

- protocol number
- study drug name (if available)

[redacted]

- patient number

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

Study drug must be discontinued after emergency unblinding.

5.5.13 Study completion and post-study treatment

A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol..

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.

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

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 4 months before initiating the treatment is recommended; elimination of adalimumab may take up to four months (Humira® SmPC 2016).

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing the Institutional Review Board (IRBs) or Independent Ethics Committee (IECs) 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" when the visits (or telephone calls) are performed.

Upon agreement between the site and the subject, drug administration at certain visits (as specified in Table 6-1 can be performed at the subject's domicile by the independent drug administrator. In such cases, concomitant medication/non-drug therapy and Adverse Events/SAEs will be collected by a telephone call.

During the period of the study from Screening to Week 68, the assessments must be performed as indicated in Table 6-1.

Subjects should be seen for all visits on the designated day or as closely as possible to the original planned visit schedule. Missed or rescheduled visits should not lead to automatic discontinuation.

[redacted]

Subjects who discontinue study treatment before completing the study can continue to attend all subsequent scheduled visits and perform all assessments except receiving study treatment, unless informed consent is withdrawn. Subjects who prematurely discontinue from the **study** should undergo an End-of-Study visit (corresponding to the Week 52 visit; see Table 6-1), 4 weeks after last study treatment and follow-up visits at 12 weeks and 18 weeks after last study treatment (assessments as listed for Week 60 and Week 68). The investigator must also contact IRT to register the subject's discontinuation from study treatment.

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

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have a duration of up to 8 weeks before randomization, during which time the subject will sign the informed consent form (ICF), be evaluated for eligibility, and allowed sufficient time for medication washout, if required (see Table 5-2), in addition to all other assessments indicated in Table 6-1.

If subjects do not have a chest X-ray or chest MRI obtained within 3 months preceding the screening visit, a chest X-ray should be performed. In order to minimize unnecessary exposure to radiation, the chest X-ray should only be performed after confirming that the subject meets all inclusion/exclusion criteria. At some sites selected by Novartis, the X-ray assessment may be replaced by MRI assessment.

Subjects evaluated at screening for eligibility should not be screen failed on the basis of a medication requiring washout, unless the subject will be unable to complete the washout in the appropriate time frame before randomization.

Subjects who prematurely withdraw from the study will not be replaced.

[redacted]

Table 6-1 Assessment schedule

	Screening		Study Duration (Weeks) Treatment Period																														
Activity	**SV1[12]**	**SV2[12] (-4 to BSL)**	**BSL**																														
Recruitment Informed Consent	X																																
[redacted]																																	
Inclusion/ Exclusion Criteria	X	X	X																														
Relevant medical history/ current medical condition	X	X																															
Drug washout evaluation	X																																
Smoking history	X																																
CV medical history	X																																
Demography	X																																
Psoriasis/ PsA medical history and previous therapies	X																																
CASPAR criteria		X																															

[redacted]

	Screening		Study Duration (Weeks) Treatment Period																																
Activity	**SV1[12]**	**SV2[12] (-4 to BSL)**	**BSL**																																
Physical exam		S	S				S		S		S		S		S		S		S		S		S		S		S		S		S			
Weight		X	X																													X		
Height		X																																
Vital signs		X	X				X		X		X		X		X		X		X		X		X		X		X		X		X			
ECG			X																															
Randomization via IRT			X																															
Administration of s.c. study treatment at study site[1, 2, 3, 4]			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			
Prior/Concomitant medication/non-drug therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology, blood chemistry, urinalysis[5, 10]		X	X								X						X														X			
Lipids[10]			X						X				X				X														X			
PPD[6] skin test or QuantiFERON TB Gold test		X																																

[redacted]

	Screening		Study Duration (Weeks) Treatment Period																														
Activity	**SV1[12]**	**SV2[12] (-4 to BSL)**	**BSL**																														
Chest X-ray/MRI[7]			S																														
Adverse Events/SAEs (incl. injection site reaction, occurrence of infections)[8]	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	X	X
Serum pregnancy test		X																															
Urine pregnancy test[9]			X								X						X					X				X					X		
ANA			X														X														X		
Anti-dsDNA			X														X														X		
[redacted]																																	
Anti-CCP		X																															
Rheumatoid factor		X																															
[redacted]																																	

	Screening		Study Duration (Weeks) Treatment Period																																
Activity	**SV1[12]**	**SV2[12] (≤4 to BSL)**	**BSL**																																
High sensitivity C-Reactive protein		X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X			
Erythrocyte Sedimentation Rate (ESR)[9]			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X			
Tender and swollen joint counts (TJC78, SJC76)		X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X			
Patient's assessment of PsA pain (VAS)			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X			
Patient's global assessment of disease activity (VAS)			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X			
[redacted]																																			
Physician's global assessment of			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X			

[redacted]

	Screening		Study Duration (Weeks) Treatment Period																																
Activity	**SV1[12]**	**SV2[12] (4 to BSL)**	**BSL**																																
disease activity (VAS)																																			
Health Assessment Questionnaire (HAQ-DI)			X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		X		
[redacted]																																			
BSA assessment			X		X		X		X		X		X				X				X				X						X				
PASI			X		X		X		X		X		X				X				X				X						X				
[redacted]																																			
[redacted]																																			
[redacted]																																			
[redacted]																																			
[redacted]																																			

	Screening		Study Duration (Weeks) Treatment Period																																
Activity	**SV1[12]**	**SV2[12] (-14 to BSL)**	**BSL**																																

[redacted]

[1]The individual administering the investigational treatment must not be the investigator or study staff involved in safety and efficacy assessments

[2]The individual contacting IRT for randomization and treatment assignment must not be the investigator or study staff involved in safety and efficacy assessments

[3]For visits scheduled through Week 4, the study treatment should not be administered less than 7 days from the previous administration

[4]For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration

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

[6]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

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

[8]AEs /SAEs occurring after the subject has provided informed consent must be reported

[9]Kits will be provided by central lab and test is to be performed locally

[10]Sample must be obtained fasting.

[redacted]

[12] Screening visits 1 and 2 will be combined for patients complying with previous / concomitant treatments wash-out requirements

[13] Subjects who discontinue the study should be scheduled for an End-of-Study study visit, 4 weeks after their last study treatment administration, at which time all of the assessments listed for the Week 52 visit will be performed. Subjects will return to the study site for the follow-up visits at 12 weeks and 18 weeks after last study treatment (assessments as listed for Week 60 and Week 68).S = assessment to be recorded on source documentation

[redacted]

	Screening		Study Duration (Weeks)																														
			Treatment Period																														
Activity	**SV1[12]**	**SV2[12] (4 to BSL)**	**BSL**					**4***	**6**	**8***	**10**	**12***	**14**	**16***	**18**	**20***	**22**	**24***	**26**	**28***	**30**	**32***	**34**	**36***	**38**	**40***	**42**	**44***	**46**	**48***	**50**	**52[13]**	**EOT[13]**	**FU[13]**
*The administration of s.c. study treatment may be done at site or at the subject's home by an independent drug administrator. Concomitant medication/non-drug therapy and Adverse Events/SAEs will be collected by telephone, if the administration of study treatment is done at home.																																	

[redacted]

6.1 Information to be collected on screening failures

Subject may discontinue from the study prior to randomization. These subjects are considered screening failures.

If a subject discontinues before entering the double-blind treatment period at baseline, 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 Serious Adverse Events (SAEs) that occurred during the screening period. AEs that are not serious will be followed by the investigator and collected only in the source data.

All subjects who have signed informed consent and are randomized into the Treatment Period of the study will have all AEs **occurring after informed consent is signed** recorded on the Adverse Event eCRF.

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

6.2 Patient 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 investigational treatment, such as date of diagnosis of PsA/Psoriasis, previous PsA/Psoriasis therapies, cardiovascular medical history, smoking history and surgical sterilization for females if applicable.

Whenever possible, diagnoses and not symptoms will be recorded.

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

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/procedures continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or 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). Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

[redacted]

6.4 Efficacy

The efficacy outcome measures used in this study are standard measures used across all PsA trials.

- American College of Rheumatology (ACR) 20, 50 [redacted] responses
  - Swollen Joint Count (SJC)/Tender Joint Count (TJC)
  - Patient's global assessment of disease activity (VAS)
  - Physician's global assessment of disease activity (VAS)
  - Patient's assessment of PsA pain intensity (VAS)
  - Health Assessment Questionnaire – Disability Index (HAQ-DI©)
  - high sensitivity C-Reactive Protein (hsCRP) and Erythrocyte Sedimentation Rate (ESR)

[redacted]

- Psoriasis Area and Severity Index (PASI)

[redacted]

All efficacy assessments should be performed prior to administration of study treatment. Details relating to the administration of all PROs are provided in Appendix 2.

6.4.1 American College of Rheumatology (ACR) response

The ACR response (Appendix 3) will be used to determine efficacy (Felson 1995). A subject is defined as an ACR20 responder if, and only if, the following three conditions hold:

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

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

[redacted]

[redacted]

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

6.4.1.1 Tender 78 joint count and swollen 76 joint count

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

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, 2 hips, 2 knees, 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 (yes, no or not applicable), needs to be ticked for all joints.

In case a joint is injected with corticosteroids (see restrictions in Section 5.5.7), this joint will be assessed as both swollen and tender in the SJC and TJC, from injection time onwards.

6.4.1.2 Patient's assessment of PsA pain

The patient's assessment of pain will be performed using a 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 a 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 today'*.

6.4.1.4 Physician's global assessment of disease activity

The physician's global assessment of disease activity will be performed using a 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 subject's global assessment of disease activity, when performing his own assessment on that subject.

6.4.1.5 Health Assessment Questionnaire – Disability Index (HAQ- DI)©

The HAQ-DI© was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. The disability assessment component of the HAQ, the HAQ-DI©, assesses a subject's level of functional ability and includes questions of fine movements of the

[redacted]

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, 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.

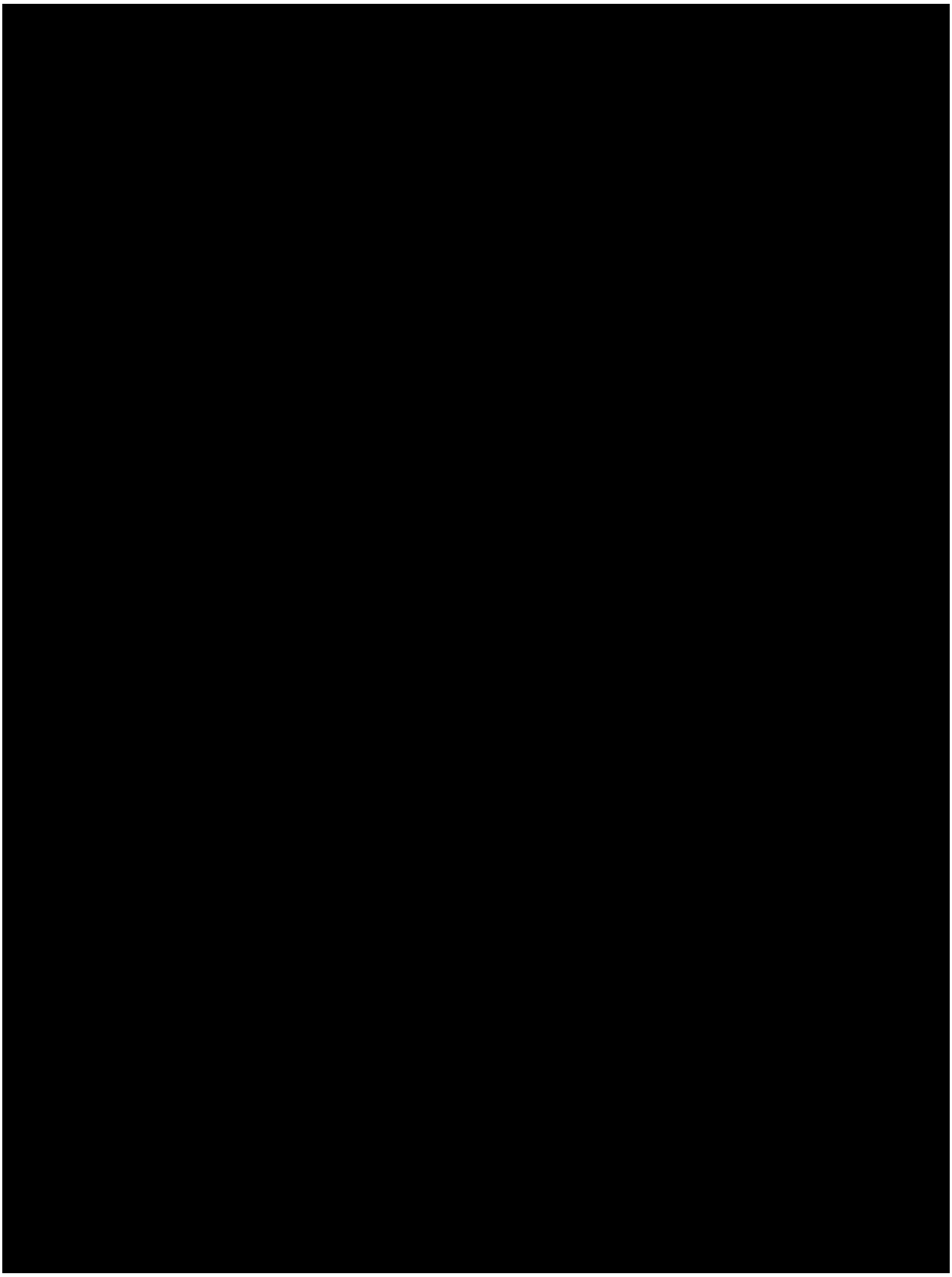
6.4.1.6 High Sensitivity C-reactive protein (hsCRP)

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 as indicated in Table 6-1.



[redacted]

Presence of enthesitis

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

[redacted]

6.4.8 Psoriasis Area and Severity Index (PASI)

The PASI (Fredriksson 1978; Weisman 2003; Gottlieb 2005) 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 6-3.

[redacted]

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

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

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

Table 6-3 The PASI scoring system

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

[redacted]

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

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

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

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

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

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0. The investigator is responsible for collecting the components or scoring signs and total regional area. More information is provided in Appendix 5.

[redacted]

6.4.10 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across many PsA trials.

[redacted]

6.5 Safety

Evaluation of all AEs and SAEs including injection site reactions, abnormal findings in ECG, physical examination, vital signs and laboratory assessments will occur. [redacted]

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

- Evaluation of AE/ SAEs
- Physical examination
- Vital signs
- Height and weight
- QuantiFERON TB-Gold test or PPD skin test
- Electrocardiogram
- Local tolerability (injection site reactions)
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab and adalimumab

[redacted]

6.5.1 Physical examination

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

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

6.5.2 Vital signs

Vital signs will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position. If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.

6.5.3 Height and weight

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

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

[redacted]

6.5.4 QuantiFERON TB-Gold test or PPD skin test

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

6.5.4.1 QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the second screening visit and the results have 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.

6.5.4.2 PPD skin test

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

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

6.5.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 6 and Appendix 7. All subjects with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

6.5.5.1 Hematology

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

6.5.5.2 Clinical chemistry

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

6.5.5.3 Urinalysis

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

6.5.5.4 Lipid panel

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

6.5.6 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 6-1 at the Baseline visit. ECGs must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection followed by vital signs and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings at baseline must be discussed with the sponsor before administration of investigational treatment.

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

6.5.7 Pregnancy and assessments of fertility

The study treatment must not be given to pregnant women; therefore, effective methods of birth control must be used for women of childbearing potential (see exclusion criteria definitions, Section 4.2).

A serum β-hCG test will be performed in all women at screening. All women who are not surgically sterile or post-menopausal (as defined in Section 4.2) at screening, will have local urine pregnancy tests as indicated in Table 6-1. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the subject must discontinue study treatment.

6.5.8 Tolerability of Investigational Treatments

Tolerability will be assessed by AEs, laboratory values, injection site reaction, [redacted].

[redacted]

6.5.9 Additional parameters

Blood will be obtained at the first screening visit (Visit 1) for anti-CCP antibodies and the Rheumatoid Factor (RF) assessment. Antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA) antibodies will also be assessed at visits/time points indicated in Table 6-1.

[redacted]

6.5.11 Appropriateness of safety measurements

The safety measures used in this study are standard for a use of a biologic in patients with PsA. A chest X-ray or MRI at screening (or within 3 months prior to screening) is performed to rule out the presence of a pulmonary malignancy of infectious process (in particular, tuberculosis).

[redacted]

The total amount of radiation exposure that results from the screening X-ray measurement is considered to involve minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

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

6.6 Other assessments

The other assessments planned for the study are:

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

[redacted]

6.6.1 Health-related Quality of Life

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)

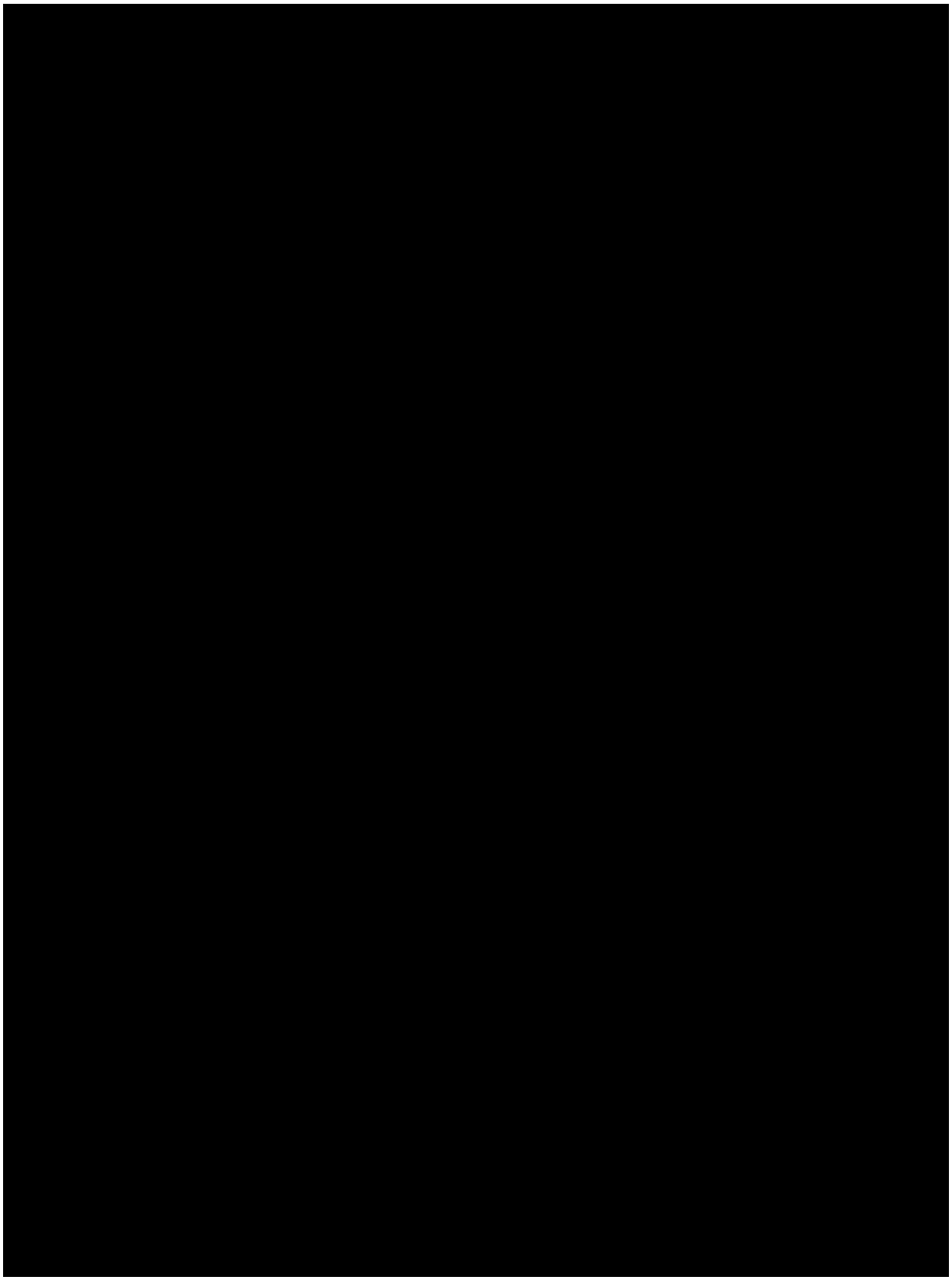
[redacted]

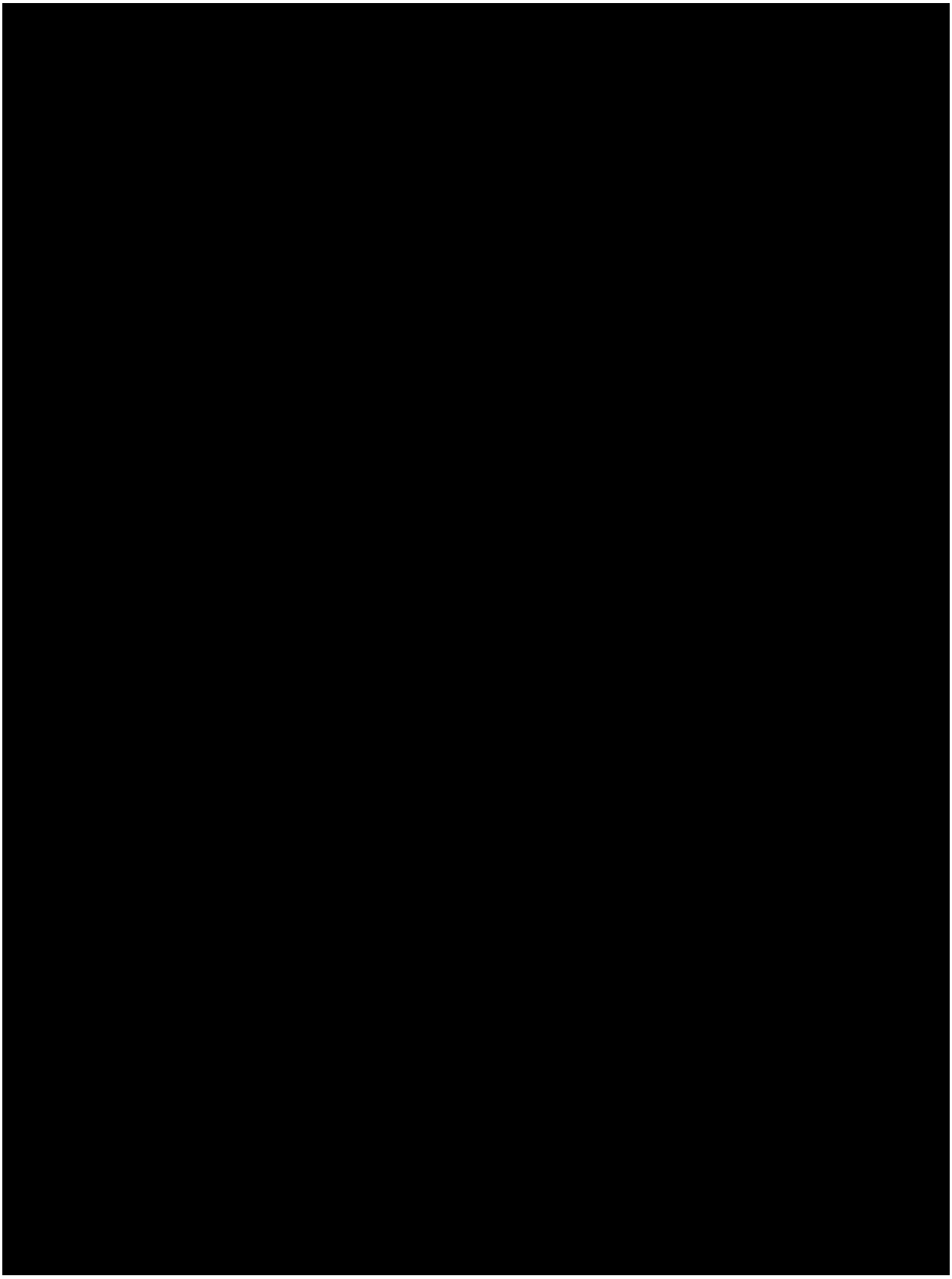
All questionnaires will be available, where possible, in the local languages of the participating countries and should be completed by subjects before they see the study physician. All questionnaires will be completed at the defined visits / time points listed in the Table 6-1 and prior to the subject seeing the investigator for any clinical assessment or evaluation. The questionnaires will be in the respondent's local language. The subject should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses. Completed questionnaires should be reviewed and assessed by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. This assessment should be documented in the source records. If AEs or SAEs are confirmed, the investigator should record the events as per instructions given in the relevant section of the protocol (see Section 7.1 and Section 7.2).

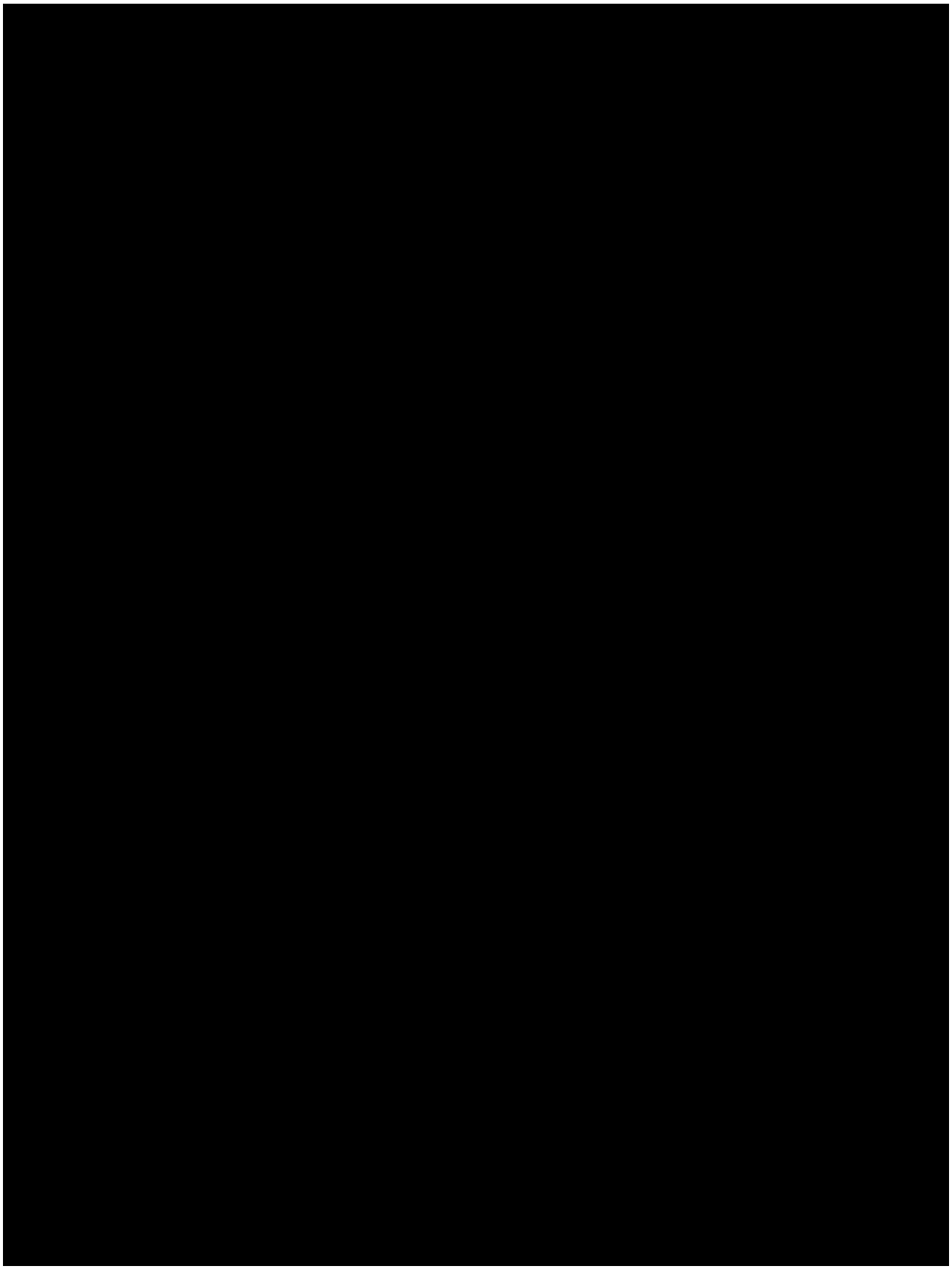
Guidelines for administering the PRO questionnaires can be found in Appendix 2.

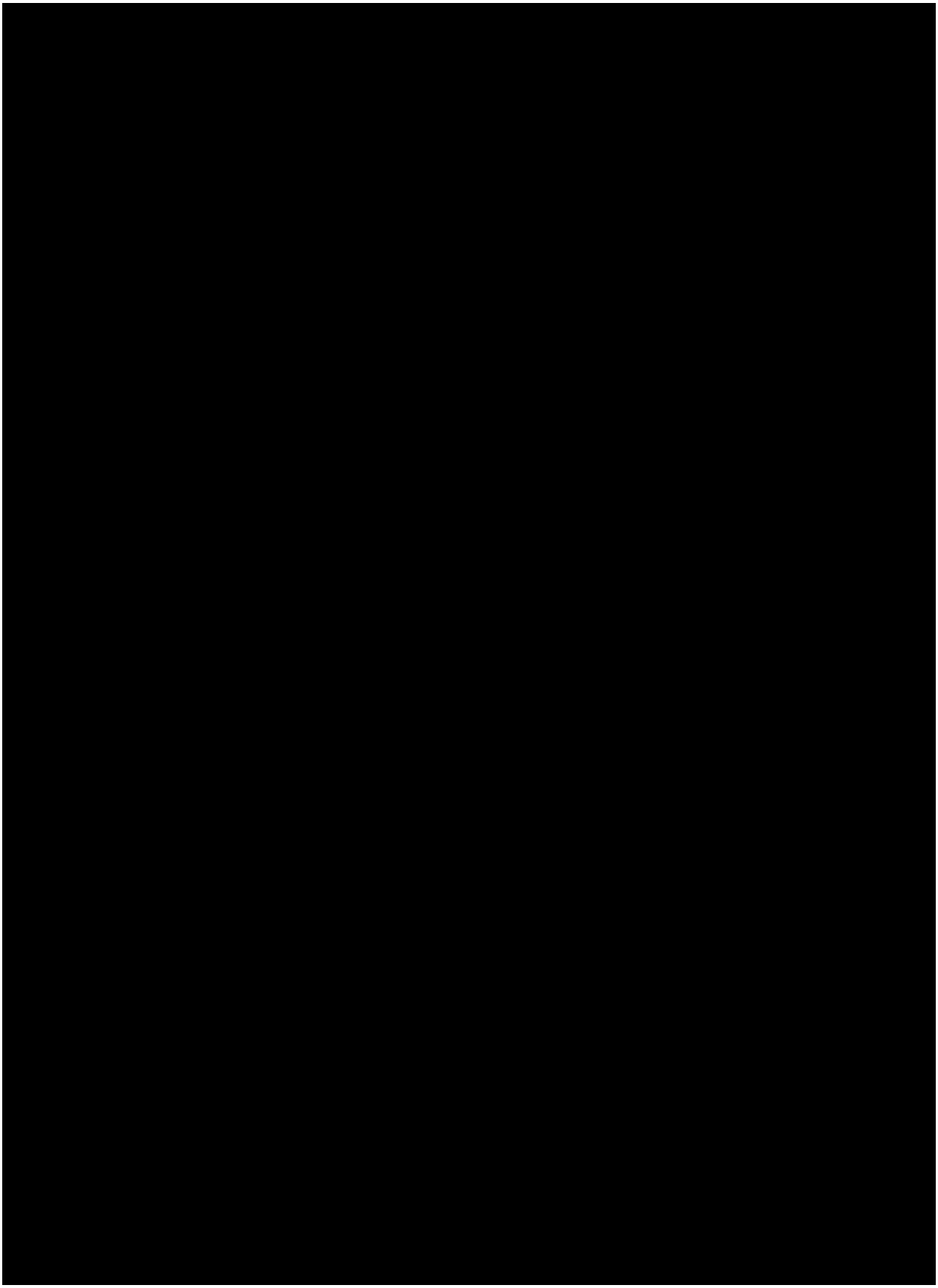
[redacted]

[redacted]









[redacted]

7 Safety monitoring

7.1 Adverse events

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

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

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

[redacted]

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

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

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in a patient with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying AEs. Alert ranges for laboratory and other test abnormalities are included in Appendix 7.

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- Its relationship to the study treatment and other investigational treatment
  - "No Relationship to study treatment or other investigational treatment" or
  - "Relationship to study treatment" or
  - "Relationship to other investigational treatment" or
  - "Relationship to both study treatment and other investigational treatment or indistinguishable"
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported
- whether it constitutes a serious adverse event (SAE - See Section 7.2 for definition of SAE) and which seriousness criteria have been met
- action taken regarding investigational treatment.

The action taken to treat the AE should be recorded on the Adverse Event eCRF.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

  - no action taken (e.g. further observation only)
  - investigational treatment dosage increased/reduced
  - investigational treatment interrupted/withdrawn
  - concomitant medication or non-drug therapy given
  - patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

[redacted]

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

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

7.2 Serious adverse events

7.2.1 Definition of SAE

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

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

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

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

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

[redacted]

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

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Drug Safety and Epidemiology as per Section 7.2.2.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 10 weeks (70days) after the last study visit, or 12 Weeks (84 days) following the last administration 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 study treatment.

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

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

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. 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 patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

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

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

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

Please refer to Table 18-1 in Appendix 6 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 18-1 in Appendix 6 should be followed up by the investigator or designated personal at the trial site as summarized below.

Detailed information is outlined in Table 18-2 in Appendix 6.

For the liver laboratory trigger:

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

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the subject. Repeats laboratory must then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF. If the elevation is confirmed, close observation of the patient will be initiated, including consideration of treatment interruption if deemed appropriate.

For the liver events:

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

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

[redacted]

7.4 Renal safety monitoring

To date, there has been no safety signal for nephrotoxicity with secukinumab in over 12,000 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests resulting in clinically significant abnormal values (see Appendix 7 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

Table 7-1 Study treatment

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

7.6 Pregnancy reporting

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

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

[redacted]

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

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and Good Clinical Practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of data capture / data entry, the adherence to the protocol and to 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. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters and provide reports to Novartis Clinical Teams to assist with trial oversight.

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

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

8.3 Database management and quality control

Data from the CRFs are entered into the study database by Novartis Data Management staff using single data entry and by referring to the scanned image of the CRF.

Novartis staff review the data entered into the CRFs 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 that 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 World health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

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

Patients/subjects will fill in their PRO data in a site based tablet. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an IRT system. The system will be supplied by Novartis, who will also manage the database. Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

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

[redacted]

8.4 Data Monitoring Committee

A Data Monitoring Committee is not planned for this study.

[redacted]

8.5 Adjudication Committee

An independent external adjudication committee may be used to monitor specific safety events, including, but not limited to clinically significant cardio- and cerebrovascular events. The events will be reviewed and adjudicated in a blinded fashion as they occur during the conduct of the trial.

Details regarding the definition of AEs of special interest as well as the adjudication process will be available in the relevant secukinumab Adjudication Committee charter.

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 comparison of secukinumab 300mg with adalimumab will be performed at Week 52 unless otherwise specified.

Efficacy and safety data for the entire treatment period will be presented by treatment groups.

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 Interactive Voice Response (IVR)) will be excluded from the randomized set.

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

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

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.

9.2 Subject demographics and other baseline characteristics

Demographics and 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.

[redacted]

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

- Gender, age, race, ethnicity, weight, height, and BMI
- ACR components and other disease-related measures (e.g. [redacted], presence of enthesitis, [redacted], time since first diagnosis of psoriatic arthritis, [redacted], subjects with psoriasis ≥ 3%).

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

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

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

Prior and concomitant medication

Prior and concomitant medications (including Rescue medications defined in Section 5.5.6) 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 to 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.

[redacted]

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

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(s)

The primary efficacy endpoint will be ACR20 response at Week 52 for superiority test to compare 300 mg secukinumab with adalimumab. The analysis of the primary efficacy endpoint will be based on the FAS subjects. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for ACR20 being tested for superiority test is that there is no difference in the proportion of subjects fulfilling the ACR20 criteria at Week 52 in the secukinumab 300 mg group vs. adalimumab.

Let pj denote the proportion of ACR20 responders at Week 52 for treatment regimens j, j=0, 1 where

0 corresponds to adalimumab,

1 corresponds to secukinumab 300 mg

In statistical terms, H1: p1 = p0, HA1: p1 $\neq$ p0, i.e.

H1: secukinumab is not different to adalimumab regimen for signs and symptoms (ACR20 response) at Week 52.

The primary endpoint of ACR20 at Week 52 in the FAS will be evaluated using a logistic regression model with treatment as a factor and weight as a covariate. Odds ratios will be computed for comparisons of secukinumab 300 mg vs. adalimumab regimen utilizing the logistic regression model fitted.

9.4.3 Handling of missing values/censoring/discontinuations

The primary and secondary estimands focus on the difference between the treatment groups in the proportion of patients achieving monotherapy ACR20 response (or other response variables) at week 52 in FAS patients. Monotherapy response is defined as achieving the requirements for the clinical response (e.g. ACR20) and not prematurely discontinuing study medication and not taking concomitant MTX/cDMARD (composite estimands). Missing data for ACR20 response and other binary efficacy variables (e.g. ACR50, [redacted], PASI90, etc.) for data up to Week 52 will be handled by multiple imputation. Multiple imputation (MI) is a simulation based approach where missing values are replaced by multiple Bayesian draws from the conditional distribution of missing data given the observed data and covariates, creating multiple completed data sets. These completed data sets can then be analyzed using standard

[redacted]

methods. Within this analysis the ACR composites or PASI score will be imputed and response variables will be derived based on the imputed scores. In the multiple imputation analysis the response status will be imputed based on the individual treatment arm information.

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-BSL values are missing then these missing values will not be imputed and this subject will be removed from the analysis of the corresponding variable, i.e. it might be that the number of subjects providing data to an analysis is smaller than the number of subjects in the FAS.

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 52 may also be evaluated using a non-parametric regression (Koch 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 BSL or disease characteristics on response.

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:

Non-responder Imputation

[redacted]

Observed data analysis

Additional sensitivity analyses will be conducted to examine the effect of taking concomitant treatment of MTX and/or other cDMARDs along with study drug and/or the effect of treatment discontinuation without rescue medication but remaining in the study on the primary endpoint.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

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

- PASI90 response at Week 52 in Superiority test for secukinumab 300 mg
- ACR50 response at Week 52 in Superiority test for secukinumab 300 mg
- Change from baseline in HAQ-DI© score at Week 52 in Superiority test for secukinumab 300 mg
- Resolution of enthesitis at Week 52 in Superiority test for secukinumab 300 mg

[redacted]

Testing strategy

The following hypotheses will be included in the hierarchical testing strategy, and type-I-errors will be set such that family-wise two-sided type-I-error of 5% is kept. The inferential testing procedure will only continue if the previous test was rejected at the appropriate type-I-error rate as specified after Figure 9-1.

Primary objectives (detailed in Section 9.4.2)

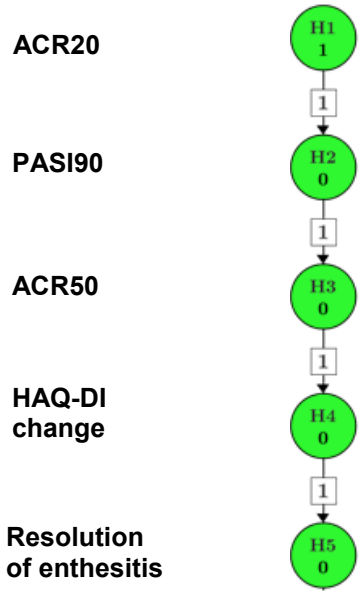
- H_1: secukinumab 300 mg is not different to adalimumab regimen with respect to ACR20 response at Week 52.

Secondary objectives

The same method of imputation for binary endpoints that is being used for the primary is also being used for secondary endpoints

- H_2: secukinumab 300 mg is not different to adalimumab regimen with respect to PASI90 response at Week 52
- H_3: secukinumab 300 mg is not different to adalimumab regimen with respect to ACR50 response at Week 52
- H_4: secukinumab 300 mg is not different to adalimumab regimen with respect to the change from baseline in HAQ-DI© at Week 52
- H_5: secukinumab 300 mg is not different to adalimumab regimen with respect to resolution of enthesitis at Week 52

Figure 9-1 Testing Strategy



- The family-wise error rate will be set to two-sided α=5% and it will be controlled with the proposed hierarchical testing strategy.
  - If H1 is rejected at α, the hypothesis H2 will be tested at α. If H2 is rejected at α, H3 will be tested at α and so on.

[redacted]

ACR50 at Week 52

Response at Week 52 to ACR50 in the FAS will be evaluated using a logistic regression model with treatment as a factor and weight as a covariate.

PASI90 response

PASI90 response at Week 52 will be evaluated using a logistic regression model with treatment as a factor and weight as a covariate.

Physical function (HAQ-DI©)

Between-treatment differences in the change in HAQ-DI© will be evaluated using a MMRM with treatment regimen, analysis visit 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 regimen and adalimumab at the appropriate analysis visits.

Resolution of enthesitis

Resolution (presence to absence) of enthesitis at Week 52 will be evaluated using a logistic regression model with treatment as a factor and weight as a covariate.

[redacted]

[redacted]

[redacted]

9.5.3 Safety variables

Adverse events

Treatment-emergent AEs (TEAEs, adverse events that started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized up to 12 weeks (84 days) after the last dose. Non-treatment-emergent AEs will be listed in a listing but not summarized.

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

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

Separate summaries will be provided for death, SAE, other TEAEs leading to study treatment interruption or study treatment 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, 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.

[redacted]

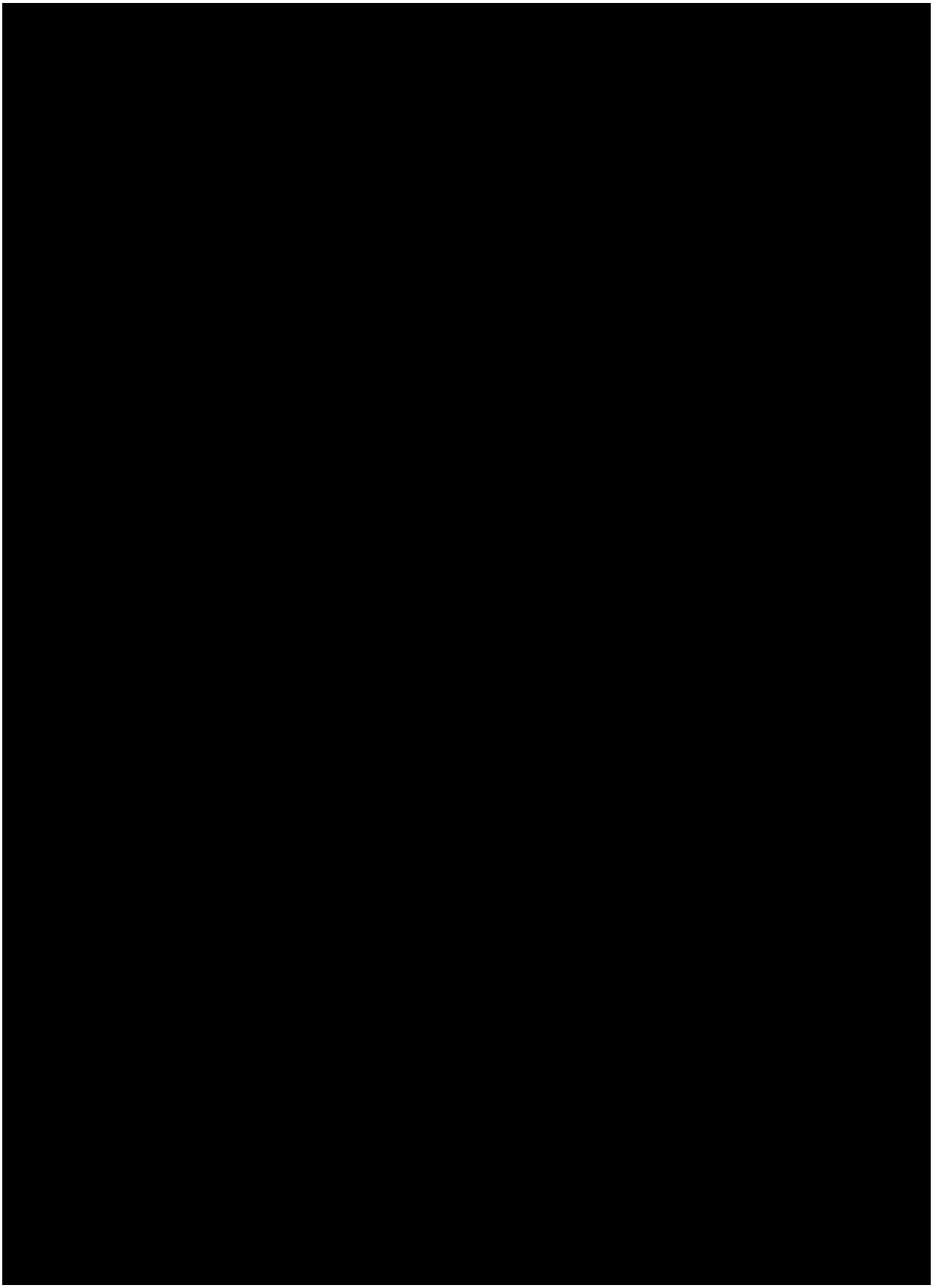
[redacted]

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.

[redacted]

[redacted]



9.6 Interim analyses

The primary analysis may be conducted when all patients complete the Week 52 visit. In the case this analysis is conducted, all patients will have final data pertaining to the Week 52 endpoints, thus no adjustment to the type I error will be made and the final analysis after the last visit (Week 68) will include the data collected from the post-treatment follow-up period.

9.7 Sample size calculation

A family-wise error will be set to two-sided α=0.05 to control for type I error. The primary objective of secukinumab 300 mg versus adalimumab with respect to ACR20 response at Week 52 will be tested at a two sided 0.05 alpha level.

An ACR20 response rate of about 50% for the TNFα inhibitor naïve without MTX use (monotherapy) population at week 48 was reported in Humira study (Gladman 2007). The response on secukinumab 300 mg is estimated to be 62% in the TNFα inhibitor naïve monotherapy population based on the lower bound of 80% confidence interval of Meta-analysis results of the study FUTURE-2 (McInnes 2015) and unpublished study FUTURE-3. With 425 subjects per treatment group there would be approximately 94% power to detect a treatment difference of 12% at a two-sided 0.05 alpha level in ACR20 response rates (Chi Square test, NQuery 7.0) between secukinumab 300 mg and adalimumab in the evaluation of the primary efficacy hypothesis at Week 52. The overall sample size will be 850 patient for a randomization ratio of 1:1 (secukinumab 300mg 425 patients, and adalimumab 425 patient). The estimated

power with the chosen sample size for other efficacy endpoints based on the data available for adalimumab and meta-analysis results of the study FUTURE-2 and study FUTURE-3 are summarized in Table 9-2. The assumptions for power calculation in Table 9-2 are presented in Table 9-1.

Table 9-1 Assumption for sample size and power calculation

Endpoint	Secukinumab 300mg expected values	Adalimumab (N=76) observed values
ACR20	62%	50%
PASI90	63%	38% (N=40)
ACR50	49%	38%
HAQ-DI change*	-0.59 (0.5)	-0.4 (0.5)(N=61)
Resolution of enthesitis	61%	33%

*mean (standard deviation)

Sources: The value for Secukinumab is from the lower bound of 80% confidence interval of a meta-analysis based on FUTURE-2 and unpublished results from FUTURE-3 data, the values for other endpoints for Secukinumab are from the means of the same meta-analysis, the values for Adalimumab are from Humira® study (Gladman 2007).

Based on Table 9-1, power calculation for superiority tests of different endpoints are presented below in Table 9-2.

Table 9-2 Power for superiority tests for primary and secondary endpoints (two-sided, α=0.05)

Endpoint	Power*
ACR20 (H1)	94%
PASI90 (H2)	99%
ACR50 (H3)	91%
HAQ-DI (H4)	99%
Resolution of enthesitis (H5)	99%

* power does not consider dependence of the endpoints in the Testing Strategy, power for PASI90 and enthesitis is based on the assumption that a subset of half of the population (213 subjects per group) has data of these two endpoints.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable

[redacted]

local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing IRB/IEC-approved informed consent (witnessed, where required by law or regulation), or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) 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 must indicate assent by personally signing and dating the informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

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

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study, and for a minimum 16 weeks or longer if local label requires it (e.g. 20 weeks for secukinumab, 5 months for adalimumab in EU) after the last dose. 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 PG ICF 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 PG assessments will in no way affect the patient'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 IRB and/or IEC approval will be obtained.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an

inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

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

11.1 Protocol amendments

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

[redacted]

12 References

References are available upon request.

Behrens F, Cañete JD, Olivieri I, et al (2015) Tumour necrosis factor inhibitor monotherapy vs combination with MTX in the treatment of PsA: a systematic review of the literature. Rheumatology (Oxford); 54:915-26.

[redacted]

Bonafede M, Johnson BH, Fox KM, et al (2013) Treatment patterns with etanercept and adalimumab for psoriatic diseases in a real-world setting. J Dermatol Treat; 24:369-73.

Cosentyx [package insert](2016). East Hanover NJ:Novartis.

Cosentyx SmPC (2016). London.EMA.

Cella DF, Tulsky DS, Gray G, et al (1993) The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. Journal of Clinical Oncology; 11(3):570-9.

European Medicine Agency (EMA) (2005) Guideline on clinical investigation of medicinal products for the treatment of psoriatic arthritis. London.

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

[redacted]

FitzGerald O, Helliwell P, Mease P, et al., (2012) Application of composite disease activity scores in psoriatic arthritis to the PRESTA data set. Ann Rheum Dis; 71:358-62.

FitzGerald O, Winchester R. (2014) Emerging evidence for critical involvement of the interleukin-17 pathway in both psoriasis and psoriatic arthritis. Arthritis Rheumatol; 66: 1077–80.

Fredriksson T, Pettersson U (1978) Severe psoriasis-oral therapy with a new retinoid. Dermatologica; 157:238-44.

Gladman D, Antoni C, Mease P, et al (2005) Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis; 64:ii14–17.

Gladman DD, Mease PJ, Ritchlin CT et al, (2007) Adalimumab for Long-Term Treatment of Psoriasis Arthritis. Arthritis Rheum; 56:476- 88

[redacted]

Gottlieb A, Griffiths CEM, Ho VC, et al (2005) Oral pimecrolimus in the treatment of moderate to severe chronic plaque-type psoriasis: a double-blind, multicentre, randomized dose-finding trial. Br J Dermatol; 152:1219-27.

[redacted]

Healy PJ, Helliwell PS (2008) Measuring clinical enthesitis in psoriatic arthritis: assessment of existing measures and development of an instrument specific to psoriatic arthritis. Arthritis Rheum; 59:686-91.

[redacted]

Helliwell PS, Fitzgerald O, Fransen J, et al (2013). The development of candidate composite disease activity and responder indices for psoriatic arthritis (GRACE project). Ann Rheum Dis; 72: 986-91.

Humira [package insert](2016). North Chicago IL:Abbvie.

Humira SmPC (2016). London.EMA.

Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al (2014) Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. Ann Rheum Dis; 73: 1020–6.

Koch GG, Tangen CM, Jung JW, et al (1998) Issues for covariance analysis of dichotomous and ordered categorical data from randomized clinical trials and non-parametric strategies for addressing them. Stat Med; 17: 1863-92.

Langley RG, Elewski BE, Lebwohl M, et al (2014) Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med; 371:326-38.

Lubeck DP (2004) Patient-reported outcomes and their role in the assessment of rheumatoid arthritis. Pharmacoeconomics; 22:27-38.

[redacted]

McInnes IB, Kavanaugh A, Gottlieb AB, et al (2013) Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet; 382: 780–9.

McInnes IB, Mease PJ, Kirkham B, et al (2015). Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet; 386: 1137–46

McInnes IB, Sieper J, Braun J, et al. (2014). Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. Ann Rheum Dis; 73:349-56.

Mease PJ, McInnes IB, Kirkham B, et al (2015) Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med; 373:1329-39.

Nikiphorou E, Negoescu A, Fitzpatrick JD, et al (2014) Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. Clin Rheumatol; 33:609-14.

[redacted]

Rosen CF, Mussani F, Chandran V, et al (2012) Patients with psoriatic arthritis have worse quality of life than those with psoriasis alone. Rheumatology (Oxford); 51:571–6.

Schoels M. (2014) Psoriatic arthritis indices. Clin Exp Rheumatol; 32:S-109-12.

Taylor W, Gladman D, Helliwell, et al (2006) Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum; 54:2665-73.

Thaçi D, Blauvelt A, Reich K, et al (2015) Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol;73:400-9.

Ware JE, Snow KK, Kosinki M, et al (1993) SF-36 Health Survey Manual and interpretation guide. Boston, MA: The Health Institute, New England Medical Center.

Ware JE, Kosinki M, Bjorner JB, et al (2008) SF-36v2® Health Survey: Administration guide for clinical trial investigators. Lincoln, RI: QualityMetric Incorporated.

Weisman S, Pollack CR, Gottschalk RW (2003) Psoriasis disease severity measures: comparing efficacy of treatments for severe psoriasis. J Dermatolog Treat; 14:158-65.

Yellen SB, Cella DF, Webster K, et al (1997) Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage; 13:63-74.

[redacted]

13 Appendix 1: The classification criteria for psoriatic arthritis (CASPAR)

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

Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis

Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.* (**2 points**)

A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. (**1 points**)

A family history of psoriasis is defined as a history of psoriasis in a first- or second- degree relative according to patient report. (**1 points**)

Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (**1 point**)

A negative test result for the presence of rheumatoid factor by any method except latex (**1 point**)

Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (**1 point**)

Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (**1 point**)

Total score:

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

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

[redacted]

14 Appendix 2: Guidelines for administering the questionnaires for patient reported outcomes

Before trial start

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

[redacted]

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

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

Questionnaire should be administered before the clinical examination

During completion

Administrator may clarify the questions but should not influence the response

Only one response for each question

Also see "Addressing Problems and Concerns"

After completion

Check for completeness and not for content*

Data should be sent from the eCRF / electronic device

Data should be reviewed by Investigator for AEs

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

Addressing Problems and Concerns

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

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

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

[redacted]

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

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

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

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

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

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

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

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

The patient asks the meaning of a question/item

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

A General Information about all questionnaire(s):

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

per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

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

[redacted]

15 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, 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 hips, 2 knees, 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©ACR20/50/[redacted]

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©) 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.

[redacted]

[redacted]

Reference: (Felson 1995)

[redacted]

[redacted]

[redacted]

[redacted]

17 Appendix 5: The Psoriasis Area and Severity Index (PASI)

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of disease is calculated as follows. In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20% and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and desquamation (scaling), which are each rated on a scale of 0 to 4. The scoring system for the signs of the disease (erythema, induration, and desquamation (scaling)) are:

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

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

0 = no involvement

1 = 1% to 9% involvement

2 = 10% to 29% involvement

3 = 30% to 49% involvement

4 = 50% to 69% involvement

5 = 70% to 89% involvement

6 = 90% to 100% involvement

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

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

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

Table 17-1 PASI Scoring Worksheet

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

[redacted]

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

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

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

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

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

f. Add these scores to get the PASI score.

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

‡ Area scoring criteria (score: % involvement).

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

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

[redacted]

18 Appendix 6: Liver event and laboratory trigger definitions and follow-up requirements

Table 18-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN
	1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any adverse event potentially indicative of a liver toxicity *

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

TBL: total bilirubin; ULN: upper limit of normal

Table 18-2 Follow up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	Complete liver eCRF	
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for *more than 2 weeks*, discontinue the study drug Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study drug immediately Hospitalize the patient	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

[redacted]

Criteria	Actions required	Follow-up monitoring
	Establish causality	
	Complete liver eCRF	
Any AE potentially indicative of a liver toxicity*	Consider study drug interruption or discontinuation	Investigator discretion
	Hospitalization if clinically appropriate	
	Establish causality	
	Complete liver eCRF	

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

TBL: total bilirubin; ULN: upper limit of normal

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

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

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

[redacted]

19 Appendix 7: Clinically notable laboratory values

- The following guidance will be used to define expanded limits and notable abnormalities of key laboratory outcomes.
- Clinically notable values will be forwarded to Novartis in the same time as sent to the investigators. Any intervention based on these laboratory values should be discussed with Novartis personnel.

Table 19-1 Clinically notable laboratory values

Laboratory variable	Notable criteria
Liver function and related variables	
SGOT (AST)	>3 x ULN
SGPT (ALT)	>3 x ULN
Bilirubin	>2 x ULN
Alkaline phosphatase	>2.5 x ULN
Renal function, metabolic and electrolyte variables	
Creatinine (serum)	>2 x ULN
Hematology variables	
Hemoglobin	20 g/L decrease from Baseline
Platelet count	<100 x 10^9/L
White blood cell count	<0.8 x LLN
Neutrophils	<0.9 x LLN

[redacted]