NOVARTIS

Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457F2305E1 / NCT01863732

An extension study to evaluate the sustainability of clinical benefits, safety and tolerability of secukinumab in patients with active Ankylosing Spondylitis

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Table of contents

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[redacted]

[redacted]

List of tables

List of figures

[redacted]

List of abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferase
AS	Ankylosing Spondylitis
ASAS	Assessment of SpondyloArthritis International Society criteria
[redacted]	[redacted]
AST	Aspartate Aminotransferase
BASDI	Bath Ankylosing Spondylitis Disease Activity
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMD	Bone Mineral Density
BME	Bone Marrow Edema
BSL	Baseline
CI	Confidence Interval
CPO	Country Pharma Organization
CRO	Contract Research Organization
[redacted]	[redacted]
DBL	Database Lock
DMARD	Disease Modifying Anti-Rheumatic Drug
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
hCG	Human Chorionic Gonadotropin
HLA	Human Leukocyte Antigen
[redacted]	[redacted]
ICF	Informed Consent Form

[redacted]

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/EC	Independent Ethics Committee
IFU	Instructions for Use
IL	Interleukin
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
i.v.	Intravenous(ly)
IVR	Interactive Voice Response
LLOQ	Lower Limit of Quantification
[redacted]	[redacted]
MRI	Magnetic Resonance Imaging
[redacted]	[redacted]
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
OPG	Osteoprotegerin
[redacted]	[redacted]
PFS	Prefilled Syringe
[redacted]	[redacted]
PoC	Proof of Concept
[redacted]	[redacted]
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
RANKL	Receptor Activator of Nuclear Factor Kappa-B Ligand
RDC	Remote Data Capture
SAE	Serious Adverse Event
s.c.	Subcutaneous(ly)
[redacted]	[redacted]
SpA	SpondyloArthritis
SUSAR	Suspected Unexpected Serious Adverse Reaction
TNF	Tumor Necrosis Factor
VAS	Visual Analog Scale

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
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
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch (period)	The planned stage of the subjects' participation in the study. Each epoch serves a purpose in the study as a whole. Typical epochs are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended.
Inadequate response to TNFα	Active disease despite stable treatment with anti-TNFα for at least 3 months at an approved dose or for at least one dose in the case of lack of tolerance.
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the subject came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the subject as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when subject permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature subject withdrawal
Subject Number	A number assigned to each subject who enrolls into the study
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reasons:

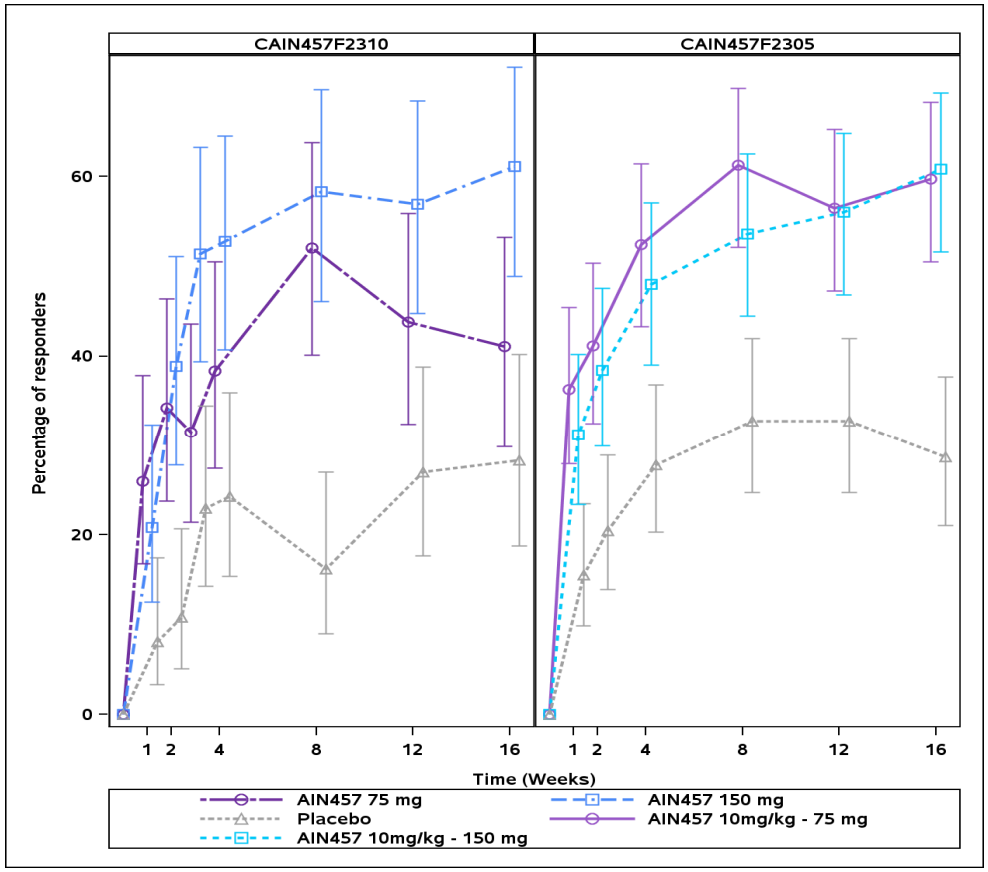
1. After approval and implementation of Amendment 1, all patients will receive study medication in an open-label fashion. The study medication for subjects on the 75 mg treatment arm will be re-evaluated for patients whose overall therapeutic response is not fully achieved with the current dose of 75 mg and may improve with a higher dose (150 mg s.c. every 4 weeks), as judged by the investigator at any time after implementation of Protocol Amendment 1.

   The 52-week efficacy data from the pivotal Phase 3 trial (CAIN457F2310) of secukinumab in active moderate to severe ankylosing spondylitis (AS) showed that secukinumab 150 mg s.c. provides robust, statistically significant, and clinically meaningful efficacy versus placebo in the treatment of AS when administered at Baseline (BSL), Weeks 1, 2, and 3, and every 4 weeks thereafter starting at Week 4, as reflected in an ASAS 20 response rate of approximately 60% at the Week 16 primary endpoint (Figure 0-1). A higher dose intravenous (i.v.) loading regimen of 10 mg/kg at BSL, Weeks 2 and 4 administered in CAIN457F2305 did not provide any additional efficacy benefit to the 150 mg s.c. maintenance regimen, with a similar Week 16 ASAS 20 response rate of approximately 60% in the 10 mg/kg - 150 mg arm.

   In contrast, the 75 mg s.c. dose was ineffective in that it failed to differentiate from placebo on the primary endpoint of ASAS 20 at Week 16 (Figure 0-1) and all secondary endpoints evaluated in a pre-defined hypothesis testing hierarchy in study CAIN457F2310, in which it was administered at BSL, Weeks 1, 2, and 3, and every 4 weeks thereafter starting at Week 4. The 75 mg s.c. loading and maintenance regimen demonstrated consistent and clinically meaningful dose separation from the 150 mg s.c. dose, with decreased treatment responses on the primary and nearly all secondary endpoints tested, including measures of disease signs and symptoms, physical function, and quality of life.

[redacted]

Figure 0-1 Time course of ASAS 20 response (estimate and 95% confidence interval (CI)) using non-responder imputation by study and treatment up to Week 16 for CAIN457F2310 and CAIN457F2305 (based on individual study results, FAS)



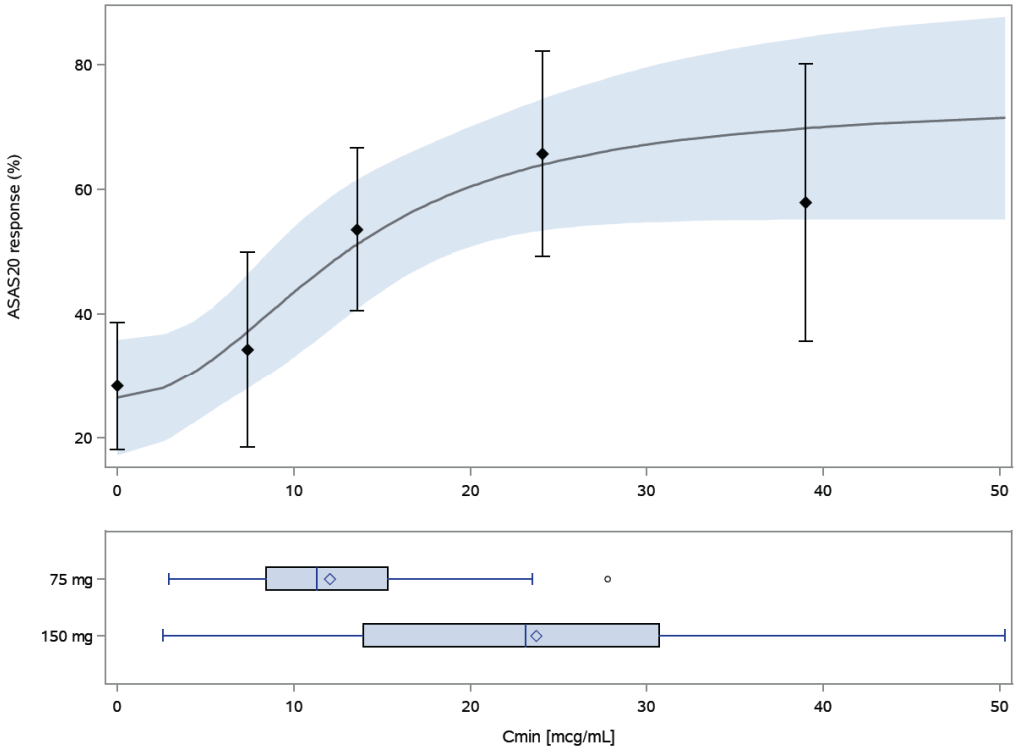
As the i.v. loading regimen (10 mg/kg x 3 doses every 2 weeks) in CAIN457F2305 resulted in similar drug exposure through Week 16 for both the 10 mg/kg-75 mg arm and the 10 mg/kg - 150 mg arm, the 10 mg/kg - 75 mg regimen was efficacious at Week 16 on the primary and all secondary endpoints. However, by Week 52, clinically meaningful dose-related differences in efficacy were apparent for higher hurdle clinical efficacy endpoints, including ASAS 40, ASAS partial remission, and BASDAI 50, which favored the 150 mg s.c. maintenance dose and demonstrated that the initial high exposure of the i.v. loading regimen cannot sustain optimal efficacy when followed by the 75 mg s.c. maintenance dose, as the 10 mg/kg - 75 mg regimen results in a lower treatment response over time on clinically relevant, higher hurdle efficacy endpoints.

In addition, pharmacokinetic analysis suggested that the 150 mg s.c. dose will provide greater benefit than the 75 mg s.c. dose because the 150 mg s.c. dose produces trough exposure levels at Week 16 of approximately 25 mcg/mL or higher, that are associated with approximately 60% probability of achieving an ASAS20 response, which was the maximal efficacy achieved with the doses tested in Phase 3 AS trials (Figure 0-2). In contrast, the lower dose of 75 mg s.c. was shown to lead to suboptimal exposure and decreased clinical benefit, as the mean exposure levels seen with the 75 mg s.c. dose are associated with an ASAS 20 response rate of approximately 40%. Thus, the 75 mg s.c.

[redacted]

dose would result in a 20% lower maximal ASAS 20 response rate compared to the 150 mg s.c. dose on an absolute basis, which is a relative decrease in efficacy of 33%.

Figure 0-2 ASAS 20 response rate *versus* Cmin concentration at Week 16 (Study CAIN457F2310)[1,2,3]



[1]The solid line and shaded area represent the mean and 95% CI from the logistic regression Emax model.

[2]Black diamonds and whiskers represent mean and 95% CI of the observed response rates in each exposure subgroups.

[3]Boxplots (with mean, median, first and third quartile, minimum and maximum values) of observed concentrations at Week 16 are represented in the bottom panel for each dose level.

The safety results of studies CAIN457F2305 and CAIN457F2310, based collectively on 590 AS patients, demonstrated a safety profile for both the 150 mg s.c. and 75 mg s.c. doses that was consistent with that observed in the larger psoriasis clinical program, consisting of over 3430 patients. In addition, there were no major dose-related safety differences between the 150 mg s.c. or 75 mg s.c. doses, whether preceded by a subcutaneous (CAIN457F2310) or intravenous (CAIN457F2305) loading regimen, that suggest an unacceptable benefit-risk profile for secukinumab 150 mg s.c.

[redacted]

Thus, given that the Phase 3 efficacy and safety results of the AS clinical program demonstrate that the proposed dose of secukinumab 150 mg s.c. provides the optimal benefit-risk assessment in AS, while the 75 mg s.c. dose is ineffective, the 75 mg s.c. dose arm will be re-evaluated in all on-going AS trials. The study medication for subjects on the 75 mg treatment arm should be escalated from 75 mg s.c. to 150 mg s.c. every 4 weeks for patients whose overall therapeutic response is not fully achieved with the current dose of 75 mg and may improve with a higher dose, as judged by the investigator. The escalation of the study medication may be determined at any site visit. For patients escalated to 150 mg, no dose reduction can be performed at a later time point.

2. Following the Week 52 DBL and interim analysis, based on the safety results of studies CAIN457F2305 and CAIN457F2310, the DMC review will no longer be required.
3. According to the CAIN457F2305E1 protocol exclusion criterion #6, women of child-bearing potential, currently defined as all women physiologically capable of becoming pregnant and unwilling to use effective contraception during the study and for 16 weeks after stopping treatment, should not be considered eligible for the study. However, there are approved secukinumab labels for the psoriasis indication that indicate a specific time window for the use of effective contraception after stopping treatment. There is currently no evidence to indicate that a specific duration of post-treatment contraception is required for patient safety. However, to align with these specifications in local prescribing information, protocol exclusion criterion #6 is changed to "Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., 20 weeks in EU)."
4. [redacted]
5. The Risks and Benefits section was updated to reflect the currently available information as released in the Investigator's Brochure.

None of the changes described in this amended protocol are due to evidence-based safety concerns.

At the time this amendment becomes effective, all the subjects would have been randomized in the study.

Changes to the protocol

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

The wording of various sub-sections to "Study objectives" (Section 2), "Study design" (Section 3.1), "Risks and benefits" (Section 3.6), "Rationale of dose/regimen, route of administration and duration of treatment" (Section 3.3), "Exclusion criteria" (Section 4.2), "Investigational treatment" (Section 5.1.1), "Treatment arms" (Section 5.2), "Treatment

[redacted]

blinding" (Section 5.4), "Permitted dose adjustments and interruptions of study treatment" (Section 5.5.5), "Efficacy" (Section 6.4), "Data Monitoring and Adjudication Committees" (Section 8.4) and "Data analysis" (Section 9) and have been amended to reflect the rationale given above.

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

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.

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

The changes described in this amended protocol require IRBs/IECs approval prior to implementation.

[redacted]

Protocol synopsis

Protocol number	CAIN457F2305E1
Title	An extension study to evaluate the sustainability of clinical benefits, safety and tolerability of secukinumab in patients with active Ankylosing Spondylitis
Brief title	Study of sustainability of clinical benefits, safety and tolerability of secukinumab in patients with active Ankylosing Spondylitis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug; Biologic
Study type	Interventional
Purpose and rationale	The purpose of this study is to obtain additional data on the sustainability of subject and clinical benefits, safety and tolerability during long-term treatment with secukinumab prefilled syringe (PFS) formulation.
Primary Objective(s) and Key Secondary Objective	To evaluate the sustainability of subject benefits as quantified by the ASAS20 (Assessment of SpondyloArthritis International Society criteria) in the whole study population during long-term treatment (Week 260) with secukinumab provided as prefilled syringes
Secondary Objectives	Objective 1: To evaluate the sustainability of subject benefits in subjects with active AS as quantified by the ASAS40 response during long-term treatment with secukinumab Objective 2: To evaluate the overall safety and tolerability of secukinumab in subjects with active AS over time up to Week 260
Study design	The multicenter extension study uses a double-blind, double-dummy, parallel-group design during the first year after which the site personnel and subject will be unblinded, making it an open-label study the remaining 2 years.
Population	The study population will consist of approximately 300 male and female subjects (≥18 years old at the time of consent) who completed the core study (CAIN457F2305) and who meet the inclusion/exclusion criteria.
Inclusion criteria	Subjects who completed the core study (CAIN457F2305) Subjects who are deemed by the investigator to benefit from continued secukinumab therapy
Exclusion criteria	History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes Deemed by the investigator to not benefit from the study drug based on lack or improvement or worsening of their symptoms Use of any investigational drug except for secukinumab during the core study
Investigational and reference therapy	Group 1: secukinumab 75 mg Group 2: secukinumab 150mg After approval and implementation of Protocol Amendment 1, the study medication for subjects on the 75 mg treatment arm should be escalated from 75 mg s.c. to 150 mg s.c. every 4 weeks for patients whose overall therapeutic response is not fully achieved with the current dose of 75 mg and may improve with a higher dose, as judged by the investigator. The

[redacted]

	escalation of the study medication may be determined at any site visit.
Efficacy assessments	Assessment of SpondyloArthritis International Society Criteria (ASAS) [redacted]
Safety assessments	Evaluation of all AEs and SAEs including injection site reactions and laboratory assessments ECG, physical examination, vital signs [redacted]
Other assessments	[redacted]
Data analysis	The primary efficacy variable is the clinical response to treatment according to the ASAS20 over time up to Week 260. The analysis of the primary variable will be based on the FAS subjects and will be descriptively summarized for each treatment over time.
Key words	ankylosing spondylitis, AS, chronic inflammatory disease, inflammatory back pain, secukinumab, prefilled syringe (PFS), subcutaneous injection, arthritides, AIN457, AIN457F

[redacted]

1 Introduction

1.1 Background

Ankylosing Spondylitis (AS) is a chronic inflammatory disease, which is mainly characterized by involvement of axial joints and bilateral sacroiliitis, but sometimes peripheral joints and extra-articular organs are involved as well. Associated extra-articular manifestations include acute anterior uveitis, cardiovascular and pulmonary abnormalities, neurologic sequelae, and both clinical and subclinical gastrointestinal findings. Decreased bone mineral density (BMD) is typical of extra-articular symptoms and many patients with AS have osteoporosis and consequent non-traumatic fractures in spite of their young age and gender (male). Generalized osteoporosis as well as regional osteopenia is common in AS with high incidence of osteoporosis or osteopenia, in spine (41–62%) and in femur (46–86%). The presence of the HLA-B27 antigen is strongly associated with AS: 90–95% of patients with AS who have European ancestry carry this marker.

It affects up to 1.1% of the population and is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden.

The first-line drug treatments of mild AS are non-steroidal anti-inflammatory drugs (NSAIDs). Treatment of NSAIDs-refractory AS is hampered by the lack of efficacy of virtually all standard disease modifying anti-rheumatic drugs (DMARDs) including methotrexate (MTX). As an exception, peripheral arthritis associated with AS responds quite well to sulfasalazine. Tumor necrosis factor (TNF) blocking agents were successfully added to the armamentarium to treat AS (Braun 2002) and subsequently demonstrated prolonged efficacy up to three years of follow-up (Braun 2005). However, upon discontinuation of TNF blockers the disease relapses quickly (Baraliakos 2005), indicating that the inflammatory process may only be suppressed but not completely abolished. Results reported in the ASSERT study, the largest study ever conducted on Magnetic resonance Imaging (MRI) evaluation of spinal lesions in AS, demonstrated a near complete resolution of inflammatory lesions at the 24 week time point (Braun 2006). However, in other reports AS inflammatory bone lesions depicted by MRI did not completely disappear under TNF antagonist therapy over a six-month study period. The bone lesions persisted despite full clinical remission was achieved (Zochling 2007). This observation suggests that the inflammatory process is still smoldering (Zochling 2007). Similarly, residual bone marrow edema (BME) as determined by MRI may represent persistent inflammatory processes in rheumatoid arthritis (RA) patients (Brown 2006) and psoriatic arthritis (PsA) patients (Anandarajah 2008) despite clinical remission. A substantial level of BME and marrow inflammation must be present to be detectable in MRI (Appel 2006), and the long-term structural consequences and thus the clinical significance of these subclinical chronic inflammatory processes in the bone have yet to be determined. Radiographic findings include syndesmophytes, with progression to total spinal fusion in some cases. Radiographs of the sacroiliac joint often show sclerosis, erosion, and, eventually, fusion.

A variety of new drug classes have been investigated during the last years for the treatment of patients with AS (Kiltz 2012). Abatacept, IL-1 and IL-6 blockade seem to have no effect in patients with active AS disease. Although, promising results have been reported for

[redacted]

thalidomide and apremilast, none of these new drugs have been shown to reach response rates compared to TNF-blockers.

Interleukin (IL)-17 antagonism by secukinumab represents a novel approach to interfere with the chronic inflammatory process by selectively targeting the predominant cytokine of the unique subset of helper T17 cells. Animal data suggest that IL-17 blockade reduces Receptor activator of nuclear factor kappa-B ligand (RANKL) dependent osteoclastogenesis upstream of TNF alpha (Koenders 2005). Emerging evidence suggests that IL-17 plays a role as an inflammatory mediator in patients with AS. Elevated levels of serum IL-17 and an increased number of circulating Th17 cells were detected in AS patients (Shen 2009). More IL-17 producing cells were detected in the facet joints of patients with AS compared with those with osteoarthritis (Appel 2008). Serum sRANKL levels and sRANKL/ Osteoprotegerin (OPG) ratios are up-regulated in patients with AS and have relationship with BMD and radiological changes (Kim 2006). In a double-blind, placebo-controlled, multicenter, proof-of-concept study that investigated 30 patients with active AS, secukinumab demonstrated high efficacy, achieving ASAS20 (Assessment of SpondyloArthritis International Society Criteria) response rate at week 6 in approximately 60% of the patients. Moreover, IL-17A blockade with secukinumab reduced spinal inflammation in patients with AS as early as week 6, as detected by MRI (Baraliakos 2011). Sagittal magnetic resonance images of the spine including T1-sequences and short-t inversion recovery-sequences performed showed a reduction of inflammation after 6 weeks, maintained up to Week 28. Early improvements were especially noted in patients with higher baseline MRI scores. This favorable response prompted the initiation of another ongoing, placebo-controlled, randomized trial to confirm the efficacy of secukinumab for the treatment of patients with active AS.

As mentioned above and in the Baraliakos 2005 publication, disease relapse occurs once a TNF blocker has been discontinued; therefore, patients will likely remain on treatment indefinitely. Continuation of the pivotal core study is needed to demonstrate the sustainability of clinical benefits, and the long-term safety and tolerability required for managing the chronic nature of AS.

1.2 Purpose

The proposed extension study CAIN457F2305E1 is designed as a 3-year extension to the phase III study CAIN457F2305. It aims to provide continuous treatment with secukinumab in prefilled syringes (PFS) for subjects who completed the phase III study CAIN457F2305, defined as the “core study”, to obtain additional data on the sustainability of subject and clinical benefits, safety and tolerability during long-term treatment.

2 Study objectives

2.1 Primary objective

To evaluate the sustainability of subject benefits as quantified by the ASAS20 (Assessment of SpondyloArthritis International Society criteria) in the whole study population during long-term (Week 260) treatment with secukinumab 75 and 150 mg provided as prefilled syringes

[redacted]

2.2 Secondary objectives

1. To evaluate the sustainability of subject benefits in subjects with active AS as quantified by the ASAS40 response during long-term treatment with secukinumab 75 or 150 mg
2. To evaluate the overall safety and tolerability of secukinumab in subjects with active AS over time up to Week 260

[redacted]

3 Investigational plan

3.1 Study design

Core Study (AIN457F2305) Study Design Summary

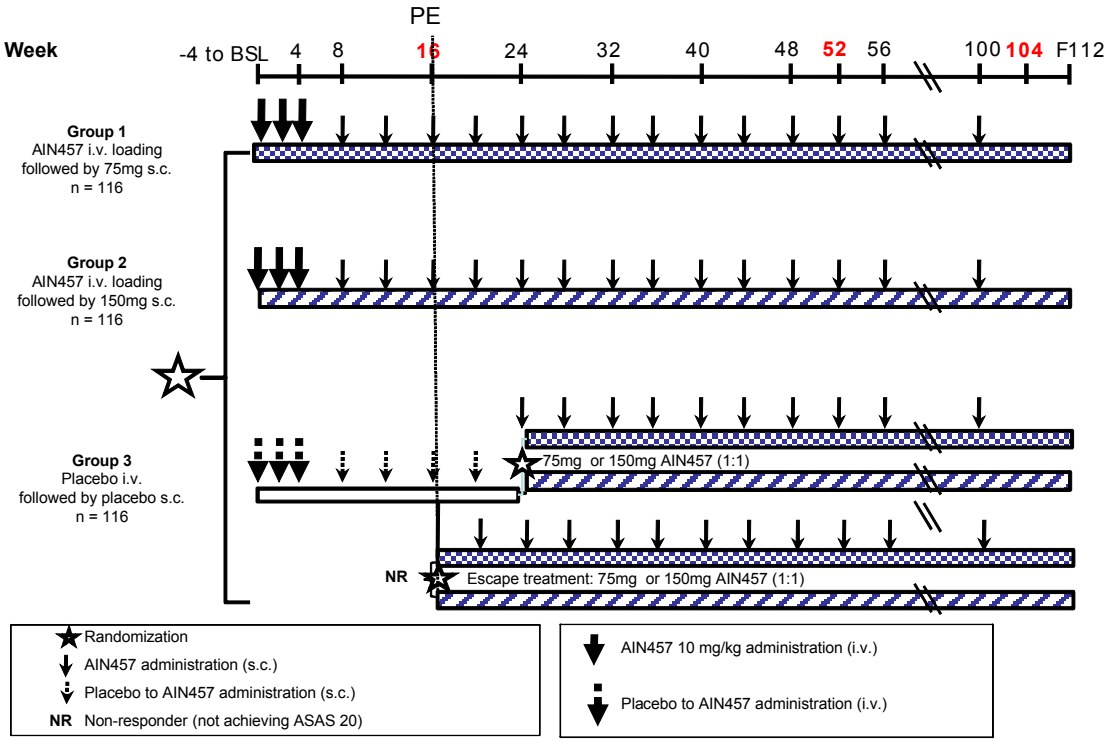
The AIN457F2305 core study used a double-blind, randomized, parallel-group, placebo-controlled design. A screening period running 4 weeks before randomization was used to assess eligibility followed by a treatment period of 2 years (Week 0 through Week 104).

[redacted]

At Week 16 (Visit 8), efficacy of secukinumab treatment was assessed based on the ASAS 20 improvement criteria and subjects were classified as responders or non-responders.

The subjects were stratified according to being TNFα inhibitor incomplete responders (TNF-IR) or TNFα inhibitor naïve subjects. Approximately 30% of subjects were TNF-IR to ensure a representative population for the assessment of efficacy and safety.

Figure 3-1 Core Study (AIN457F2305) Study Design



Extension Study (AIN457F2305E1) Study Design

The multicenter extension study uses a double-blind, double-dummy, parallel-group design from Week 104E1 to Week 156 upon which the site personnel and subject will be unblinded, making it an open-label study through Week F268 (follow-up visit). All week numbers used in the extension study are relative to the randomization visit of the core study. This study will offer continuation of treatment for subjects completing the core study and who are deemed by the investigator to benefit from continued secukinumab therapy. The total combined duration of treatment for the core study and this extension study is five years.

At Week 104 of the core study, subjects eligible for the extension will complete the assessments associated with the core study visit per the core study protocol and will subsequently continue into the extension study on the same dose. A new Informed Consent must be signed before proceeding into the extension study.

- Group 1: secukinumab 75 mg plus placebo 150 mg dosed every four weeks from Week 104E1 through Week 152. Starting on Week 156 (after unblinding), only secukinumab 75 mg will be dosed.

- Group 2: secukinumab 150 mg plus placebo 75 mg dosed every four weeks from Week 104E1 through Week 152. Starting on Week 156 (after unblinding), only secukinumab 150 mg will be dosed.

The treatment will be offered in prefilled syringes (PFS) in the extension study. This is a change from the core study, which used s.c. injections prepared from lyophilisate. Subjects will be instructed in detail how to self-administer the s.c. injection using the PFS formulation. Each injection will be administered into an appropriate injection site of the body (thighs, arms, or abdomen). For the first 3 months of the study (through Week 116), all injections will be performed at the study site. Starting on Week 120, the subject is allowed to self-administer the study medication at home or continue to present at monthly intervals to the study site for injection administrations, based on the subject's preference and the investigator's judgment. Site staff will administer the injection to subjects who are not able or unwilling to self-administer the PFS injection.

At Week 156 or after approval and implementation of Protocol Amendment 1, whichever occurs first, site personnel and the subject will be unblinded as to their current treatment regimen. The subject will continue to receive the same dose of secukinumab and will no longer receive the placebo PFS. After approval and implementation of Protocol Amendment 1, the study medication for subjects on the 75 mg treatment arm should be escalated from 75 mg s.c. to 150 mg s.c. every 4 weeks for patients whose overall therapeutic response is not fully achieved with the current dose of 75 mg and may improve with a higher dose, as judged by the investigator. The escalation of the study medication may be determined at any site visit..

For patients escalated to secukinumab 150 mg s.c. every 4 weeks, no dose reduction can be performed and if the patient is unable to tolerate the 150 mg dose of secukinumab alternative treatment options should be considered only after discontinuation from the study (Section 5.5.9).

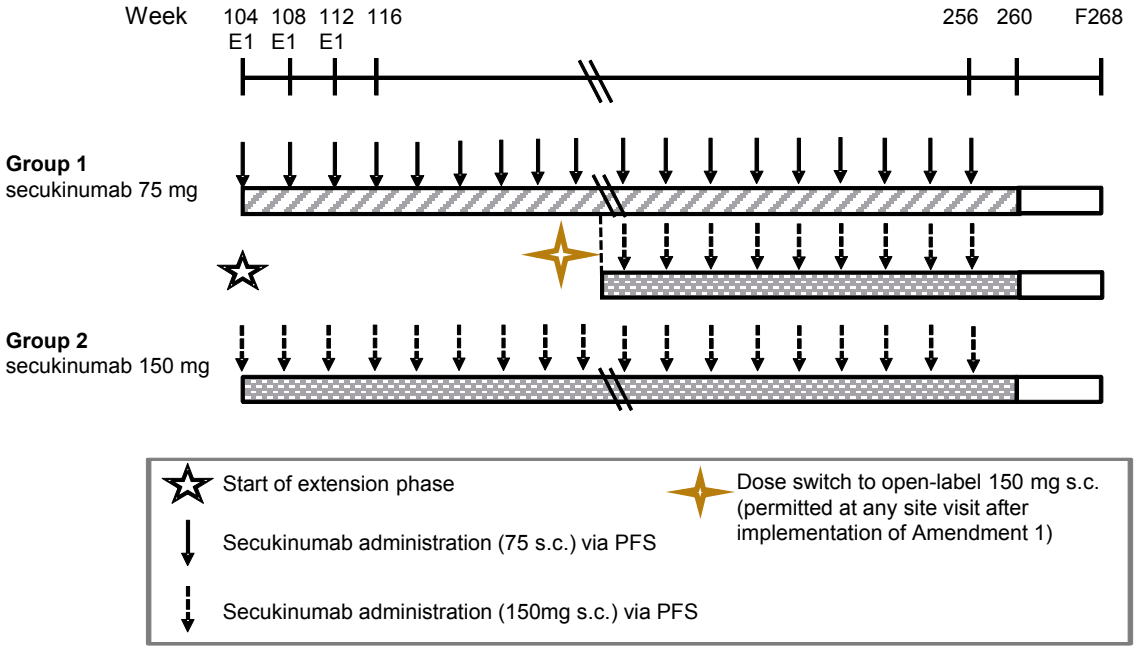
Assessments for safety, efficacy, [redacted] will be performed according to the assessment schedule (Table 6-1, Table 6-2, Table 6-3).

A follow-up visit is to be done 12 weeks after the last study treatment administration for all subjects (regardless of whether they complete the entire study as planned or discontinue prematurely).

This long-term extension study extends the pivotal 2-year registration study CAIN457F2305 by an additional 3 years and therefore may be affected by agency review or potential product approval considerations. Thus, the extension trial may be amended (via a future protocol amendment) based on clinical data analysis, Data Monitoring Committee recommendations, and/or on eventual agency recommendations for product usage in this indication.

[redacted]

Figure 3-2 Extension Study (AIN457F2305E1) Study Design



3.2 Rationale of study design

This 3-year extension study will offer continuous secukinumab therapy to eligible subjects from the core study and will provide further long-term subject and clinical benefits, safety and tolerability data for two dosing regimens of secukinumab (75 and 150 mg s.c.). The study design is in line with other long-term studies in Ankylosing Spondylitis. The first year is blinded to protect the integrity of the data in the ongoing core study.

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

The dosing regimen selected in this extension study is the same regimen used during the core study treatment period. The overall duration (2 year core and 3 year extension) of 5 years is based on the need for long-term treatment exposure in subjects suffering from a chronic illness such as Ankylosing Spondylitis in order to adequately evaluate the efficacy and safety profile of a new agent. The analysis of the 2 Phase III studies conducted in AS patients (see Rationale for Protocol Amendment 1) led to the conclusion that to increase the likelihood of maintaining a clinically meaningful response during the entire duration of the trial, the dose of secukinumab should be escalated from 75 mg s.c. every 4 weeks to 150 mg s.c. every 4 weeks for patients whose overall therapeutic response is not fully achieved and may improve with a higher dose, as judged by the investigator.

Bioequivalence between the secukinumab lyophilisate and prefilled syringe formulation has been established in study CAIN457A2106 in 150 healthy volunteers in which the pharmacokinetics, safety and tolerability of a prefilled syringe and the lyophilisate formulation were compared. The confidence intervals for geometric mean ratios of Cmax,

AUClast and AUCinf for the two formulations were within the 0.8-1.25 boundaries and therefore, the prefilled syringe met the standard criteria for assuming bioequivalence. The use of the prefilled syringe was safe and well tolerated. Therefore, in study CAIN457F2305E1 it is considered appropriate to use secukinumab in prefilled syringes for the administration of secukinumab in the same dosing regimens as in the maintenance doses of the core study (CAIN457F2305) which used a lyophilisate formulation.

Subcutaneous injection through prefilled syringes (PFS) offers the option of self-administration by the subject and is likely to provide a better treatment experience and added convenience. Subjects with chronic diseases who are able to self-inject their medication gain control of their treatment schedule and their treatment setting, thus allowing greater independence, better adherence, improved therapeutic outcomes and freedom in their social, domestic and professional lives resulting in economic benefits to both the subject and the healthcare system (Kivitz 2006; Chilton 2008). Self-injection may also offer psychological benefits over administration by healthcare professionals, including improved self-esteem (Hamm 2000).

3.4 Rationale for choice of comparator

There is no placebo or active control group in this study given the purpose and main objectives are to extend treatment of subjects who completed the core study. The use of two different doses of secukinumab (i.e. 75 and 150 mg) will allow comparison between the doses in terms of sustainability of clinical benefits, safety and tolerability.

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses on an approximately annual basis may be planned for purposes of publication as subjects continue treatment in this extension study. Additional analyses may be performed to support health authority interactions as necessary. Study design adaptations are not currently planned unless mandated by agency requests, Data Monitoring Committee recommendations or potential product approval considerations.

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria, close clinical monitoring, and extensive guidance for the investigators provided in the Investigator's Brochure.

As of 12 Jul 2014, up to 10900 subjects have been enrolled into the secukinumab clinical program, of which over 8600 subjects have received secukinumab. Both Healthy subjects and patients have received secukinumab across various indications (plaque psoriasis, RA, AS, PsA, multiple sclerosis, uveitis, Crohn's disease, dry eye, polymyalgia rheumatica) as single and /or multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. Key results from the larger completed Phase II and III studies support a favorable benefit-risk profile for secukinumab in AS patients.

The risk profile of secukinumab in AS is informed by the safety experience from arthritides and psoriasis trials. In the dose-ranging RA trial CAIN457F2201 of 237 patients, the most common side effects were infections in about 20-30% of the patients, with most being mild to moderate. Gastrointestinal disorders were experienced by 8-12% of patients, skin rashes by 7-

10%, joint muscle aches by 5-8%, and headaches by 1-3% of patients. However, these side effects were also seen in patients who received placebo.

Secukinumab has been studied most extensively in psoriasis, and side effects seen in psoriasis patients treated with secukinumab include upper respiratory tract infections (nasopharyngitis, rhinitis) (very common: in more than 1 in 10 patients); oral herpes, rhinorrhea, diarrhea and urticaria (common: in more than 1 in 100 but fewer than 1 in 10 patients); oral candidiasis, tinea pedis, neutropenia, and conjunctivitis (uncommon: in more than 1 in 1,000 but fewer than 1 in 100 patients). Hypersensitivity reactions to secukinumab, including urticaria and rare events of anaphylactic reaction, were also observed in clinical studies. Additionally, worsening of Crohn's disease, in some cases serious, was seen in studies of Crohn's disease and psoriasis, in patients receiving secukinumab or placebo.

Taking into account the available safety data for the individual risks outlined in the Investigator's Brochure, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar or improved in comparison with approved cytokine targeting therapies. In some trials, infections were numerically higher in the secukinumab treatment groups than in the placebo cohorts although no dose-dependent increase in rates of serious infections was observed. This indicates that there does not appear to be a direct exposure-related effect on host defense. From the standpoint of the overall risk-benefit assessment, the current study with secukinumab is justified.

4 Population

It is estimated that approximately 279 to 316 (75-85%) subjects will enter this extension study from the core study.

4.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed
2. Subjects must have completed the core study
3. Subjects who are deemed by the investigator to benefit from continued secukinumab therapy

4.2 Exclusion criteria

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

1. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
2. Any subject who is deemed not to be benefiting from the study drug based upon lack of improvement or worsening of their symptoms
3. Use of any investigational drug except for secukinumab during the core study
4. Any subject taking other concomitant biologic immunomodulating agent(s) except secukinumab during the core study

[redacted]

5. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
6. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during the entire study or longer if required by locally approved prescribing information (e.g., 20 weeks 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) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - 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) with spermicidal foam/gel/film/cream/ vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without 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.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will provide the following:

- Investigational Treatment:
    - Secukinumab 75 mg/150 mg provided in 0.5 mL/1.0 mL PFS for s.c. injection
    - Secukinumab placebo provided in 0.5 mL/1.0 mL PFS for s.c. injection required for blinding

At extension study entry, subjects will be provided with detailed instructions and guidance on how to self-administer the s.c. injection using the PFS and following the Instructions for Use

[redacted]

(IFU). The investigational drug will be administered by the subject into the appropriate injection site of the body. Site staff will administer the injection to subjects who are not able or unwilling to self-administer the PFS injection.

Note: The prefilled syringes do not need to be prepared at the site. The prefilled syringes are packed in double-blinded fashion for the double-blinded portion of the study and open-label fashion for the open-label portion. PFS are labeled as:

- Blinded
  - AIN457 75mg/0.5ml/Placebo
  - AIN457 150mg/1ml/Placebo
- Open-label
  - AIN457 75mg/0.5ml
  - AIN457 150mg/1ml

5.1.2 Additional study treatment

No additional treatment other than the investigational treatment is requested in this trial.

5.2 Treatment arms

All subjects will continue to receive the same dose of secukinumab they were receiving during the treatment period of the phase III core study. The two treatment groups are:

- Group 1: secukinumab 75 mg plus placebo 150 mg dosed every four weeks from Week 104E1 through Week 152. Starting on Week 156 (after unblinding), only secukinumab 75 mg will be dosed.
- Group 2: secukinumab 150 mg plus placebo 75 mg dose every four weeks from Week 104E1 through Week 152. Starting on Week 156 (after unblinding), only secukinumab 150 mg will be dosed.

After approval and implementation of the Protocol Amendment 1, the study medication for subjects on the 75 mg treatment arm should be escalated from 75 mg s.c. to 150 mg s.c. every 4 weeks for patients whose overall therapeutic response is not fully achieved with the current dose of 75 mg and may improve with a higher dose, as judged by the investigator.

5.3 Treatment assignment, randomization

At Week 104 of the core study, all eligible and consenting subjects from the core study will be enrolled via Interactive Response Technology (IRT) and will continue to receive the same dose of secukinumab that they were receiving during the treatment period of the core study. The investigator or his/her delegate will contact IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. IRT will then specify a unique medication number for the first package of investigational treatment to be dispensed to the subject.

5.4 Treatment blinding

This is a 3-year extension of a 2-year double-blind, double-dummy, randomized treatment trial. Subjects, investigator staff and persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization in the core study until Week

156, or until approval and implementation of Protocol Amendment 1, whichever occurs first, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the following exception: bioanalyst, (2) The identity of the treatments will be concealed by the use of study treatments in form of prefilled syringes for s.c. injections, filled with secukinumab or placebo that are identical in appearance.

A double-dummy design is used because the identity of the study treatments (PFS) cannot be disguised due to their different volume forms (0.5 mL versus 1.0 mL)

The bioanalyst will have access to the randomization list to facilitate analysis of [redacted] samples to ensure appropriate sample dilution factors are applied, avoiding unnecessary repeat analyses.

Unblinding before Week 156 will only occur in the case of subject emergencies (see Section 5.5.10). Subjects will be unblinded at Week 156, or after approval and implementation of Protocol Amendment 1, whichever occurs first, and will continue receiving the same secukinumab treatment open-label.

5.5 Treating the subject

5.5.1 Subject numbering

During the core study, each subject was uniquely identified by a Subject Number which was 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 by another subject. This being an extension study, the subject numbers will remain the same as that of the core study; new subject numbers will not be assigned.

5.5.2 Dispensing the investigational treatment

The investigational treatment packaging has a label with a unique medication number which corresponds to one of the 2 treatment arms and a specific visit. Investigator staff will identify the investigational treatment package(s) to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

After Week 116, if subjects opt for domiciliary treatment/home administrations (at protocol specified time points) then the investigator will dispense via IRT an appropriate number of investigational treatment packages for domiciliary administrations. The investigator will detach the outer part of the label and affix it to the source document (Drug Label Form). Detailed instructions on the self-administration of the study treatment will be described in the Instructions For Use (IFU) provided to each subject and made available to the site staff and investigator. These instructions should be reviewed in detail by the subject and the site personnel.

[redacted]

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

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

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

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

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

5.5.4 Instructions for prescribing and taking study treatment

All study treatment (75 mg/150 mg secukinumab, and 0.5 mL/1.0 mL placebo) will be self-administered subcutaneously by the subjects every four weeks throughout the study. The PFS will be provided by the site staff to the subject, who will self-administer the injections at the specified study time point. Site staff will administer the injection to those subjects who are not able to self-administer the PFS injection. Detailed instructions on the self-administration of the study treatment will be described in the Instructions For Use (IFU) and provided to each subject. It shall be recorded on the corresponding eCRF(s) whether the subject self-administered the PFS or whether site staff or caregiver administered the PFS and whether it was administered at home or at the site.

The first study treatment administration will occur at Week 104E1 after the inclusion/exclusion criteria have been confirmed, all study scheduled assessments have been performed and the scheduled blood samples have been drawn. Through Week 116, all doses of study treatment will be self-administered by the subject at the study site under the supervision of a site staff member after the study assessments for the visit have been completed. After Week 116, the subjects will be allowed to self-administer the PFS at home (see Domiciliary Administration below).

The trial-related safety and efficacy procedures will be conducted as indicated in Table 6-1, Table 6-2, and Table 6-3. While at the site visits, subjects will be asked to refer to the IFU and to proceed with self-injection. At study visits requiring pre-dose blood samples (Table 6-1, Table 6-2, Table 6-3), the subject will self-administer study treatment only after the blood samples have been collected.

[redacted]

[redacted]

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record CRF. Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

The investigator should promote compliance by instructing the subject to take the study treatment exactly as prescribed 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 take the study treatment as prescribed.

Administration

Single syringes will be packed in individual boxes. The site and patient should refer to the IFU for storage and handling instructions.

The study treatment solution should be injected subcutaneously into the arm, abdomen or thigh area. Each new injection should be given at least one inch from the previously used site. If the subject chooses the abdomen, 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 subject has scars or stretch marks. Injection sites should be alternated to reduce the risk of reaction.

Used safety syringes should be disposed immediately after use in a sharps container or according to the regulatory needs of the respective countries.

Domiciliary administration

After Week 116, subjects will be allowed to self-administer the PFS at home when they are not visiting the site for any other trial-related procedures. Subjects will be allowed to self-administer treatment at home (after Week 116) only if they have exhibited correct use for self-administering the PFS at the site during the first 4 visits for treatment during the extension study. At such time points, if requested by the subject, a caregiver would also be allowed to administer the study medication. Optional site visits have been included in the assessment tables between the visits at which trial-related procedures are not to be conducted at the site. Subjects will be allowed to self-administer the PFS at home or to visit the site during the optional visits to self-administer the PFS under the supervision of the site staff. If the subject is not able or not confident to self-administer the PFS, he/she should visit the site every 4 weeks during the treatment period and the site staff will administer the PFS.

Prior to self-administration at home, subjects should contact the investigator/site staff in the case they are experiencing any AE/SAEs or have any concerns.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted until approval and implementation of Protocol Amendment 1. After approval and implementation of the Protocol Amendment 1, the

[redacted]

study medication for subjects on the 75 mg treatment arm should be escalated from 75 mg s.c. to 150 mg s.c. every 4 weeks for patients whose overall therapeutic response is not fully achieved with the current dose of 75 mg and may improve with a higher dose, as judged by the investigator. The escalation of the study medication may be determined at any site visit. For patients escalated to 150 mg, no dose reduction can be performed at a later time point.

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

The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 12 weeks.

These changes must be recorded on the Dosage Administration Record CRF.

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. Serious consideration should be given to withdraw subjects who require significant amounts of rescue medication (see Section 5.5.8 for prohibited treatments).

Any use of rescue medication must be recorded in the Prior/Concomitant medications eCRF page.

5.5.7 Concomitant treatment

The investigator should instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded (see Section 5.5.8 for prohibited treatments).

Guidelines for the use of specific medications are provided below:

Methotrexate (MTX)

Subjects taking MTX (7.5 – 25 mg/week) should be maintained on a stable dose throughout the study unless a change is deemed necessary by the investigator. Any change in dose should be recorded on the appropriate eCRF page.

Folic acid

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

[redacted]

Sulfasalazine

Subjects taking Sulfasalazine (≤ 3 g/day) should be maintained on a stable dose throughout the study unless a change is deemed necessary by the investigator. Any change in dose should be recorded on the appropriate eCRF page.

Systemic corticosteroids

The dose and regimen of systemic corticosteroids (oral or intramuscular) may be modified as deemed appropriate and necessary and as per investigator's judgment and subject need. Any change in the dose of systemic corticosteroids during the trial must be recorded on the corresponding eCRF page.

Intra-articular corticosteroids

As per investigator's judgment and subject need, intra-articular corticosteroid injections can be performed. The total dose administered must be recorded on the corresponding eCRF page.

Non-steroidal anti-inflammatory drugs (NSAIDS)(COX-1 or COX-2 inhibitors) and acetaminophen/paracetamol

Changes to the NSAIDS intake regimen is permitted throughout the study.

Subjects taking NSAIDs, low strength opioids or paracetamol/acetaminophen PRN can continue to do so in the study; however, they have to refrain from any intake during at least the 24 hours before a visit with disease activity assessment.

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

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 is NOT allowed during this extension study unless otherwise stated.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Any other biologic agent (e.g. etanercept, infliximab, adalimumab, tocilizumab, rituximab, abatacept)*	Discontinue study treatment
Any other investigational treatment or participation in another interventional trial	Consult with Novartis study team
Live vaccines should not be given until 12 weeks after last study treatment administration	Interrupt study treatment

*These agents fall under the category of biologic immunomodulators

5.5.9 Discontinuation of study treatment and premature subject withdrawal

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

[redacted]

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information. Study treatment must be discontinued. Even if the subject is not willing to come back for all assessments, every effort should be done to collect the scheduled x-ray assessments for this subject.

For subjects who discontinue study treatment a Dosage Administration Record eCRF should be completed, giving the date and primary reason for stopping study treatment. For subjects remaining in the trial, all Week 260 assessments must be performed 4 weeks after last study treatment administration and a follow-up visit (F268) should be conducted 12 weeks after last study treatment administration (Table 6-1, Table 6-2, Table 6-3). Any unused study drug must be returned to the site.

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

5.5.9.1 Discontinuation of study treatment

The investigator should discontinue study treatment for a given subject and/or withdraw the subject from study if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent
- Emergence of the following adverse events:
  - Any severe or serious adverse event that is not compatible with administration of study medication, including adverse events that require treatment with an unacceptable co-medication
  - 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.
  - Life-threatening infection
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (a general guidance on clinically notable laboratory values is provided in Appendix 1).
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any other protocol deviation that results in a significant risk to the subject's safety

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

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

For subjects who discontinue study treatment, a Dosage Administration Record eCRF should be completed giving the date and primary reason for stopping study treatment.

[redacted]

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

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

5.5.9.2 Withdrawal of consent

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 continue participating in the study; that is, the subject does not want any further visits, assessments, or study-related contacts, 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. No further attempts to contact the subject are allowed.

5.5.9.3 Lost to follow-up

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

5.5.9.4 Replacement

Subjects who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled subjects.

5.5.10 Emergency breaking of treatment assignment

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study drug 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 (GTL) that the code has been broken.

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

[redacted]

emergency code breaks) to the subject in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

In the case of emergency unblinding, the investigator should consult with the local Novartis CPO whether study medication should be discontinued.

In the case of accidental unblinding, subjects will not be replaced by an equal number of newly enrolled subjects.

5.5.11 Study completion and post-study treatment

A subject will be considered to have completed the study if he/she received treatment for 260 weeks in the combined core study and extension study (last dose being administered at Week 256) and upon completion of the scheduled study assessments and procedures up to and including Visit F268.

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

A Study Phase Completion evaluation (associated with the last visit of the subject's phase of the study: e.g. Week 156, Week 208 or Week 260) must also be performed when a subject prematurely withdraws from the study for whatever reason. In any case, the investigator or site staff must contact IRT as soon as possible to record the subject's study completion (Visit F268) or discontinuation.

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

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated for a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1, Table 6-2, and Table 6-3 list all of the assessments and indicate with an "X" when the visits are performed. Subjects should be seen for all visits on the designated day or as close to it as possible. There should be at least 2 weeks between each study treatment administration.

Subjects who discontinue study treatment should also return 12 weeks after the last study drug administration for the assessments indicated by an asterisk (*) in Table 6-1, Table 6-2, and Table 6-3. If they 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 or by sending

[redacted]

appropriate correspondence (i.e. certified letter) immediately. At this contact, the safety (e.g. potential occurrence of AE or SAE) and the primary reason for a subject's premature withdrawal should be determined. Documentation of attempts to contact the subject should be recorded in the source documentation.

Order of assessments

- [redacted]
- All remaining study visit procedures (e.g. laboratory sample collection, vital signs, measurements etc.) must be completed prior to study treatment dosing
- Contact IRT to register the subject visit
- PFS medication boxes are made available to the subject who will then self-inject the study treatment under guidance and supervision, as necessary, of a site staff member

[redacted]

Table 6-1 Assessment schedule - Part 1: Week 104E1 to Week 156

Epoch	Treatment period 3													
Week (relative to baseline of phase III study)	104E1[1]	108E1	112E1	116	120	124	128	132	136	140	144	148	152	156[9*]
Optional Site Visit[2]					X	X		X	X		X	X	X	
Obtain Informed consent	X													
Inclusion/Exclusion criteria	X													
Physical exam[3]				X			X			X				X
Weight							X							X
Vital signs				X			X			X				X
Hematology, blood chemistry, urinalysis				X			X			X				X
Urine pregnancy test				X			X			X				X
ECG							X							X
Administration of study treatment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Conc. Medication/non-drug therapy	Update as necessary													
Adverse events/SAE[5]	Update as necessary													
Patient's global assessment of disease activity (VAS)				X			X			X				X
Patient's assessment of Spinal pain (VAS)				X			X			X				X
[redacted]														

[redacted]

Epoch	Treatment period 3													
Week (relative to baseline of phase III study)	104E1[1]	108E1	112E1	116	120	124	128	132	136	140	144	148	152	156[9*]
[redacted]														
Lipids[8]							X							X
Cardiovascular panel														X
Treatment period 3 completion form														X

[1] This visit corresponds to the Week 104 visit of the core study. Only those assessments which are unique to the extension study are mentioned here and the assessment carried out as part of Week 104 of the core study are not mentioned; however, those assessments need to be carried out as per core study protocol.

[2] Optional visits – Week 120, 124, 132, 136, 144, 148, 152. At these optional visits only those subjects who are unable to self-administer the PFS injections at home will visit the site and site staff will supervise self-administration or administer the PFS injection for them. Other subjects who can self-administer the PFS injection can do so at home at these optional visits.

[3] These assessments are source documentation only and will not be entered into the eCRF

[4] The study treatment (PFS) has to be administered every 4 weeks. From Week 104E1 to 116, subjects will visit the site every 4 weeks for administering the PFS injection (by self or by site staff). After Week 116, at visits marked as optional visits, subjects can self-administer the study PFS at home or may visit the site to receive the PFS administration by site staff.

[5] AEs/SAEs occurring after the subject has signed the informed consent must be captured on the appropriate eCRF page.

[redacted]

[redacted]

[8] Sample must be obtained fasting.

[9] Site staff and subjects will be unblinded. Subjects will no longer receive placebo PFS after unblinding.

[redacted]

Epoch	Treatment period 3													
Week (relative to baseline of phase III study)	104E1[1]	108E1	112E1	116	120	124	128	132	136	140	144	148	152	156[9*]

* For all subjects who discontinue or withdraw from the study, the investigator should ensure that the subject completes an end of treatment visit (corresponding to the last visit for the subject's current period of treatment) 4 weeks after last study treatment and also return after an additional 8 weeks for a final follow-up, F268 (12 weeks after last study treatment). The final visit should be performed before any new treatment is initiated.

Table 6-2 Assessment schedule - Part 2: Week 160 to Week 208

Epoch	Treatment period 4												
Week	160	164	168	172	176	180	184	188	192	196	200	204	208*
Optional Site Visit[1]	X	X		X	X		X	X		X	X	X	
Physical exam[2]			X			X			X				X
Weight						X							X
Vital signs			X			X			X				X
Hematology, blood chemistry, urinalysis			X			X			X				X
Urine pregnancy test			X			X			X				X
ECG						X							X
Administration of study treatment[3]	X	X	X	X	X	X	X	X	X	X	X	X	X
Conc. Medication/non-drug therapy	Update as necessary												
Adverse events/SAE[4]	Update as necessary												
Patient's global assessment of disease activity (VAS)			X			X			X				X
Patient's assessment of spinal pain (VAS)			X			X			X				X
[redacted]													

Epoch	Treatment period 4												
Week	160	164	168	172	176	180	184	188	192	196	200	204	208*
[redacted]													
Lipids[6]						X							X
Cardiovascular panel													X
Treatment period 4 completion form													X

[1] Optional visits – Week 160, 164, 172, 176, 184, 188, 196, 200, 204. At these optional visits only those subjects who are unable to self-administer the PFS injections at home will visit the site and site staff will supervise self-administration or administer the PFS injection for them. Other subjects who can self-administer the PFS injection can do so at home at these optional visits.

[2] These assessments are source documentation only and will not be entered into the eCRF

[3] The study treatment (PFS) has to be administered every 4 weeks. From Week 104E1 to 116, subjects will visit the site every 4 weeks for administering the PFS injection (by self or by site staff). After Week 116, at visits marked as optional visits, subjects can self-administer the study PFS at home or may visit the site to receive the PFS administration by site staff.

[4] AEs/SAEs occurring after the subject has signed the informed consent must be captured on the appropriate eCRF page.

[redacted]

[6] Sample must be obtained fasting.

* For all subjects who discontinue or withdraw from the study, the investigator should ensure that the subject completes an end of treatment visit (corresponding to the last visit for the subject's current period of treatment) 4 weeks after last study treatment and also return after an additional 8 weeks for a final follow-up, F268 (12 weeks after last study treatment). The final visit should be performed before any new treatment is initiated.

[redacted]

Table 6-3 Assessment schedule - Part 3: Week 212 to Week 260 and follow-up visit F268

Epoch	Treatment period 5													
Week	212	216	220	224	228	232	236	240	244	248	252	256	260*	F268*
Optional Site Visit[1]	X	X		X	X		X	X		X	X	X		
Physical exam[2]			X			X			X				X	
Weight						X							X	
Vital signs			X			X			X				X	
Hematology, blood chemistry, urinalysis			X			X			X				X	
Urine pregnancy test			X			X			X				X	
ECG						X							X	
Administration of study treatment[3]	X	X	X	X	X	X	X	X	X	X	X	X		
Conc. Medication/non-drug therapy	Update as necessary													
Adverse events/SAE[4]	Update as necessary													
Patient's global assessment of disease activity (VAS)			X			X			X				X	
Patient's assessment of spinal pain (VAS)			X			X			X				X	
[redacted]														

[redacted]

Epoch	Treatment period 5													
Week	212	216	220	224	228	232	236	240	244	248	252	256	260*	F268*
[redacted]														
Lipids[7]						X							X	
Cardiovascular panel													X	
Treatment period 5 completion form													X	
Follow-up completion form														X

[1] Optional visits – Week 212, 216, 224, 228, 236, 240, 248, 252, 256. At these optional visits only those subjects who are unable to self-administer the PFS injections at home will visit the site and site staff will supervise self-administration or administer the PFS injection for them. Other subjects who can self-administer the PFS injection can do so at home at these optional visits.

[2] These assessments are source documentation only and will not be entered into the eCRF

[3] The study treatment (PFS) has to be administered every 4 weeks. From Week 104E1 to 116, subjects will visit the site every 4 weeks for

[redacted]

Epoch	Treatment period 5													
Week	212	216	220	224	228	232	236	240	244	248	252	256	260*	F268*

administering the PFS injection (by self or by site staff). After Week 116, at visits marked as optional visits, subjects can self-administer the study PFS at home or may visit the site to receive the PFS administration by site staff.

[4] AEs/SAEs occurring after the subject has signed the informed consent must be captured on the appropriate eCRF page.

[5] Only done in a sub-population at selected sites

[redacted]

[7] Sample must be obtained fasting

* For all subjects who discontinue or withdraw from the study, the investigator should ensure that the subject completes an end of treatment visit (corresponding to the last visit for the subject's current period of treatment) 4 weeks after last study treatment and also return after an additional 8 weeks for a final follow-up, F268 (12 weeks after last study treatment). The final visit should be performed before any new treatment is initiated.

[redacted]

6.1 Information to be collected on screening failures

Not applicable for this extension study.

6.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data collected on all subjects and recorded in the eCRF of the core study (CAIN457F2305) will be carried forward in this extension study (CAIN457F2305E1). Both the core study and the extension study data will be entered in the same database.

6.3 Treatment exposure and compliance

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

Drugs administered prior to start of treatment and other drugs continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page for the core study.Compliance will be assessed by a Novartis monitor using information provided by the authorized site personnel.

6.4 Efficacy

- Assessment of SpondyloArthritis International Society criteria (ASAS)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

6.4.1 Assessment of SpondyloArthritis International Society criteria (ASAS)

The ASAS response measures consist of the following assessment domains (Sieper 2009):

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale

[redacted]

2. Patient's assessment of back pain, represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
4. Inflammation represented by mean duration and severity of morning stiffness, represented by the average of the last 2 questions on the 6-question BASDAI as measured by VAS scale

Additional assessment domains:

5. Spinal mobility measured by BASMI (cervical rotation, maximal intermalleolar distance, spinal lateral flexion, lumbar flexion (modified Schober index), tragus-to-wall distance)
6. C reactive protein (acute phase reactant)

6.4.1.1 ASAS Response Criteria (ASAS 20)

The ASAS Response Criteria (ASAS 20) is defined as an improvement of at least 20% and absolute improvement of at least 10 units on a 0-100 mm scale in at least 3 assessment domains 1 to 4 and no worsening of more than 20% and 10 units on a 0-100 mm scale in the remaining unit.

6.4.1.2 ASAS Response Criteria (ASAS 40)

The ASAS Response Criteria (ASAS 40) is defined as an improvement of at least 40% and absolute improvement of at least 20 units on a 0-100 mm scale in at least 3 assessment domains 1 to 4 and no worsening at all in the remaining domain.

6.4.1.3 ASAS 5/6 improvement criteria

The ASAS 5/6 improvement criteria is an improvement of $\geq$ 20% in at least five of all six domains.

6.4.1.4 ASAS partial remission criteria

The ASAS partial remission criteria is defined as a value not above 2 units in each of the domains 1 to 4 on a scale of 10.

6.4.1.5 Patient's global assessment of disease activity (VAS)

The patient's global assessment of disease activity will be performed using a 100 mm visual analog scale (VAS) ranging from not severe to very severe, after the question *"How active was your disease on average during the last week?*".

6.4.1.6 Patient's assessment of back pain intensity (VAS)

The patient's assessment of back pain will be performed using a 100 mm VAS ranging from no pain to unbearable pain, after the question "*Based on your assessment, please indicate what is the amount of back pain at any time that you experienced during the last week?*" and *"Based on your assessment, please indicate what is the amount of back pain at night that you experienced during the last week?"*.

[redacted]

6.4.1.7 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those subjects with AS. The ten questions were chosen with a major input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subjects' ability to cope with everyday life. A 0 through 10 scale (captured as a continuous VAS) is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

6.4.1.8 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem), which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

1. Fatigue
2. Spinal pain
3. Joint pain / swelling
4. Areas of localized tenderness (called enthesitis, or inflammation of tendons and ligaments)
5. Morning stiffness duration
6. Morning stiffness severity

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness is taken (questions 5 and 6). The resulting 0 to 10 score is added to the scores for questions 1 through 4. The resulting 0 to 50 score is divided by 5 to give a final 0 – 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and subjects with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at AS. BASDAI is a quick and simple index taking between 30 seconds and 2 minutes to complete.

6.4.1.9 BASDAI 50

BASDAI 50 response is defined as at least a 50% improvement (decrease) in total BASDAI score, as compared to the baseline total BASDAI score (Braun 2003; Rudwaleit 2004).

[redacted]

[redacted]

[redacted]

6.4.10 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across all AS trials and are required for filing.

This study involves exposure to radiation from x-rays of the cervical and lumbar spine. The radiation exposure by these procedures is not necessary for medical care but is intended for research purposes only.

The amount of cumulative *annual* radiation in this study is about 3.42 mSv for the x-ray procedures and is based on effective doses for various diagnostic radiological procedures reported in literature (Mettler 2008). This exposure is comparable to the natural radiation an average person receives in one year. The radiation between 3 mSv and 50 mSv is considered 'minimal' (Stabin 2009). Therefore, the radiation exposure in this study involves minimal risk and is necessary to obtain the research information desired.

6.5 Safety

- Physical examination
- Vital signs
- Height and weight
- Electrocardiogram
- Local tolerability (injection site reactions)
- Laboratory evaluations (hematology, clinical chemistry, lipid panel, urinalysis)
- Pregnancy and assessment of fertility

[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.

[redacted]

6.5.1 Physical examination

A physical examination will be performed at scheduled visits as indicated in Table 6-1, Table 6-2, and Table 6-3. 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 systems.

Information for all physical examination 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

This 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

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing) (both without shoes) will be measured. The baseline height from the core study will be used in this trial. Therefore, height will not be collected in this trial

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

6.5.4 Laboratory evaluations

A central laboratory will be used in this study. All laboratory tests should be conducted at the central laboratory except for [redacted] urinalysis/urine pregnancy tests. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 1. All 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.

6.5.4.1 Hematology

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

6.5.4.2 Clinical chemistry

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

[redacted]

6.5.4.3 Lipid panel

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

6.5.4.4 Cardiovascular panel

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

6.5.4.5 Urinalysis

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

6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 6-1, Table 6-2, and Table 6-3.

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

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

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

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

6.5.6 Local tolerability (injection site reactions)

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

The assessment of pain, redness, swelling, induration, hemorrhage and itching will be performed by a physician and will be recorded on the Adverse Events eCRF, including the severity (mild, moderate, severe) and the duration.

6.5.7 Pregnancy and assessments of fertility

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

All women who are not surgically sterile when enrolling into the study will have local urine pregnancy tests as indicated in Table 6-1, Table 6-2, and Table 6-3. A positive urine pregnancy test requires immediate interruption of study medication until serum β-hCG is performed and found to be negative. If positive, the subject must be discontinued from the trial.

[redacted]

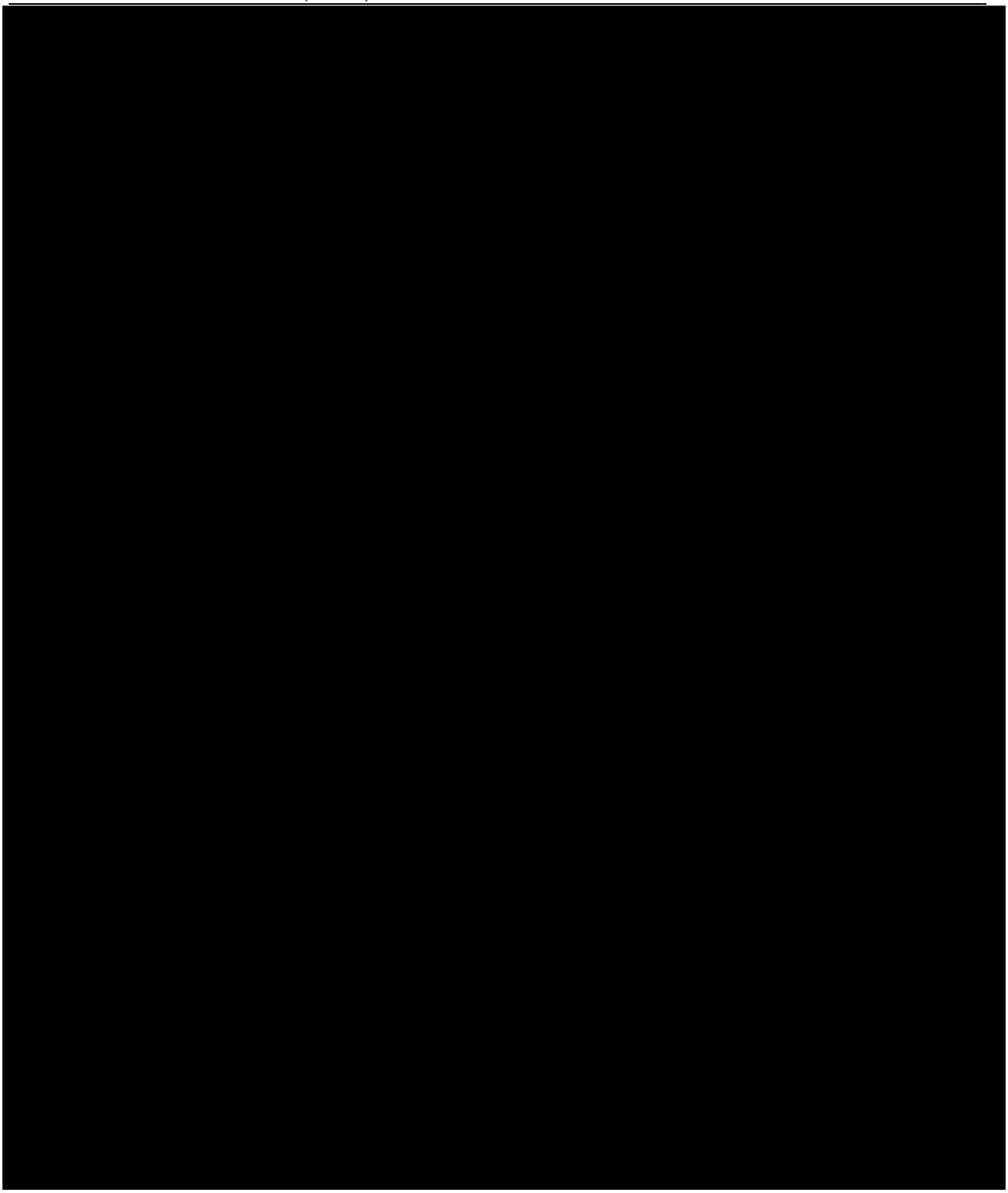
[redacted]

6.5.9 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in AS.

[redacted]

[redacted]



7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or

clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the 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.

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

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

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

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

- the severity grade [mild, moderate, severe]
  - 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 (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

[redacted]

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

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

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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); investigational treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

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

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

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

[redacted]

7.2 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 12 weeks following the last administration of study treatment or 30 days after the subject has stopped study participation 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.

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

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the OC/RDC system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

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

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational 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 investigational 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 Directive 2001/20/EC or as per national regulatory requirements in participating countries.

[redacted]

7.3 Pregnancy reporting

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

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

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

8.1 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the 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

[redacted]

the data entered into the electronic Case Report Forms are complete and accurate. After DBL, the investigator will receive copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

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

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO). Novartis Data Management staff will perform a reconciliation of the data entered into the eCRF versus what is received from the central laboratory. At a minimum this reconciliation will include header reconciliation, visit window checks, duplicate record checks, out of range checks as defined by the Clinical Trial Team and checks to address missing laboratory data.

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

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

8.4 Data Monitoring Committee

An independent data monitoring committee (DMC) reviewed the safety data of this trial at regular intervals. Details regarding the DMC process are available in relevant secukinumab DMC charters. Following the Week 52 DBL and interim analysis, the DMC review will no longer be required.

8.5 Adjudication Committee

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

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

[redacted]

9 Data analysis

Summary statistics for continuous variables will generally include the number of subjects (N), minimum, lower quartile, mean, median, upper quartile, and maximum. For categorical or binary variables, the number and percent of subject in each category will be presented. The 95% confidence intervals will be provided to evaluate the treatment efficacy.

Data will be presented by a combination of the 'original' and 'switch' treatment groups. These treatment groups represent the treatment combinations the subjects experience over the course of the entire trial in case of re-randomization and dose escalation.

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

9.1 Analysis sets

The following analysis sets will be used in this study:

Full analysis set (FAS): The FAS will be comprised of all subjects enrolled in the study.

Safety set: The safety set includes all subjects enrolled in the study who took at least 1 dose of study treatment during the study.

9.2 Subject demographics and other baseline characteristics

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

9.3 Treatments

9.3.1 Study Treatment

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

9.3.2 Concomitant medication

Concomitant medications will be summarized by treatment group. Any medication given at least once between the start of the first dose in this extension trial and the date of the last study visit in the extension study will be a concomitant medication, including those which were started before Week 104E1 and continued into the extension study 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 medical surgeries and procedures will be summarized by primary system organ class and MedDRA preferred term.

[redacted]

The number and percentage of subjects receiving concomitant rheumatoid arthritis therapy will be presented by treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to rheumatoid arthritis therapies previously.

9.4 Analysis of the primary and key secondary variable(s)

9.4.1 Variable(s)

The primary efficacy variable is the clinical response to treatment according to the ASAS20 over time up to Week 260. The analysis of the primary variable will be based on the FAS subjects.

9.4.2 Statistical model, hypothesis, and method of analysis

No formal hypotheses are proposed for this study. The proportion of subjects meeting the ASAS20 will be descriptively summarized for each treatment over time. Treatment efficacy will be assessed by providing the 95% confidence interval of treatment response according to the ASAS criteria. No statistical comparison is expected to be performed between treatment groups.

9.4.3 Handling of missing values/censoring/discontinuations

Efficacy data will be presented using all available data at the given time point of analysis.

Additionally, under the assumption of missing at random, multiple imputation by treatment may be performed for baseline weight as well as for all baseline and post-baseline efficacy variables of interest during the trial.

9.4.4 Supportive analyses

Sensitivity analysis may be performed to assess the robustness of missing data handling. These may include multiple imputation for ASAS20.

9.5 Analysis of secondary [redacted] variables

9.5.1 Efficacy variables

For binary variables, the proportion of responders will be summarized over analysis visits. For continuous variables, the change from baseline (of core) will be presented. The 95% confidence intervals will be provided to evaluate the long-term treatment efficacy of the secondary binary variables of interest. Summary statistics for continuous variables include mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum.

Secondary variables include:

- The proportion of subjects achieving ASAS40

[redacted]

[redacted]

[redacted]

No statistical comparisons between any of the treatment groups (75 mg treatment arm and 150 mg treatment arm including patients who escalated from 75 mg s.c. to 150 mg s.c. every 4 weeks)will be provided for the analysis of the secondary [redacted] variables.

9.5.2 Safety variables

Adverse events

Treatment emergent adverse events (events started after the first dose of study treatment in the extension or events present prior to the first dose of study treatment in core study but increased in severity based on preferred term and within 84 days after last dose of secukinumab) will be summarized.

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

The incidence of AEs will be presented per 100 subject years of exposure.

Separate summaries will be provided for death, serious adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including study treatment discontinuation).

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

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

[redacted]

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 of core study and post baseline values.

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.

Vital signs

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

ECG

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

[redacted]

[redacted]

9.6 Interim analyses

Interim analyses may be planned in order to support regulatory filing and for purposes of publication after subjects complete additional years of treatment in this extension study. Additional analyses may be performed to support heath authority interactions, as necessary.

9.7 Sample size calculation

It is estimated that approximately 75% to 85% of subjects enrolled in the core study will complete the entire treatment period and be eligible for entry into the extension study, which is equivalent to about 279 to 316 subjects.

[redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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

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

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, 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.

[redacted]

10.4 Publication of study protocol and results

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

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

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

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for subject safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

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[redacted]

13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

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

Clinically notable values will be forwarded to Novartis at the same time that they are sent to investigators.

Table 13-1 Safety Analyses: Expanded Limits and Notable Criteria

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

HEMATOLOGY VARIABLES

Hemoglobin: ≥20 g/L decrease from baseline

Platelet count: <100x10E9/L

White blood cell count: <0.8 x LLN

Neutrophils: <0.9 x LLN

[redacted]

13.3 Appendix 3: Modified New York criteria

Clinical criteria

- Low back pain and stiffness for more than 3 months that improves with exercise, but is not relieved by rest
- Limitation of motion of the lumbar spine in the sagittal and frontal planes
- Limitation of chest expansion relative to normal values correlated for age and sex

Radiological criterion

- Sacroiliitis grade ≥ 2 bilaterally or grade 3-4 unilaterally

Definite AS if the radiological criterion is associated with at least one clinical criterion

[redacted]

13.4 Appendix 4: Assessment of SpondyloArthritis International Society criteria (ASAS)

The ASAS response measures consist of the following assessment domains (Sieper 2009):

Main ASAS domains:

1. Patient's global assessment of disease activity measured on a VAS scale
2. Patient's assessment of back pain represented by either total or nocturnal pain scores, both measured on a VAS scale
3. Function represented by BASFI average of 10 questions regarding ability to perform specific tasks as measured by VAS scale
4. Morning stiffness represented by the average of the last 2 questions on the 6-question BASDAI regarding morning stiffness as measured by VAS scales

Additional assessment domains:

5. [redacted]
6. [redacted]

13.4.1 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI is a set of 10 questions designed to determine the degree of functional limitation in those subjects with AS. The ten questions were chosen with a major input from subjects with AS. The first 8 questions consider activities related to functional anatomy. The final 2 questions assess the subject's ability to cope with everyday life. A 10cm visual analog scale is used to answer the questions. The mean of the ten scales gives the BASFI score – a value between 0 and 10.

13.4.2 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI consists of a 0 through 10 scale (0 being no problem and 10 being the worst problem, captured as a continuous VAS), which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?
2. How would you describe the overall level of AS **neck, back or hip pain** you have had?
3. How would you describe the overall level of pain/swelling in joints other than **neck, back, hips** you have had?
4. How would you describe the overall level of **discomfort** you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of **morning stiffness** you have had **from the time you wake up**?
6. How long does your morning stiffness last from the time you wake up?

To give each symptom equal weighting, the mean (average) of the two scores relating to morning stiffness (questions 5 and 6) is taken. The resulting 0 to 10 number is added to the scores from questions 1-4. The resulting 0 to 50 score is divided by 5 to give a final 0 to 10 BASDAI score. Scores of 4 or greater suggest suboptimal control of disease, and subjects

[redacted]

with scores of 4 or greater are usually good candidates for either a change in their medical therapy or for enrollment in clinical trials evaluating new drug therapies directed at Ankylosing Spondylitis. BASDAI is a quick and simple index, taking between 30 seconds and 2 minutes to complete.

13.4.3 Bath Ankylosing Spondylitis Metrology Index (BASMI)

Cervical rotation

Cervical rotation is measured twice with the subject supine on plinth, head in neutral position, forehead horizontal (if necessary head on pillow or foam block to allow this, must be documented for future reassessments). Gravity goniometer placed centrally on the forehead. Subject rotates head as far as possible to the left, keeping shoulders still, ensure no neck flexion or side flexion occurs and the angle between the sagittal plane and the new plane after rotation is recorded. The better reading of the two is recorded. The same is repeated for the right side. Record the mean of the better reading from the right side and the better reading from the left side.

Tragus to wall distance

Tragus to wall distance is measured twice with the subject's heels and back rested against the wall. The chin should be at usual carrying level and the subject takes maximal effort to touch the head against the wall. The distance between the tragus and the wall is assessed and the better of the two assessments is to be reported.

Spinal lateral flexion (lumbar lateral flexion)

Subject stands with heels and buttocks touching the wall, knees straight, shoulders back, hands by the side. The subject is then asked to bend to the right side as far as possible without lifting the left foot/heel or flexing the right knee, and maintaining a straight posture with heels, buttocks, and shoulders against the wall. The distance from the third fingertip to the floor when subject bends to the side, is subtracted from the distance when subject stands upright. The better of two tries is recorded. The maneuver is repeated on the left side. Record the mean of the better reading from the right side and the better reading from the left side.

Lumbar flexion (modified Schober index)

Set marks in upright position 5 cm below and 10 cm above lumbosacral junction (spinal section of a line joining the dimples of Venus). Measure distraction of the marks when the subject bends forward as far as possible, keeping the knees straight. The better of two tries is recorded.

Maximal intermalleolar distance

Subject is lying down with the legs separated as far as possible with knees straight and toes pointed upwards. Alternatively, the subject stands and separates the legts as far as possible. The distance between medial malleoli is measured and the better of the two measurements is recorded.

[redacted]

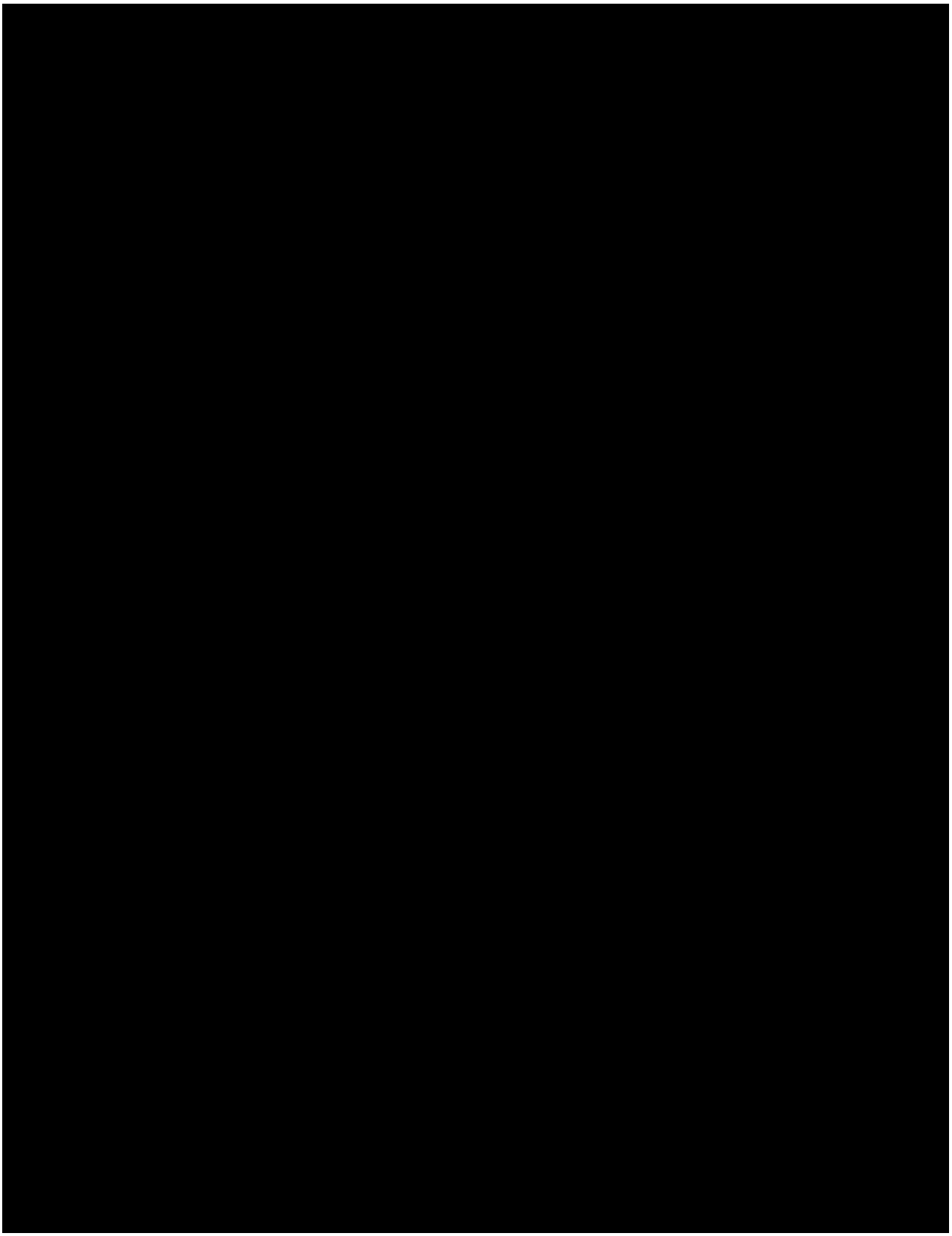
Chest expansion

Chest expansion is measured with the subject hands resting on or behind the head. The measurement is taken at the fourth intercostal level anteriorly. The difference between maximal inspiration and expiration in cm is recorded twice and the better of the two measurements is reported.

Occiput-to-wall distance

Occiput to wall distance is measured twice with the subject's heels and back rested against the wall. The chin should be at usual carrying level and the subject takes maximal effort to touch the head against the wall. The distance between the occiput and the wall is assessed and the better of the two assessments is to be reported.

[redacted]



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