NOVARTIS

Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol [CAIN457F2306E1] / NCT01892436

A three-year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in patients with active psoriatic arthritis

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine aminotransferase/Serum Glutamic Pyruvate Transaminase (SGPT)
ANA	Anti-nuclear antibodies
ANCOVA	Analysis of covariance
Anti-CCP	Anti-cyclic citrullinated peptide antibodies
AS	Ankylosing Spondylitis
AST	Aspartate Aminotransferase/Serum Glutamic Oxaloacetic Transaminase (SGOT)
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BSL	Baseline
BUN	Blood Urea Nitrogen
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CRP (hsCRP)	(high sensitivity) C-Reactive Protein
DAS	Disease Activity Score
DMARD	Disease Modifying Anti-rheumatic Drug
DMC	Data Monitoring Committee
DNA	Desoxyribonucleic acid
DS&E	Drug Safety & Epidemiology
dsDNA Ab	Anti-double stranded DNA antibodies
eCRF	Electronic Case Report/Record Form
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked Immunosorbent Assay
EMA/EMEA	European Medicnices (Evaluation) Agency

[redacted]

EoS	End of Study
ESR	Erthrocyte Sedimentation Rate
[redacted]	[redacted]
FACIT-Fatigue©	Functional Assessment of Chronic Illness Therapy - Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	Follicle-stimulating Hormone
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
GTL	Global Trial Leader
HAQ-DI©	Health Assessment Questionnaire – Disability Index
hCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC/EC	Independent Ethics Committee
[redacted]	[redacted]
IFU	Instructions for Use
IL	Interleukin
IN	Investigator Notification
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intra Uterine Device
IUS	Intra Uterine System
i.v.	intravenous
[redacted]	[redacted]
LDL	Low Density Lipoprotein
[redacted]	[redacted]
LLN	Lower limit of normal

[redacted]

LLOQ	Lower Limit of Quantification
LOCF	Last observation carried forward
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mmHG	Millimeter mercury
MTX	Methotrexate
NSAID	Non-Steroidal Anti-Inflammatory Drug
NovDTD	Novartis Drug/Therapy Dictionary
PASI	Psoriasis Area and Severity Index
PFS	Pre-filled Syringe
PK	Pharmacokinetic
PoC	Proof of Concept
PRO	Patient Reported Outcome
PsA	Psoriatic Arthritis
QoL	Quality of Life
RA	Rheumatoid Arthritis
RBC	Red blood cells
RDC	Remote Data Capture
RF	Rheumatoid Factor
SAE	serious adverse event
s.c.	Subcutaneous
[redacted]	[redacted]
SJC	Swollen joint count
SpA	Spondyloarthritides
SUSAR	Suspected Unexpected Serious Adverse Reaction
TJC	Tender joint count
TNF	Tumor Necrosis Factor
TNFα-IR	TNFα Inhibitor Incomplete/Inadequate Responders
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
VAS	Visual Analog Scale
WBC	White blood cells

[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 patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	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.
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
Subject Number	A number assigned to each patient who enrolls into the study
Part	A subdivision of a single protocol into major design components. These parts often are independent of each other and have different populations or objectives. For example, a single dose design, a multiple dose design that are combined into one protocol, or the same design with different patient populations in each part.
Period	A subdivision of a cross-over study
Premature patient withdrawal	Point/time when the patient 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 patient, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

[redacted]

Amendment 2

Amendment rationale

This protocol amendment is primarily issued for the following reasons:

1. **Removing Week 260 X-Ray (hands/wrists + feet) assessment**

Due to limited scientific value of the week 260 X-Rays beyond which is provided by the week 208 X-Rays, business priorities and initiation of an additional PsA study that will evaluate skeletal X-Rays, the Week 260 X-Rays included in the current study are now being deleted in this Amendment 2.

2. **Introducing updated Novartis standard language for SAE reporting**
3. **Adding further specifications with respect to statistical analysis**

Changes to the protocol

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

The wording of various sub-sections to "Study objectives" (Section 2),"Visit Schedule and Assessments" (Section 6), "Safety monitoring" (Section 7) and "Data Analysis" (Section 9) have been amended to reflect the rationale given above.

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

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

The changes described in this amended protocol are non-substantial and do not require IRB/IEC approval prior to implementation.

Amendment 1

Amendment rationale

This protocol amendment is primarily issued for the following reasons:

1. **Allowing dose escalation of secukinumab administered sc every 4 weeks from 75 mg to 150 mg or 300 mg, and from 150 mg to 300 mg**

75 mg sc dose of secukinumab provides insufficient exposure:

Phase 3 studies in patients with active PsA (CAIN457F2306 and CAIN457F2312) demonstrated the superior efficacy of secukinumab 150 mg sc and 300 mg sc

[redacted]

(CAIN457F2312 only) regimens over placebo. Secukinumab 150 mg sc and 300 mg sc regimens had a rapid onset of response and similar magnitude of efficacy across several endpoints.

In contrast, based on the results of CAIN457F2312, secukinumab 75 mg sc is considered an inadequate dose, as the primary endpoint was met but overall, when evaluated against the 150 and 300 mg sc doses, 75 mg sc did not provide clinically meaningful responses in arthritic signs and symptoms, skin clearance and physical function:

- ACR20 response rates at Week 24 were 54%, 51%, 29.3% and 15.3% with 300mg, 150mg, 75mg and placebo respectively.
- PASI75 response rates at Week 24 were 63.4%, 48.3%, 28% and 16.3% with 300mg, 150mg, 75mg and placebo respectively.
- PASI90 response rates at Week 24 were 48.8%, 32.8%, 12% and 9.3% with 300mg, 150mg, 75mg and placebo respectively.
- DAS-28 CRP mean change from baseline at Week 24 was -1.61, -1.58, -1.12 and -0.96 with 300mg, 150mg, 75mg and placebo respectively.
- SF36-PCS mean change from baseline at Week 24 was 7.25, 6.39, 4.38 and 1.95 with 300mg, 150mg, 75mg and placebo respectively.

This trend from CAIN457F2312 is reflected in the week 104 results of CAIN457F2306, indicating that in the present longer term efficacy extension study, a higher dose could be more beneficial to patients. Secukinumab 150mg had clinically superior ACR50 and PASI75/90 response rates compared to 75mg at Week 104:

- ACR50 response rates at Week 104 were 46.4 % and 35.5% with 150mg and 75mg respectively.
- PASI75 response rates at Week 104 were 82.9 % and 70.2% with 150mg and 75mg respectively.
- PASI90 response rates at Week 104 were 69.5 % and 50.0% with 150mg and 75mg respectively.

As a conclusion, there is strong evidence that the 75 mg dose administered every 4 weeks in PsA patients provides insufficient exposure to achieve optimal, clinically relevant improvements in all subgroups and across multiple domains in this debilitating multifaceted chronic disease.

300 mg sc dose of secukinumab offers increased benefit for TNFα-inadequate responder patients and in patients with moderate to severe plaque psoriasis:

While secukinumab 150 mg sc and 300 mg sc regimens are both more efficacious than placebo regardless of TNFα inhibitor status, the 300 mg sc regimen provided the greatest efficacy across multiple PsA domains including ACR20, ACR50, ACR70, HAQ-DI, PASI 75, PASI 90, SF-36 PCS, and presence of dactylitis and enthesitis in TNF-IR patients.

Evidence of dose response was shown in TNF-IR patients favoring secukinumab 300 mg sc over 150 mg sc at the Week 24 efficacy endpoint used for the primary and secondary efficacy analyses of CAIN457F2312, while the 75 mg sc dose showed overall lower efficacy. Indeed, ACR20/50/70 response rates at Week 24 in TNF-IR patients were higher with secukinumab

[redacted]

300 mg sc compared to 150 mg sc (45.5% vs 29.7%, 27.3% vs 18.9%% and 15.2% vs 10.8% respectively), while 75 mg sc failed to differentiate from placebo in all ACR endpoints. This trend was maintained up to week 52.

Furthermore, secukinumab 300 mg sc was more efficacious than 150 mg sc in achieving clinically meaningful improvements in skin disease, particularly with respect to clear/almost clear skin (PASI 90, IGA mod 2011 0/1) in patients with moderate to severe psoriasis (defined as ≥ 10% BSA). There was a clear dose response favoring secukinumab 300 mg sc in the higher thresholds of skin clearance. The difference between 300 mg sc and 150 mg sc regimens was more pronounced in the more difficult-to-achieve PASI 90 and IGA mod 2011 0/1 endpoints, with 21.9% and 27.4% more patients with ≥ 10% BSA compared to 8.2% and 3.3% more patients with < 10 % BSA reaching PASI 90 and IGA mod 2011 0/1 responses, respectively, at Week 24. Therefore, secukinumab 300 mg sc afforded greater improvement in plaque psoriasis than 150 mg sc, particularly in the achievement of clear/almost clear skin, in patients with moderate to severe psoriasis (≥ 10% BSA).

In addition, pertaining to safety assessments, there were no clinically meaningful differences among the secukinumab doses of 300 mg sc, 150 mg sc and 75 mg sc in the exposure adjusted incidences rates of the key risks over the entire treatment period in the 2 phase 3 trials in PsA patients. The overall safety in the PsA population was consistent with prior extensive experience in psoriasis, and shows that secukinumab 300 mg sc and 150 mg sc are acceptable for chronic use in adult patients with active PsA.

Thus, given all the results outlined above, and in order to maintain a high proportion of clinically meaningful response during the entire duration of the extension study, the dosing options available, at the investigator's discretion, are:

1. The dose of secukinumab should be escalated from 75 mg sc every 4 weeks to 150 mg sc every 4 weeks for patients whose signs and symptoms are not fully controlled with the current dose of 75 mg, and may improve with higher dose as judged by the investigator.
2. Further, the dose should also be escalated to 300 mg sc every 4 weeks for patients currently on 75 mg or 150 mg dose whose signs and symptoms are not fully controlled, and may improve further with an increase in dose as judged by investigator.
3. Dose escalation from secukinumab 75 mg to 300 mg can be done either in one step or in two steps (first 150 mg then 300 mg based on investigator’s judgement).

2. Clarification on the duration of contraception

According to protocol exclusion criterion #4 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 #4 is changed to

[redacted]

"Women of child-bearing potential (WoCBP), 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)."

3. Data monitoring committee review no longer required

Based on the safety results of studies CAIN457F2306 and CAIN457F2312, the DMC review will no longer be required.

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

At the time of this amendment, enrolment into the extension study was complete with 460 patients enrolled and 432 patients still under treatment as of September 6, 2015.

Changes to the protocol

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

The wording of various sub-sections to "Study objectives" (Section 2) "Investigational Plan" (Section 3), "Population" (Section 4), "Treatment" (Section 5), "Data analysis" (Section 9), " Data Monitoring Committee" (Section 8.4) and "Appendix 4" (Section 13.4) have been amended to reflect the rationale given above.

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

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

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

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

[redacted]

Protocol synopsis

Protocol number	CAIN457F2306E1
Title	A three year extension study to evaluate the long term efficacy, safety and tolerability of secukinumab in subjects with active psoriatic arthritis
Brief title	Extension study up to 3 years for secukinumab in psoriatic arthritis
Sponsor and Clinical Phase	Novartis, Phase III
Investigation type	Drug / Biological
Study type	Interventional
Purpose and rationale	The extension study CAIN457F2306E1 is designed as a 3-year extension to the phase III core study CAIN457F2306. It aims to provide continuous treatment with secukinumab in pre-filled syringes (PFS) for subjects who completed the core study CAIN457F2306, to obtain further long term efficacy, safety and tolerability information in subjects with active psoriatic arthritis receiving secukinumab every 4 weeks.
Primary Objective	To evaluate the long-term efficacy of secukinumab (provided as pre-filled syringes) with respect to ACR20, ACR50 and ACR70 response over time up to Week 260 in subjects with active psoriatic arthritis and who complete the phase III study CAIN457F2306
Secondary Objectives	1. To evaluate the long-term efficacy of secukinumab with respect to: a. Changes in HAQ-DI relative to baseline over time up to Week 260 b. The proportion of subjects with improvements from baseline in HAQ-DI meeting or exceeding minimal clinically important difference (MCID) c. The changes in DAS28 (utilizing hsCRP) relative to baseline over time up to Week 260 d. The proportion of subjects achieving low disease activity (DAS28 ≤ 3.2) and disease remission as defined by DAS28 (DAS28 < 2.6) over time up to Week 260 2. To evaluate the long term safety and tolerability of secukinumab as assessed by vital signs, clinical laboratory variables, and adverse events monitoring over time up to Week 260
Study design	This study will employ a parallel group, double blind design for the first year (up to and excluding Week 156) followed by an open-label design for the next two years (Week 156 onwards). Investigators will use their clinical judgment to decide if it is beneficial for subjects to enter the extension study based upon overall improvement and response to therapy during the 2 year period of the core study CAIN457F2306. The total combined duration of treatment for the core study and this extension study is five years. At Week 104 of the core study CAIN457F2306, eligible subjects will

[redacted]

	complete the assessments associated with the core study visit and will subsequently continue in the extension study on the same dose (every 4 weeks) that they were receiving during the core study.
Population	The study population will consist of male or female subjects of at least 18 years of age. All subjects who completed the core study CAIN457F2306, who comply with the inclusion and exclusion criteria of this study, who are deemed by investigators to benefit from continued secukinumab therapy and provide a new informed consent are eligible to enter into this extension study. Approximately 460-520 subjects will be eligible for enrollment in study CAIN457F2306E1.
Inclusion criteria	1. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed 2. Subjects must have participated in core study CAIN457F2306, and must have completed the entire treatment period 3. Subjects who are deemed by the investigator to benefit from continued secukinumab therapy
Exclusion criteria	1. Any subject taking other concomitant biologic immunomodulating agent(s) except secukinumab 2. Any subject who is deemed not to be benefiting from the study drug based upon lack of improvement or worsening of their symptoms
Investigational and reference therapy	All subjects will continue to receive the same dose of secukinumab they were receiving during the treatment period of the core study. No re-randomization is planned. The two treatment groups are: <u>Till Week 152</u> • Group 1: secukinumab 75mg plus placebo matching high dose once every four weeks till Week 152 • Group 2: secukinumab 150mg plus placebo matching low dose once every four weeks till Week 152 <u>Starting with Week 156 (open label period of study)</u> • Group 1: secukinumab 75mg once every four weeks till (and including) Week 256, or escalated to secukinumab 150mg or 300mg once every four weeks till and including Week 256, after implementation of Amendment 1 • Group 2: secukinumab 150mg once every four weeks till (and including) Week 256, or escalated to secukinumab 300 mg once every four weeks till and including Week 256, after implementation of Amendment 1
Efficacy assessments	• ACR20, 50, 70 • HAQ-DI • hsCRP/ESR • DAS28 response/remission

[redacted]

Safety assessments	• Evaluation of all AEs and SAEs including injection site reactions and infections • Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis) • ECG, physical examination, vital signs
Other assessments	• Pharmacokinetics • [redacted] • [redacted]
Data analysis	The primary efficacy variable is the clinical response to treatment according to ACR20, ACR50 and ACR 70 improvement in disease activity over time up to Week 260. The analysis of the primary variables will be based on the FAS. No formal hypotheses are planned for this study. The proportion of subjects meeting the ACR criteria (ACR20, ACR50, and ACR70) will be descriptively summarized for each treatment. Summary statistics for continuous variables will 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 subjects in each category will be presented. 95% confidence intervals will be provided in order to assess the magnitude of treatment efficacy.
Key words	Secukinumab, psoriatic arthritis, long term extension study

[redacted]

1 Introduction

1.1 Background

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondyloarthritides (SpA). The scientific community is split over the question whether to view these conditions together or consider them as separate entities (Nash 2005). For example, inflammatory back pain associated with psoriasis fits two classifications (1) AS with psoriasis or (2) psoriatic spondylitis (Gladman 2007). However, while diverse in their clinical presentations, common environmental as well as genetic factors associated with susceptibility to SpA are suspected (Turkiewicz 2007). This latter notion was recently corroborated by findings in a large-scale single nucleotide polymorphism (SNP) scan study, where IL23R variants that were previously linked to Crohn`s disease and psoriasis (diseases that may both co-exist with spondylarthritides) conferred risk to developing ankylosing spondylitis (Barrett 2008). Together, a common pathway including the IL-23/IL-17 axis may play a role in seronegative SpA including PsA.

PsA is a frequent chronic immune-mediated disease encompassing a spectrum of overlapping clinical entities (Moll and Wright 1973). About 10 - 40% of patients with psoriasis suffer from PsA. Recent efforts were aimed at defining more stringent classification criteria for standardized recruitment into clinical trials (Taylor 2006). PsA is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden. It is not only more common but also more severe than previously thought (Gladman 2004). The majority of patients will have psoriasis prior to the occurrence of the associated arthritis and are typically under treatment for their skin disease. For musculoskeletal disease manifestations initially NSAIDs are used to alleviate symptoms. Typically disease modifying anti-rheumatic drugs (DMARDs) are used for PsA including methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide, however, these are often inadequate because they only partially control established disease (Mease 2008).

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

IL-17 antagonism represents a novel therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant pro-inflammatory cytokine of the T helper 17 cell subset. Additional effects of anti-IL17 on bone homoeostasis via RANKL and IL-1, upstream of TNFα, can be inferred from animal studies (Koenders 2005). Assuming a potential role of IL-17 cells in the inflammatory infiltrate in PsA, it can be speculated that locally disturbed homeostasis of osteoclastogenic and osteoblastogenic

[redacted]

mechanisms characteristic of PsA might be affected by IL-17 blockade thus potentially providing a therapeutic advancement to prevent structural damage in PsA.

Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that neutralizes IL-17A activity. IL-17A is the key cytokine in the newly discovered Th17 pathway which is thought to be an important mediator of autoimmunity. Neutralization of IL-17A has strong pre-clinical and clinical target validation and documentation of efficacy in a proof of concept study (CAIN457A2101) and a phase II study (CAIN457F2201) in Rheumatoid Arthritis (RA). IL-17A has been shown to play a pivotal direct pathogenic role in both inflammatory and destructive joint tissue manifestations of RA and has direct effects on matrix metalloprotease (MMP) activation and stimulation of osteoclast-mediated bone resorption (Stamp 2004; Witowski 2004; Moseley 2003). A proof-of concept study conducted in subjects with PsA (CAIN457A2206; n=42) suggests that a clinically meaningful response for signs and symptoms is induced as early as 2 weeks after start of secukinumab treatment, with further improvement up to Week 6 and maintenance of response up to Week 16. Therefore, treatment with secukinumab may also reduce loss of cartilage and erosion of bone in PsA and may result in improvement of symptoms and functional joint manifestations in afflicted patients. Furthermore, in a completed proof of concept study (CAIN457A2102), the effects of secukinumab administered at 3 mg/kg as a single intravenous infusion were compared with that of placebo in thirty-six subjects with active chronic plaque-type psoriasis. The study demonstrated efficacy at the 4- week endpoint and continuous efficacy at 12 weeks based on Psoriasis Area and Severity Index (PASI) and Investigator's Global Assessment mod (IGA mod 2011) endpoints.

As of January 2013, approximately 7400 subjects have been enrolled into the secukinumab clinical program, of which approximately 6000 subjects have received secukinumab. Overall, healthy volunteers and patients across various indications (psoriasis, RA, AS, PsA, multiple sclerosis, uveitis, Crohn's disease, dry eye, polymyalgia rheumatica) have received secukinumab at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25mg to 300mg s.c. In total, 606 PsA patients have been enrolled into the core study (CAIN457F2306) with secukinumab. Safety results from all completed studies show comparable numbers of adverse events in subjects treated with secukinumab compared to placebo without indication of any specific organ toxicity. Please refer to the Investigator Brochure for a more detailed review of the pre-clinical and clinical information on secukinumab.

1.2 Purpose

Study CAIN457F2306 is a 2 year Phase III study which enrolled 606 patients with active PsA. The study CAIN457F2306E1 is designed as a 3-year extension to the core study CAIN457F2306. It aims to provide continuous treatment with secukinumab in pre-filled syringes (PFS) for subjects who completed the core study CAIN457F2306 in order to obtain further longer term efficacy, safety and tolerability information.

[redacted]

2 Study objectives

2.1 Primary objectives

To evaluate the long-term efficacy of secukinumab (provided as pre-filled syringes) with respect to ACR20, ACR50 and ACR70 response over time up to Week 260 in subjects with active PsA and who complete the phase III study CAIN457F2306

2.2 Secondary objectives

1. To evaluate the long-term efficacy of secukinumab with respect to:
   a. Changes in HAQ-DI relative to baseline over time up to Week 260
   b. The proportion of subjects with improvements from baseline in HAQ-DI meeting or exceeding minimal clinically important difference (MCID) over time up to Week 260
   c. The changes in DAS28 (utilizing hsCRP) relative to baseline over time up to Week 260
   d. The proportion of subjects achieving low disease activity (DAS28 $\leq$ 3.2) and disease remission as defined by DAS28 (DAS28 < 2.6) over time up to Week 260
2. To evaluate the long term safety and tolerability of secukinumab as assessed by vital signs, clinical laboratory variables, and adverse events monitoring over time up to Week 260

[redacted]

3 Investigational plan

3.1 Study design

Core study (CAIN457F2306) design is provided in Appendix 11.

This extension study will employ a parallel group, **double blind design for the first year (up to and excluding Week 156)** followed by an **open-label design for the next two years (Week 156 onwards)**. The blinding during first year of this extension study is required to ensure that 52-week data from the core study are cleaned and locked before unblinding the subjects in the extension study.

Investigators will use their clinical judgment to decide if it is beneficial for subjects to enter the extension study based upon overall improvement and response to therapy during the 2-year period of the core study CAIN457F2306.

The total combined duration of treatment for the core study and this extension study is 5 years. As this long-term study extends the pivotal registration study CAIN457F2306 by an additional 3 years it may be affected by an agency's review or potential product approval considerations. If the product is approved during study conduct, dose groups in this extension study may be amended (via a future protocol amendment) based on agency recommendations for product usage in this indication.

At Week 104 of the study CAIN457F2306, eligible subjects will complete the assessments associated with the core study visit and will subsequently continue in the extension study on the same dose (secukinumab 75mg or secukinumab 150mg every 4 weeks) that they were receiving during the core study.

At each study treatment time point till Week 152, two s.c. injections in the form of PFS will be administered. This is necessary to maintain the blind, as secukinumab is available in either 0.5 ml (75 mg) PFS or 1.0 ml (150 mg) PFS. Placebo to secukinumab is also available in 0.5 ml and 1.0 ml PFS to match the active drug.

- Group 1: secukinumab 75 mg (0.5mL) plus placebo (1mL) once every four weeks till (and including) Week 152
- Group 2: secukinumab 150 mg (1mL) plus placebo (0.5mL) once every four weeks till (and including) Week 152

At each study treatment time point starting at Week 156, one or two s.c. injections in the form of PFS will be administered. This will be open label treatment.

- Group 1: secukinumab 75 mg (0.5mL) once every four weeks till (and including) Week 256. After approval and implementation of Amendment 1, patients may be escalated to 150 mg or 300 mg as judged appropriate by the investigator.
- Group 2: secukinumab 150 mg (1mL) once every four weeks till (and including) Week 256. After approval and implementation of Amendment 1, patients may be escalated to 300 mg as judged appropriate by the investigator.

Study treatment dose adjustments are not permitted until Week 156.

[redacted]

Starting from Week 156 (i.e. during the open label study period), after approval and implementation of Amendment 1, the secukinumab dose should be escalated from 75 mg to 150 mg for patients whose signs and symptoms are not fully controlled with the current dose of 75 mg, and may improve with higher dose as judged by the investigator.

Further, the dose should also be escalated to 300 mg for patients currently on 75 mg or 150 mg, and whose signs and symptoms are not fully controlled and may improve further with an increase in dose as judged by the investigator.

Dose escalation from secukinumab 75 mg to 300 mg can be done either in one step or in two steps (first 150 mg, then 300 mg based on investigator's judgement).

For patients escalated to 150 mg or 300 mg, no dose reduction can be performed at a later stage.

Subjects will continue to be on background methotrexate (MTX) (if they were already taking MTX at the start of core study CAIN457F2306) throughout the study. The dose of MTX may be adjusted as deemed appropriate by the investigator.

In addition subjects will be allowed to start or adjust the dose of corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) as deemed appropriate by the investigator.

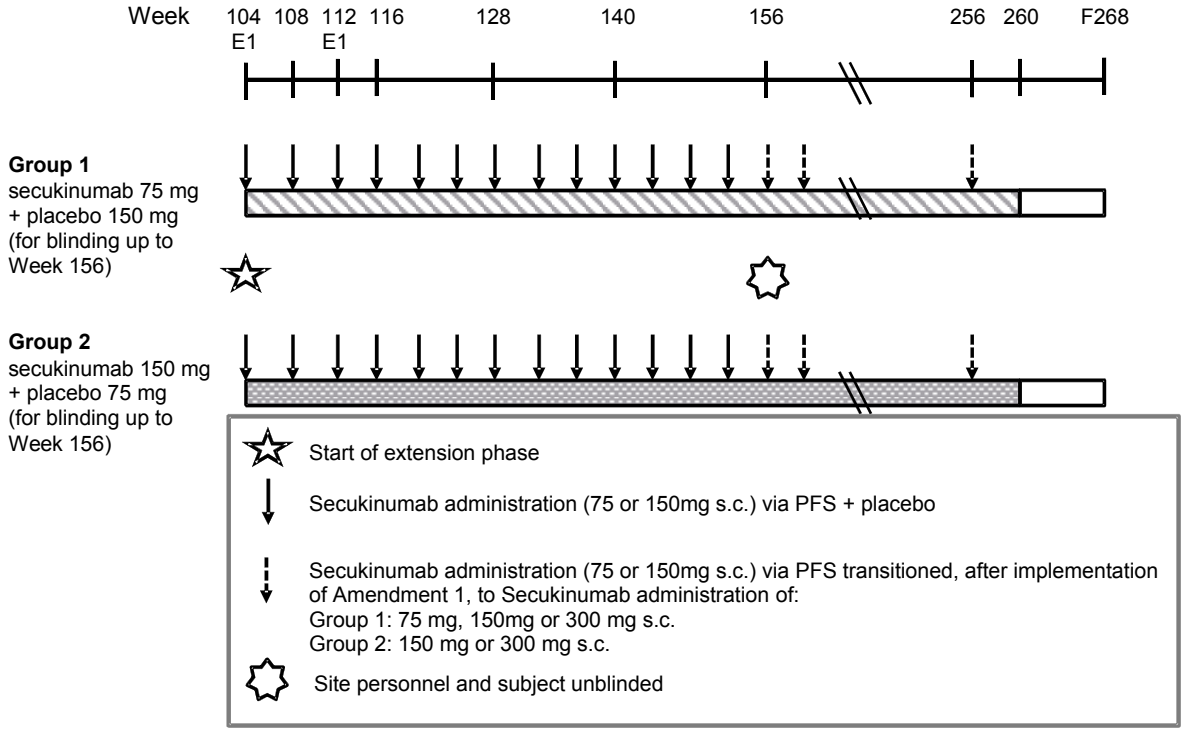
Before enrolment in this extension study, all subjects electing to continue will sign an Informed Consent form. After approval and implementation of Amendment 1, all subjects electing to continue will sign a new version of the Informed Consent form. Detailed instructions for self-administration of the s.c injection using the PFS formulation will be provided to each subject. Each injection will be administered into an appropriate injection site of the body. For the first 6 months of the extension study (up to Week 128), all injections will be performed at site. Starting from Week 132 subjects will have the choice of self-administration at home or continuing with administration at site, based on personal preference and the investigator's clinical judgment. Site staff or caregiver (once trained) will administer the injection to subjects who are not able or feel insecure to self-administer the PFS injection.

On-site visits to assess safety and efficacy will be scheduled at 4-16 week intervals during the study. Assessments for safety, efficacy, PK [redacted] will be performed according to the assessment schedule.

Efficacy assessments will be performed at regular intervals in this study, and after careful evaluation of disease status/activity, investigators should discontinue subjects who are deemed not to be benefiting from the study treatment, based on lack of improvement or worsening of their symptoms. Moreover, subjects are free to discontinue participation in the study at any time for lack of efficacy or for any other reason.

[redacted]

Figure 3-1 Extension Study (CAIN457F2306E1) design



3.2 Rationale of study design

This 3 year extension study will offer continuous secukinumab therapy to eligible subjects from the core study CAIN457F2306 and will provide sufficient long-term efficacy and safety data that could be used at the time of initial licensing submission or later reports to the health authority agencies. The regular assessments of disease activity ensure that subjects who are experiencing worsening of disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time.

The first year of this extension study was kept blinded to allow sufficient time for cleaning and locking of the 52-week data from the core study.

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

The doses and regimen selected for secukinumab phase III study (CAIN457F2306) were projected to deliver efficacy while at the same time ensuring subject safety. The proposal to continue treatment with s.c. doses of 75 mg and 150 mg administered every four weeks, as well as the additional treatment duration of up to 156 weeks (leading to an overall treatment period [core plus extension] of 260 weeks) was based on the need for long-term treatment exposure in subjects suffering from a chronic illness such as psoriatic arthritis.

The extension study initially continued to evaluate two doses (75mg and 150mg) using PFS in order to characterize the long-term safety profile for a higher and a lower secukinumab dose.

[redacted]

The analysis of the 2 Phase III studies conducted in PsA patients (see Rationale for Amendment 1) led to the conclusion that to maintain a clinically meaningful response during the entire duration of the extension study, the dose of secukinumab should be escalated from 75 mg sc every 4 weeks to 150 mg sc every 4 weeks for patients whose signs and symptoms may be improved with a higher dose, as judged by the investigator. Further, the dose should also be escalated to 300 mg sc every 4 weeks for patients currently on 75 mg or 150 mg dose, as judged by investigator.

The dose escalation from secukinumab 75 mg sc to 300 mg sc can be done either in one step or in two steps (first 150 mg sc and then 300 mg sc). These dose modifications are implemented through Amendment 1.

Secukinumab can be currently administered by intravenous infusion or by subcutaneous injection by reconstitution of lyophilisate. Drug delivery using this formulation either for intravenous infusion or subcutaneous injection requires commitment to regular clinic or hospital visits to allow for reconstitution and administration by allied health professionals. Subcutaneous injection through PFS offers the option of self-administration by the patient and is likely to provide a better treatment experience and added convenience. Patients 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, which can result in economic benefits to both patients 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).

Bioequivalence between the secukinumab lyophilisate and pre-filled syringe formulation has been established in study CAIN457A2106 in 150 healthy volunteers in which the pharmacokinetics, safety and tolerability of a PFS 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 PFS met the standard criteria for assuming bioequivalence. The use of the PFS was safe and well- tolerated. Therefore, in study CAIN457F2306E1, it is considered appropriate to use secukinumab in PFS for the administration of secukinumab in the same doses and regimen as in the core study (CAIN457F2306) which used the lyophilisate formulation.

3.4 Rationale for choice of comparator

There is no placebo control group or active comparator in this study given the purpose and main objectives. However, the current design will allow assessment of multiple doses in terms of long term efficacy and safety.

3.5 Purpose and timing of interim analyses/design adaptations

Interim analyses are planned in order to support regulatory filing and for purposes of publication after subjects complete year 1 (Treatment period 3), and year 2 (Treatment period 4) of treatment in this extension study. Additional analyses may be performed to support heath authority interactions, as necessary.

[redacted]

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring, and extensive guidance for the investigators provided in the Investigator's Brochure (IB).
As of July 2014, up to 10900 subjects have been enrolled into the secukinumab clinical program, of which over 8600 subjects have received secukinumab. Overall, healthy volunteers and patients across various indications (psoriasis, RA, AS, PsA, multiple sclerosis, uveitis, Crohn's disease, dry eye, polymyalgia rheumatica) have received secukinumab at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25mg to 300mg s.c.. Key results from the larger completed Phase II and III studies support a favorable benefit-risk profile for secukinumab in PsA patients.

Secukinumab has shown either preliminary or confirmed efficacy in several inflammatory diseases. The safety profile of secukinumab is primarily based on the aggregate safety data from 10 large completed phase II/III psoriasis trials. The evaluation of safety data from completed PsA trials did not show additional safety concerns. Secukinumab was generally safe and well-tolerated. The most frequently reported adverse events are infections, especially upper respiratory tract with secukinumab relative to placebo. There was an increase in mucosal or cutaneous candidiasis with secukinumab compared to placebo, but the cases were mild or moderate in severity, non-serious, and responsive to standard treatment.

There was a small increase in mild neutropenia cases with secukinumab compared to placebo. Common Toxicity Criteria (CTC) AE grade 3 neutropenia (<1.0-0.5×10^9/L) was uncommonly observed with secukinumab, most were transient and reversible without a temporal relationship to serious infections. Hypersensitivity reactions include urticarial and rare event of anaphylactic reaction to secukinumab were also observed in clinical studies.

Taking into account the available safety data for the individual risks outlined in the IB, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar or improved compared to approved cytokine targeting therapies. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring and extensive guidance to the investigators, provided in the current version of the Investigator's Brochure (IB).

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

4 Population

Eligible subjects are those who complete the full study treatment period of the core study (CAIN457F2306) and comply with the eligibility criteria of this extension study. These criteria include signed Informed Consent and/or Amended Informed Consent specific to CAIN457F2306E1 and the subject being deemed **by the investigator to benefit from continued secukinumab therapy**.

In total, 460 patients were enrolled in study CAIN457F2306E1.

[redacted]

4.1 Inclusion criteria

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

1. Subjects must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed
2. Subjects must have participated in core study CAIN457F2306, and must have completed the entire treatment period
3. Subjects must be 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 patients.

1. Any subject taking other concomitant biologic immunomodulating agent(s) except secukinumab
2. Any subject who is deemed not to be benefiting from the study treatment based upon lack of improvement or worsening of their symptoms
3. 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
4. Women of child-bearing potential (WoCBP), 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 partner sterilization (at least 6 m 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. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

[redacted]

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 study treatment

- **Investigational treatment**: Secukinumab 75mg/0.5mL solution or 150 mg/1mL solution for injection is provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe).
- **Placebo (for maintaining the blind till Week 152)**: Placebo to secukinumab 0.5mL solution or 1 mL solution for injection is provided in PFS for s.c. administration (a single use pre-filled 1mL long glass syringe). It contains a mixture of inactive excipients, matching the composition of secukinumab 75mg/150 mg.

At enrolment, subjects will be provided with detailed Instructions for Use (IFU) for self-administration of the PFS injection. The investigational treatment will be administered by the subject into the appropriate injection site of the body. The site staff or caregiver (once trained) will administer the PFS injection to subjects who are not able or feel insecure to self-administer the injection.

Note: The pre-filled syringes (**for use till Week 152**) are packed in a double blinded fashion and do not need to be prepared at the site. Secukinumab and placebo PFS are labeled as –

- AIN457 150mg/1mL/Placebo
- AIN457 75mg/0.5mL/Placebo

Note: The pre-filled syringes (**for use starting at Week 156**) are packed in an open label fashion and do not need to be prepared at the site. Secukinumab PFS are labeled as –

- AIN457 75mg/0.5mL
- AIN457 150mg/1mL

5.1.2 Additional study treatment

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

[redacted]

5.2 Treatment arms

All subjects will initially continue to receive the same dose of secukinumab they were receiving during the treatment period of the core study (CAIN457F2306). No re-randomization is planned.

Subjects from the two treatment arms will receive following treatments:

Till Week 152

- Group 1: secukinumab 75 mg plus placebo 1mL once every four weeks till (and including) Week 152
- Group 2: secukinumab 150 plus placebo 0.5mL mg once every four weeks till (and including) Week 152

Starting with Week 156, after approval and implementation of Amendment 1, the allowed doses within both treatment arms will be modified as described below.

- Group 1: secukinumab 75 mg once every four weeks till (and including) Week 256. After implementation of Amendment 1: secukinumab 75 mg, 150 mg or 300 mg.
- Group 2: secukinumab 150 mg once every four weeks till (and including) Week 256. After implementation of Amendment 1: secukinumab 150 mg or 300 mg.

The dose should be escalated from 75 mg to 150 mg sc for patients whose signs and symptoms are not fully controlled, as judged by the investigator, with the current 75 mg. Further the dose should also be escalated to 300 mg for patients currently on 75 mg or 150 mg dose, and whose signs and symptoms are not controlled well, as judged by investigator. The dose escalation from secukinumab 75 mg sc to 300 mg sc can be done either in one step or in two steps (first 150 mg sc and then 300 mg sc based on investigator's judgement). These dose modifications are implemented through Amendment 1.

As this long term study extends the pivotal registration study CAIN457F2306 by an additional 3 years it may be affected by agency review or potential product approval considerations. If the product is approved during study conduct, dose groups in this extension study may be amended (via a future protocol amendment) based on eventual agency recommendations for product usage in this indication.

5.3 Treatment assignment, randomization

There is no re-randomization in this extension study. At Week 104E1, all eligible subjects from core study will be enrolled via Interactive Response Technology (IRT) and will continue to receive same dose of secukinumab that they were receiving during the treatment period of core study CAIN457F2306. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will then specify a unique medication number for the first package of investigational treatment to be dispensed to the subject.

[redacted]

5.4 Treatment blinding

This will be a double-blind, double-dummy treatment trial **till Week 156**. Subjects and investigative site staff will remain blinded to the identity of the treatment until Week 156, using the following methods:

1. Randomization/treatment assignment data (from the core study) are kept strictly confidential until the time of unblinding and will not be accessible by subjects or investigative site staff
2. The identity of the treatments will be concealed by the use of investigational treatments that are all identical in packaging, schedule of administration and appearance

A double-dummy design is used because the identity of the study treatments (PFS) (75mg vs. 150mg) cannot be disguised due to their different volumes (0.5 ml vs. 1.0 ml).

Up to Week 156, unblinding investigative site staff will only occur in the case of subject emergencies (see Section 5.5.10).

Starting at Week 156, the treatment arm for individual subjects will be unblinded and the study will be conducted open-label.

5.5 Treating the subject

5.5.1 Subject numbering

Each subject is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a subject, the Subject Number will not be reused. This being an extension study, the subject numbers will remain same as that of core study CAIN457F2306; new subject numbers will not be assigned.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

The investigational treatment packaging has a 2-part label. A unique medication number printed on each part of this label corresponds to one of the two treatment arms. 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 132, if subjects opt for domiciliary treatment/home administration (at time points specified in Table 6-1, Table 6-2, and Table 6-3) the investigator will dispense, via IRT, an appropriate number of investigational treatment packages for domiciliary administrations. Detailed instructions on the self-administration of the study treatment will be described in the IFU. The IFU will be provided to each subject and 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.

The investigator must maintain an accurate record of the receipt 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 treatments (75 mg secukinumab or 150 mg secukinumab; after implementation of Amendment 1 secukinumab 75 mg, 150 mg or 300 mg) will be self-administered subcutaneously by subjects every four weeks throughout the study. The caregiver or site staff will administer the injection only to those subjects who are not able to self-administer the PFS injection.

Each subject will require two PFS per dose (i.e. two uniquely numbered medication packages) till (and including) Week 152. Starting at Week 156 and implementation of Amendment 1, subject will require one or two PFS per dose, depending on the dose they are assigned to as per investigator's judgement. Week 156 is the beginning of the open-label study period.

Up to Week 128, all doses of study treatment will be self-administered by the subject at the study site after the study visit assessments have been completed. Starting at Week 132 the subjects will be allowed to self-administer the PFS at home.

All study medication packages assigned to the subject during the study will be in the IRT database. It shall be recorded on the corresponding eCRF(s) whether the subject self-administered the PFS, or whether site staff or the caregiver administered the PFS and whether it was administered at home or at site.

The PFS will be provided by site staff to the subject, who will self-administer the injections at the specified study time point. Detailed instructions for self-administration of study treatment will be described in the IFU that are to be provided to each subject.

Initially self-injection will take place under the supervision of a site staff member. At Week 104E1 visit the subjects will be instructed by the site staff, using the IFU, on how to self-inject via PFS. Subjects will be asked to raise questions (if any), and then to proceed with

[redacted]

self-injection. The first study treatment administration will occur at the Week 104E1 visit after inclusion/exclusion criteria have been confirmed, all study scheduled assessments have been performed and the scheduled blood samples have been drawn.

At subsequent site visits, subjects will be asked to refer to the IFU and to proceed with self-injection.

At each subsequent study visit at site, all study assessments, including the completion of Patient Reported Outcomes (PROs) and pre-dose blood sample collection (wherever required) (Table 6-1, Table 6-2 and Table 6-3), should be completed prior to the self-administration of the study treatment.

All dosages dispensed to the subject and all dose changes during the study must be recorded on the Dosage Administration Record eCRF. 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. For those subjects who opt for domiciliary / home administrations (at protocol specified time points) site staff will dispense (via IRT), at the prior site visit, an appropriate number of investigational treatment packages for the applicable upcoming domiciliary administrations.

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

Administration

Secukinumab solution for s.c. injection will be provided in PFS. Two s.c. injections should be self-administered at each visit / time-point (secukinumab 75mg in 0.5mL plus placebo 1mL or secukinumab 150mg in 1mL plus placebo 0.5mL) till (and including Week 152). Starting at Week 156, placebo injections will not be required. Hence, upon implementation of Amendment 1, one or two s.c. injections would be dispensed for each dosing time point, depending on the secukinumab dose the patient is assigned to by the investigator.

Subjects will be instructed at Week 104E1 by site staff on how to self-inject secukinumab via PFS, in accordance with the IFU. The study treatment solution should be injected subcutaneously into an appropriate injection site, and each injection should be given at a different site.

Each new injection should be given at least one inch from the previously used site. If subject chooses the abdomen, 2 inches area around navel should be avoided. Investigational treatment should not be injected into areas where the skin is tender, bruised, red, or hard, or where the subject has scars or stretch marks. Injection sites should be rotated to reduce the risk of reaction.

Single syringes will be packed in individual boxes. The boxes containing the PFS with study treatment solution should be kept at 2 to 8°C (36°F to 46°F, do not freeze) and protected from light. Prior to administration, the unopened boxes containing the PFS should be allowed to come to room temperature in a place protected from light for approximately 20 minutes. Used

[redacted]

syringes should be disposed immediately after use in a sharps container OR according to the regulatory requirements in the respective country.

The caregiver or site staff will administer the injection only to those subjects who are not able to self-administer the PFS injection.

Domiciliary administration

Starting with week 132 (after initial 24 weeks of extension study of self-administered treatment under the supervision of site staff), subjects will be allowed to self-administer the PFS at home when they are not visiting the site for any other trial related procedures. The trial related safety and efficacy procedures will be conducted every 12-16 weeks during Treatment Periods 3, 4 and 5.

The subjects will be allowed to self-administer treatment at home (starting from Week 132) only if they have exhibited correct use for self-administering the PFS at the site during the first 24 weeks of treatment. At such time points, if requested by subjects, a caregiver would also be allowed to administer study medication after having received proper training by site staff and having exhibited ability to perform the injection procedure to the subject at the site.

It should be recorded on the corresponding eCRF(s) whether the subject self-administered the PFS and whether it was administered at home or at the site.

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

If the subject is not able / not confident to self-administer the PFS, and the caregiver is unable/unwilling to perform the injection, he/she should visit the site every 4 weeks during the treatment period and site staff will administer the PFS.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted until Week 156.

After approval and implementation of Amendment 1, patients previously treated with secukinumab 75 mg may receive either 75 mg, 150 mg or 300 mg, and patients previously treated with secukinumab 150 mg may receive 150 mg or 300 mg, as deemed appropriate by the investigators. The decision may be taken at any on-site visit. When dose escalation has been performed for one patient, no dose reduction can be performed at a later stage.

Study treatment interruption is also not permitted with the following exceptions:

- 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

[redacted]

administered due to a medical urgency, study treatment should be interrupted for 12 weeks.

The reason for any study treatment interruption must be recorded on the corresponding eCRF page.

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. All medication changes must be recorded in the Prior/ Concomitant medications eCRF page.

Subjects will continue to be on background MTX (if they were already taking MTX at the start of core study CAIN457F2306) throughout the study. The dose of MTX may be adjusted as deemed appropriate and necessary at the investigator's discretion in this extension study.

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

5.5.7 Concomitant treatment

The investigator should instruct the subject to notify the study site of any new medications he/she takes after enrollment into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after enrollment must be recorded on the Concomitant medications Dose Administration Record in the CRF.

Methotrexate

In subjects on MTX , dose of MTX (≤25 mg/week) may be adjusted as deemed appropriate and necessary at the investigator's discretion.

Folic acid

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

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.

[redacted]

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

Subjects taking NSAIDs, low strength opioids or paracetamol/acetaminophen PRN can continue to do so in the study; however, they must 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

Prohibited treatments	Action to be taken
Any other biologic agent (e.g. etanercept, infliximab, adalimumab)*	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

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

- Withdrawal of informed consent
- Emergence of the following adverse events:
  - 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 keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed
  - Life-threatening infection
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 1).
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab

[redacted]

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

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

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

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

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

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature withdrawal from the study and record this information on the appropriate Study Phase Disposition CRF.

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 returns after an additional 8 weeks for a final follow-up visit (12 weeks after last study treatment, see Table 6-1, Table 6-2 and Table 6-3). The final visit should be performed before any new treatment is initiated.

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, emails etc.

Replacement

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

5.5.10 Emergency breaking of treatment assignment

During the blinded study period, emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency 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 Leader (GTL) that the code has been broken.

[redacted]

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 the protocol number (CAIN457F2306E1), investigational treatment name if available, subject number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

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 the IRT as soon as possible to record the subject's study completion (Visit F268) and/or discontinuation.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include 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 as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing 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. Subjects should not receive study medication within less than 2 weeks after the previous administration.

[redacted]

During the treatment periods, subjects may be seen at an unscheduled visit, e.g. if they experience deterioration of their condition, or AEs that in the opinion of the investigator need intervention or repeated laboratory testing. During these unscheduled visits, study treatment will not be administered. Subjects who discontinue study treatment will continue to be followed for safety assessments. They are not considered withdrawn from the study.

Subjects who discontinue study treatment before completing the study, and those who prematurely withdraw from the study for any reason should be scheduled for a study visit 4 weeks after their last study treatment administration, at which time all the assessments listed for EoT for the given treatment period (Week 156 or 208 or 260) will be performed (see Section 5.5.9). Subjects will then return to the study site 12 weeks after the last study treatment administration for further assessments as indicated under the follow-up visits (F268).

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 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.

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

Order of assessments:

- Subject to complete PROs prior to any investigator assessments.
- Investigator to complete investigator assessments (Physician's global assessment of disease activity)
- All remaining study visit procedures (e.g., laboratory sample collection, vital signs measurements etc.) must be completed prior to study treatment dosing.
- Study treatment administration (administration by site staff or self-administration as per assessment schedule).

[redacted]

Table 6-1 Assessment schedule (Week 104E1 to Week 156)

Epoch	**Treatment Period 3**													
Week (relative to baseline of core study CAIN457F2306)	**104E1**	**108**	**112E1**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156 and TD and/or PSW**
Informed consent	X													
Inclusion/exclusion criteria	X													
Physical examination	*			S			S			S				S
Weight	*						X							X
Vital signs	*			X			X			X				X
ECG	*						X							X
Administration of s.c. study treatment via PFS at study site	X	X	X	X	X	X	X			X				X
Administration of s.c. study treatment via PFS at home[1]								X	X		X	X	X	
Hematology, blood chemistry, urinalysis	*			X			X			X				X
Urine pregnancy test[2]	*			X			X			X				X
Concomitant medication/non-drug therapy	Update as necessary throughout the study													
AE/SAE (including injection site reaction, occurrence of infection)	Update as necessary throughout the study													
X-Ray (hands/wrists + feet)	*													X[5]
ANA	*													X
Anti-dsDNA	*													X
[redacted]														
PK assessments (at pre-dose)	*													X
High sensitivity C-Reactive protein (hsCRP)	*			X			X			X				X
Erythrocyte Sedimentation Rate (ESR)[2]	*			X			X			X				X
Tender and swollen joint counts (TJC78, SJC76)	*			X			X			X				X
Patient's assessment of PsA pain (VAS)	*			X			X			X				X
Patient's global assessment of disease activity (VAS)	*			X			X			X				X
Physician's global assessment of disease activity (VAS)	*			X			X			X				X
Health Assessment Questionnaire (HAQ-DI)	*			X			X			X				X

[redacted]

Epoch	**Treatment Period 3**													
Week (relative to baseline of core study CAIN457F2306)	**104E 1**	**108**	**112 E1**	**116**	**120**	**124**	**128**	**132**	**136**	**140**	**144**	**148**	**152**	**156 and TD and/or PSW**
[redacted]														
Lipids[4]	*						X							X
Cardiovascular panel	*													X
Treatment period 3 completion form														X

TD = Investigational treatment discontinuation; **PSW** = Premature subject withdrawal. Subjects who prematurely discontinue treatment or are withdrawn prematurely during treatment period 3 should return for assessments associated with Week 156 (4 weeks after last study treatment) and the follow-up visit (Week F268) 12 weeks after last study treatment.

X = assessment to be recorded in clinical data base

S = assessment to be recorded on source documents

* These assessments shall be conducted as part of the core study CAIN457F2306 and will not be repeated in this extension study

[1] Subjects who are unable to self-administer the PFS injection at home will visit the site and site staff will administer PFS injection for them

[2] Kits will be provided by central lab and tests are to be performed locally

[redacted]

[4] Fasting (more than 12 hours) samples to be obtained

[5] Subjects who discontinue will have their X-rays taken only if more than 6 months have elapsed since their last X-rays

[redacted]

Table 6-2 Assessment schedule (Week 160 to Week 208)

Epoch	**Treatment Period 4**												
Week (relative to baseline of core study CAIN457F2306)	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208 and TD and/or PSW**
Physical examination			S			S			S				S
Weight						X							X
Vital signs			X			X			X				X
ECG						X							X
Administration of s.c. study treatment via PFS at study site			X			X			X				X
Administration of s.c. study treatment via PFS at home[1]	X	X		X	X		X	X		X	X	X	
Hematology, blood chemistry, urinalysis			X			X			X				X
Urine pregnancy test[2]			X			X			X				X
Concomitant medication/non-drug therapy	Update as necessary throughout the study												
AE/SAE (including injection site reaction, occurrence of infection)	Update as necessary throughout the study												
X-Ray (hands/wrists + feet)													X[5]
ANA													X
Anti-dsDNA													X
[redacted]													
PK assessments (at pre-dose)													X
High sensitivity C-Reactive protein (hsCRP)						X							X
Erythrocyte Sedimentation Rate (ESR)[2]						X							X
Tender and swollen joint counts (TJC78, SJC76)						X							X
Patient's assessment of PsA pain (VAS)						X							X
Patient's global assessment of disease activity (VAS)						X							X
Physician's global assessment of disease activity (VAS)						X							X
Health Assessment Questionnaire (HAQ-DI)						X							X
[redacted]													

[redacted]

Epoch	**Treatment Period 4**												
Week (relative to baseline of core study CAIN457F2306)	**160**	**164**	**168**	**172**	**176**	**180**	**184**	**188**	**192**	**196**	**200**	**204**	**208 and TD and/or PSW**
[redacted]													
Lipids[4]						X							X
Cardiovascular panel													X
Treatment period 4 completion form													X

TD = Investigational treatment discontinuation; **PSW** = Premature subject withdrawal. Subjects who prematurely discontinue treatment or are withdrawn prematurely during treatment period 4 should return for assessments associated with Week 208 (4 weeks after last study treatment) and the follow-up visit (Week F268) 12 weeks after last study treatment.

X = assessment to be recorded in clinical data base

S = assessment to be recorded on source documents

[1] Subjects who are unable to self-administer the PFS injection at home will visit the site and site staff will administer PFS injection for them

[2] Kits will be provided by central lab and tests are to be performed locally

[redacted]

[4] Fasting (more than 12 hours) samples to be obtained

[5] Subjects who discontinue will have their X-rays taken only if more than 6 months have elapsed since their last X-rays

[redacted]

Table 6-3 Assessment Schedule (Week 212 to Week 260 and Follow-up)

Epoch	**Treatment Period 5**													**Post Treatment FU**
Week (relative to baseline of core study CAIN457F2306)	**212**	**216**	**220**	**224**	**228**	**232**	**236**	**240**	**244**	**248**	**252**	**256**	**260**	**268 and TD and/or PSW**
Physical examination			S			S			S				S	S
Weight						X							X	X
Vital signs			X			X			X				X	X
ECG						X							X	
Administration of s.c. study treatment via PFS at study site			X			X			X					
Administration of s.c. study treatment via PFS at home[1]	X	X		X	X		X	X		X	X	X		
Hematology, blood chemistry, urinalysis			X			X			X				X	X
Urine pregnancy test[2]			X			X			X				X	X
Concomitant medication/non-drug therapy	Update as necessary throughout the study													
AE/SAE (including injection site reaction, occurrence of infection)	Update as necessary throughout the study													
X-Ray (hands/wrists + feet) (until implementation of Amendment 2)													X[5]	
ANA													X	
Anti-dsDNA													X	
[redacted]														
PK assessments (at pre-dose)													X	X
High sensitivity C-Reactive protein (hsCRP)						X							X	X
Erythrocyte Sedimentation Rate (ESR)						X							X	X
Tender and swollen joint counts (TJC78, SJC76)						X							X	
Patient's assessment of PsA pain (VAS)						X							X	
Patient's global assessment of disease activity (VAS)						X							X	
Physician's global assessment of disease activity (VAS)						X							X	
Health Assessment Questionnaire (HAQ-DI)						X							X	

[redacted]

Epoch	**Treatment Period 5**													**Post Treatment FU**
Week (relative to baseline of core study CAIN457F2306)	**212**	**216**	**220**	**224**	**228**	**232**	**236**	**240**	**244**	**248**	**252**	**256**	**260**	**268 and TD and/or PSW**
[redacted]														
Lipids[4]						X							X	
Cardiovascular panel													X	
Treatment period 5 completion form													X	
Follow-up period completion form														X

TD = Investigational treatment discontinuation; **PSW** = Premature subject withdrawal. Subjects who prematurely discontinue treatment or are withdrawn prematurely during treatment period 5 should return for assessments associated with Week 1260 (4 weeks after last study treatment) and the follow-up visit (Week F268) 12 weeks after last study treatment.

X = assessment to be recorded in clinical data base

S = assessment to be recorded on source documents

[1] Subjects who are unable to self-administer the PFS injection at home will visit the site and site staff will administer PFS injection for them

[2] Kits will be provided by central lab and tests are to be performed locally

[redacted]

[4] Fasting (more than 12 hours) samples to be obtained

[5] Subjects who discontinue will have their X-rays taken only if more than 6 months have elapsed since their last X-rays. After implementation of Amendment 2, no X-Rays need to be obtained

[redacted]

6.1 Information to be collected on screening failures

Not applicable since data on subjects who do not enter extension study after completion of the core study (CAIN457F2306) will be collected in the same study database.

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 (CAIN457F2306) will be carried forward in this extension study (CAIN457F2306E1). Both, the core study (CAIN457F2306) and extension study (CAIN457F2306E1) 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.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in Section 5.5.5. Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

6.4 Efficacy

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

- American College of Rheumatology (ACR) 20, 50 and 70 responses
- Swollen Joint Count (SJC)/Tender Joint Count (TJC)
- Patient's assessment of PsA pain intensity (VAS scale)
- Patient's global assessment of disease activity (VAS scale)
- Physician's global assessment of disease activity (VAS scale)
- Health Assessment Questionnaire – Disability Index (HAQ-DI©)
- Erythrocyte Sedimentation Rate (ESR) and high sensitivity C-Reactive Protein (hsCRP)
- [redacted]
- [redacted]
- Disease Activity Score (DAS28) [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- Physician global fingernail disease severity assessment (VAS)

All efficacy assessments should be performed prior to administration of study treatment.

Details relating to the administration of all PROs are provided in Appendix 10.

6.4.1 American College of Rheumatology (ACR) response

The primary efficacy variable is the clinical response to treatment according to ACR20, ACR50 and ACR 70 improvement in disease activity over time up to Week 260. A subject will be considered a responder according to ACR20 criteria if he/she has at least:

- 20% improvement in tender 78-joint count
- and 20% improvement in swollen 76-joint count
- and 20% improvement in at least 3 of the following 5 measures:
  - Patient's assessment of PsA pain (measured on a VAS 100 mm)
  - Patient's global assessment of disease activity (measured on a VAS 100 mm)
  - Physician's global assessment of disease activity (measured on a VAS 100 mm)
  - Patient self-assessed disability (Health Assessment Questionnaire [HAQ-DI©] score)
  - Acute phase reactant (C-reactive protein [hsCRP] or ESR)

Similarly, a subject will be considered a ACR50 (or ACR70) responder if he/she shows at least 50% (or 70%) improvement as per the above mentioned criteria.

The ACR response is to be assessed at the visits/time points shown in Table 6-1, Table 6-2 and Table 6-3.

[redacted]

6.4.1.1 Tender 78 joint count and swollen 76 joint count

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

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

[redacted]

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

6.4.1.2 Patient's assessment of PsA pain intensity

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

6.4.1.3 Patient's global assessment of disease activity

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

6.4.1.4 Physician's global assessment of disease activity

The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question *"Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today"*. To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that patient.

6.4.1.5 HAQ-DI

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

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

Details relating to the administration of all PROs are provided in Appendix 10.

6.4.1.6 High Sensitivity C-reactive protein (hsCRP)

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

[redacted]

Since the results of this test may unblind study personnel, the hsCRP results from samples collected during the treatment period till Week 152 will be revealed only during the open label part of this study.

6.4.1.7 Erythrocyte sedimentation rate (ESR)

Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at scheduled visits (see Table 6-1, Table 6-2 and Table 6-3).

6.4.2 Radiographic assessments

Separate radiographs of each hand/wrist (PA) and each foot (AP) will be taken at Week 156, 208 and 260.

From time of implementation of Amendment 2, radiographs at Week 260 will not be obtained as part of the study.

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

[redacted] Radiologists will be trained on the X-ray acquisition and further details will be provided in a manual for the radiologists, e.g. joint placement and beam positioning.

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

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

Subjects who discontinue study treatment before the end of the trial, hands/wrists and feet X-rays will be taken at the time of study treatment discontinuation. However, if a radiograph of hands/wrist and feet was performed within last 6 months of early discontinuation visit then it does not need to be performed. Likewise, if a scheduled X-ray at Week 156, 208 or 260 is scheduled less than 6 months after any prior hands/wrists and feet X-rays, it does not need to be performed. All following X-rays will be performed as scheduled.

[redacted]

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

[redacted]

6.4.4 DAS28 [redacted]

The DAS28 is a measure of disease activity based on Swollen and Tender Joint Counts, ESR or CRP and the Patient Global Assessment. A DAS28 score > 5.1 implies active disease, ≤ 3.2 low disease activity, and < 2.6 remission. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

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

6.4.12 Appropriateness of efficacy assessments

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

6.5 Safety

- Evaluation of AE/ SAEs
- Physical examination
- Vital signs
- Weight
- Electrocardiogram
- Local tolerability (injection site reactions)

[redacted]

- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- [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

6.5.1 Physical examination

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

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

6.5.2 Vital signs

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) (without shoes) will be measured.

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

Height will not be measured in this study as it is already measured in the core study CAIN457F2306.

6.5.4 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected listed below (except urinalysis, UPT and ESR). 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.

[redacted]

6.5.4.1 Hematology

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

6.5.4.2 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.

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 AEs (see Section 7).

6.5.6 Pregnancy and assessments of fertility

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

All women who are not surgically sterile at screening 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 treatment until serum β-hCG is performed and found to be negative. If positive, the subject must be discontinued from the trial.

[redacted]

6.5.7 Tolerability of secukinumab

Tolerability will be assessed by adverse events, laboratory values, injection site reaction [redacted]

[redacted]

6.5.9 Additional parameters

Blood will be obtained at time points indicated in Table 6-1, Table 6-2 and Table 6-3 for assessing ANA and anti-dsDNA antibodies.

6.5.10 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in PsA and for this subject population. The specific focus on infection rates in addition to the other safety measures ensures the ability to deliver data on a critical safety endpoint for this class of therapy. The radiation exposure that results from X-ray measurements is not necessary for medical care but is intended for research purposes only. The total amount of radiation from all X-ray measurements performed in this study (3 X-rays of hands/wrists and feet) is estimated to be around 1 mSv over 3 years, and is approximately equivalent to a uniform whole body exposure of 26 weeks of exposure to natural background radiation. For effective radiation doses under 3 mSv (300 mrem), the risk is considered to be "minimal". Therefore, the radiation exposure in this study involves minimal risk and is

[redacted]

necessary to obtain the research information desired and ensure reliable safety measures before the treatment with a biologic.

6.6 Other assessments

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

6.6.1 Health-related Quality of Life

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

- HAQ-DI (see Section 6.4.1.5)
- [redacted]
- [redacted]

All questionnaires will be available, where possible, in the local languages of the participating countries and should be completed by subjects before they see the study physician. Only the original paper questionnaires provided can be used (i.e. these pages must not be photocopied)

All questionnaires will be completed at the defined visits/ time points listed in Table 6-1, Table 6-2 and Table 6-3 and prior to the subject seeing the investigator for any clinical assessment or evaluation. The questionnaires will be in the respondent's local language. The subject should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses. The original questionnaires will be kept with the subject's file as the source document.

Completed questionnaires should be reviewed and assessed by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also for any unsolicited comments written by the subject. This assessment should be documented in the source records. If AEs or SAEs are confirmed the investigator should record the events as per instructions given in the relevant section of the protocol (see Section 7). Investigators should not encourage the subjects to change the responses reported in the completed questionnaires.

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

[redacted]

[redacted]

[redacted]

6.6.2 Pharmacokinetics

Pharmacokinetic (PK) samples will be obtained for all subjects, and secukinumab concentrations will be assessed in serum. The PK samples will be collected pre-dose at scheduled visits as indicated in Table 6-1, Table 6-2 and Table 6-3. The PK Sample Log can be found in the Appendix 2.

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

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

The bioanalyst will provide the samples' concentration data to the team under blinded conditions. The bioanalyst will keep this information confidential until Week 156

PK sample handling, labeling and shipment instructions

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

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

Analytical methods

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

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

[redacted]

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 patient 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: 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 investigational 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)

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

[redacted]

hospitalization is for*:*

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since 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 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.

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 investigational treatment or 30 days after the subject has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

[redacted]

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to *each specific component of study treatment, (if study treatment consists of several components)* complete the SAE Report Form in English, and submit the completed form to Novartis within 24 hours of becoming aware of the event. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.
Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the 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.

7.3 Liver safety monitoring

There has been no safety signal for liver toxicity with secukinumab to date in over 6000 patients exposed and from a mechanism of action standpoint there is no effect of blocking IL-17A on the liver. Liver function tests will be obtained at regular intervals but special measures for liver safety monitoring are not planned.

7.4 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 of any pregnancy outcome.

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

[redacted]

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 investigational 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 the data entered into the electronic Case Report Forms are complete and accurate. After database lock or upon premature site discontinuation, the investigator will receive copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff or designee will 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 will be 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

[redacted]

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 NovDTD Reference List, which employs the Anatomical Therapeutic Chemical (ATC) 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.

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

Randomization codes and 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. All the data from the vendor database will be sent electronically to Novartis.

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

8.4 Data Monitoring Committee

A 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 charter. As of Amendment 1 and based on the safety results of studies CAIN457F2306 and CAIN457F2312, the DMC review will no longer be required.

8.5 Adjudication Committee

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

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

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 as appropriate to evaluate the efficacy of the treatment regimens.

[redacted]

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 with at least one post baseline assessment of efficacy. Subjects will be analyzed according to the treatment assigned to.

Safety set: The safety set includes all subjects enrolled in the study who took at least 1 dose of study treatment during the study. Subjects will be analyzed according to the treatment received.

9.2 Subject demographics and other baseline characteristics

Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group and for all subjects in the FAS population of 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

Study treatment

The analysis of study treatment data will be based on the safety set. The number of active injections received will be presented by treatment group. The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of subjects with cumulative exposure levels will be presented.

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

[redacted]

The number and percentage of subjects receiving concomitant psoriatic 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 psoriatic arthritis therapies previously.

9.4 Analysis of the primary variable(s)

9.4.1 Variable(s)

The primary efficacy variable(s) is the clinical response to treatment according to ACR20, ACR50 and ACR 70 improvement in disease activity over time up to Week 260. ACR response criteria denote the response (i.e., improvement) in signs & symptoms of the disease of a subject compared to baseline of the core study. The analysis of the primary variables will be based on the FAS. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

9.4.2 Statistical model, hypothesis, and method of analysis

No formal hypotheses are planned for this study.

The proportion of subjects meeting the ACR criteria (ACR20, ACR50, and ACR70) will be descriptively summarized for each treatment group. Treatment efficacy will be evaluated by the 95% confidence interval of the proportion of subjects responding to treatment according to the ACR criteria. No statistical comparison is expected to be performed between treatment doses.

Results will be presented for the FAS, as well as subgroups by TNF-α status (naive or IR).

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 all baseline and post-baseline efficacy variables of interest during the trial.

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

9.4.4 Supportive analyses

Sensitivity analyses may be performed to assess the robustness of missing data handling. This may include multiple imputation for ACR20/50.

[redacted]

9.5 Analysis of secondary and exploratory 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), when available, will be presented. The 95% confidence intervals will be provided to evaluate the long-term efficacy of the treatments for the secondary variables of interest.

No statistical comparisons between treatments will be provided for the analysis of secondary and exploratory variables.

Secondary and exploratory variables include:

- The change from baseline in HAQ-DI
- The proportion of subjects with improvements from baseline in HAQ-DI ≥ minimal clinically important difference (MCID)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- The change from baseline in DAS28
- The proportion of subjects achieving low disease activity (DAS28 ≤ 3.2) and disease remission as defined by DAS28 (DAS28 < 2.6)
- [redacted]
- [redacted]
- [redacted]
- [redacted]

9.5.2 Safety variables

Adverse events

Treatment emergent adverse events (i.e. events started after the first dose of secukinumab in core study or events present prior to the first dose of secukinumab 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

[redacted]

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 events, a summary of those types of events as reported by the investigator and confirmed by adjudication will be provided.

Laboratory data

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

[redacted]

Vital signs

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

ECG

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

[redacted]

[redacted]

9.5.4 Pharmacokinetics

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

Pharmacokinetic variables

The following pharmacokinetic parameter will be determined: Cmin,ss. Cmin,ss will be determined using Phoenix software. Individual serum concentrations in µg/ml will be listed. All concentrations below the limit of quantification or missing data will be labeled as such in the concentration data listings. Concentrations below the Limit of Quantification will be treated as zero in summary statistics for concentration data only.

[redacted]

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

Statistical methods for pharmacokinetic analyses

Summary statistics by visit/time will be provided for the above mentioned parameter and will include arithmetic and geometric means, SD, median, minimum and maximum. Individual concentrations will be listed by subject.

[redacted]

9.6 Interim analyses

Interim analyses are planned in order to support regulatory filing and for purposes of publication after subjects complete year 1 (Treatment period 3), and year 2 (Treatment period 4) of treatment in this extension study. Additional analyses may be performed to support health authority interactions, as necessary.

9.7 Sample size calculation

It is estimated that 80~90% of subjects originally randomized to secukinumab will complete the entire treatment period and be eligible for entry into the extension (320~360 subjects). Likewise, 70~80% of the subjects originally randomized to placebo (140~160 subjects) will be eligible. In total, it is estimated that 460~520 subjects will be eligible for enrollment in this extension study.

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

[redacted]

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.

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.

[redacted]

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.

12 References

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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. Any action based on these laboratory values should be discussed with Novartis personnel.

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

	Notable criteria	
Laboratory variable	Standard units	SI units
Liver function and related variables		
SGOT (AST)	>3 x ULN	>3 x ULN
SGPT (ALT)	>3 x ULN	>3 x ULN
Total 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]

13.2 Appendix 2: Blood collection logs

[redacted]

Table 13-3 Blood collection log for pharmacokinetics

Week	Timepoint	Volume	PK sample number	Dose Reference ID
Week 156	26208 h (pre-dose)	2 ml	8	1
Week 208	34944 h (pre-dose)	2 ml	9	1
Week 260	43680 h (anytime)	2 ml	10	1
Week 268	45024 h (anytime)	2 ml	11	1

[redacted]

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

Number of tender joints:

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

The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 ankle, 2 tarsus, 10 metatarsophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal joints of the feet.

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

Number of swollen joints:

Joints are to be scored as either swollen (1) or not swollen (0). The 76 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Patient's assessment of PsA pain

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

Patient's global assessment of disease activity

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

Physician's global assessment of disease activity

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

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI©

ACR20/50/70*

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

- in the two following measures:
  - Tender joint count
  - Swollen joint count

[redacted]

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

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

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

Reference: (Felson 1995)

[redacted]

13.5 Appendix 5: Disease Activity Score 28(DAS28)

The Disease Activity Score 28 (DAS28) is a combined index to measure the disease activity in patients with RA. [redacted]

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

Using the DAS, several thresholds have been developed for high disease activity, low disease activity or remission. Also response criteria have been developed based on the DAS28, so when the DAS28 of a patient is measured at two time-points (e.g. before the start of a treatment and after 3 months), the patients clinical response can be assessed.

The DAS28 in clinical trials

Comparing the DAS28 from one patient on two different time-points, it is possible to define improvement or response. [redacted]

[redacted]

Tender and swollen 28-joint count:

The 28-joints assessed for DAS28 include the 2 shoulders, 2 elbows, 2 wrists, 2 knees, 10 metacarpophalangeal (MCP) and 10 proximal interphalangeal (PIP) joints.

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

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

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

DAS28 = 0.56 * sqrt(TJC28 + 0.28 * sqrt(SJC28) + 0.70 * ln(ESR) + 0.014 * GH

[redacted]

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

Disease Activity Scores using C-reactive protein

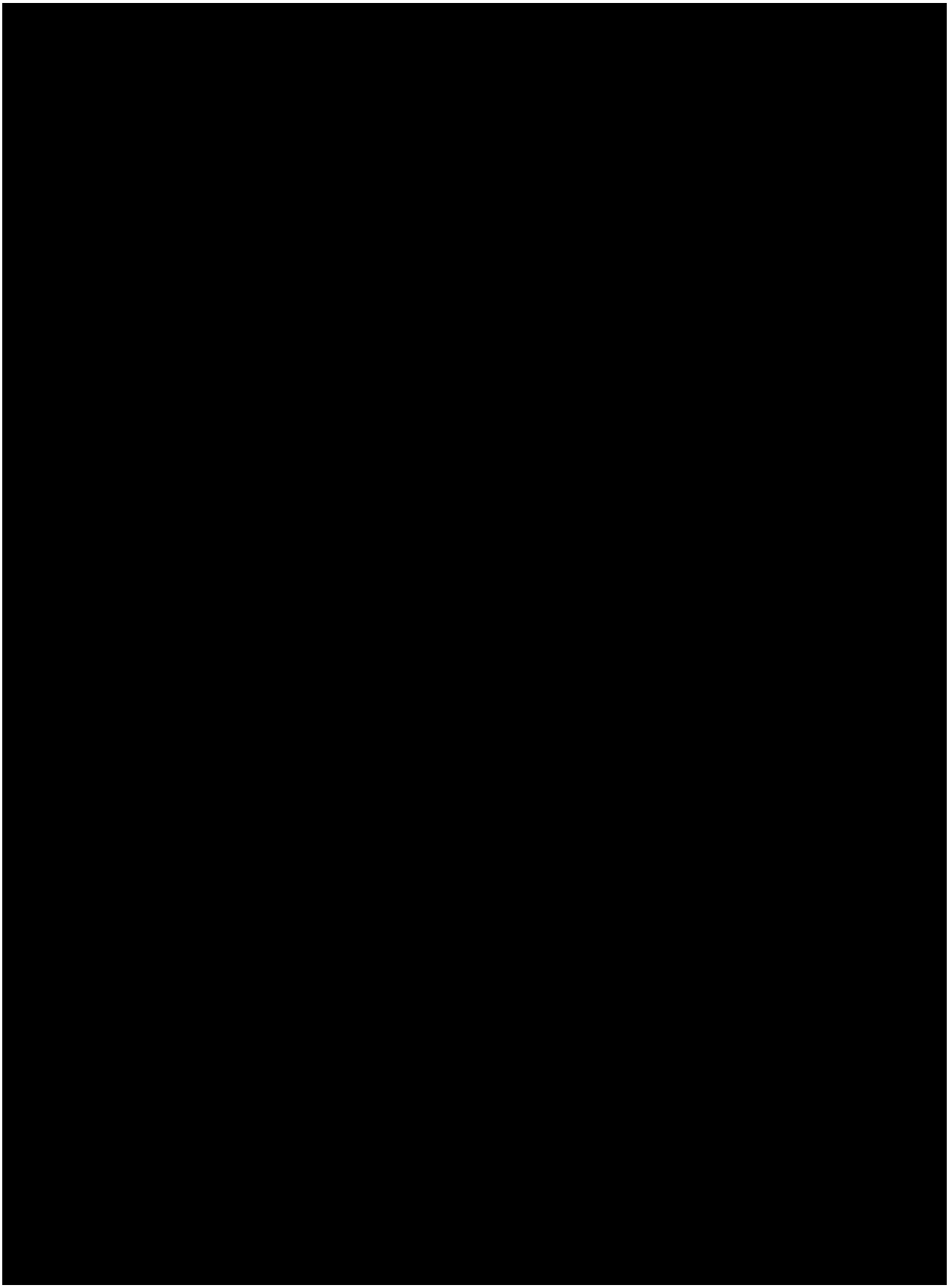
C-reactive protein (CRP) or hsCRP may be used as an alternative to ESR in the calculation of the DAS28, using the formulas below. CRP is a more direct measure of inflammation than ESR, and it is more sensitive to short-term changes (Kushner 1991). CRP production is associated with radiological progression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

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

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

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

[redacted]



13.9 Appendix 9: Health Assessment Questionnaire (HAQ) ©

The HAQ© (Fries JF et al. 1980) is a validated measure of physical disability and functional status. It has four dimensions: disability, pain, drug side effects and dollar costs, although, the latter three are rarely used in clinical trials. In this trial only the disability dimension will be used. The disability dimension consists of 20 multiple choice items concerning difficulty in performing eight common activities of daily living; dressing and grooming, arising, eating, walking, reaching, personal hygiene, gripping and activities. Patients choose from four response categories, ranging from 'without any difficulty' to 'unable to do'. The ACR Rheumatology Committee on Outcome Measures in RA recommends the use of this questionnaire in clinical trials.

Scoring of the HAQ©

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

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

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

Within each of the 8 categories only the item indicating the most severe impairment contributes to the category score. If the patient requires the use of aids, devices, or help from another to accomplish any of the activities in an associated category, then the score for that category will be assigned the value 2, unless the score is already 3 (i.e. scores of 0 or 1 are increased to 2). Associated categories are defined in the "HAQ PACK". From the scores for each category a Standard Disability Index (SDI) is computed by summing the computed scores for each category and dividing by the number of categories answered. The SDI is not computed if the patient does not have scores for at least 6 categories. This SDI is the HAQ© score, which will be used in the statistical analyses of this instrument. The range for this score is (0, 3).

HAQ© Data Collection

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

[redacted]

to the attention of the patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

The investigator must complete the patient/visit information on the questionnaire and ensure that the site number, subject number and initials (if applicable) are identical to the Case Record Form. As there are no source data for this questionnaire, the data queries will be restricted to patient/visit information.

[redacted]

13.10 Appendix 10: Guidelines for administering the PRO questionnaires

Before trial start

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial and identify any items where a patient's response might highlight issues of potential concern. *For example, one question in the* [redacted] *If a patient responds 'most or all of the time', then the study coordinator should inform the study investigator.*

Before completion

1. Subjects should be provided with the correct questionnaire
   - At the appropriate visits, and
   - In the appropriate language
2. Subjects should have adequate space and time to complete the forms
3. Patients should be provided with a firm writing surface (such as a table or a clip board) and a pencil
4. Questionnaire should be administered before the clinical examination

During completion

1. Administrator may clarify the questions but should not influence the response
2. Only one response for each question
3. Subjects should initial and date the last page of the questionnaires
4. Also see 'Addressing Problems and Concerns'

After completion

1. Check for completeness and not for content*
2. Check for multiple responses that were made in error
3. Data should be transcribed from the completed questionnaire to the appropriate screen on the e-CRF / electronic device.
4. File completed questionnaire in the patient study files**

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

**If for some reason paper questioner is utilized for completion.

Addressing Problems and Concerns

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

[redacted]

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

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

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

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

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

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

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

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

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

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

The patient asks the meaning of a question/item

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

[redacted]

A General Information about all questionnaire(s):

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

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

[redacted]

13.11 Appendix 11: Study design of core study CAIN457F2306

The AIN457F2306 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).

At baseline (BSL), eligible subject were randomized to one of three treatment groups:

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

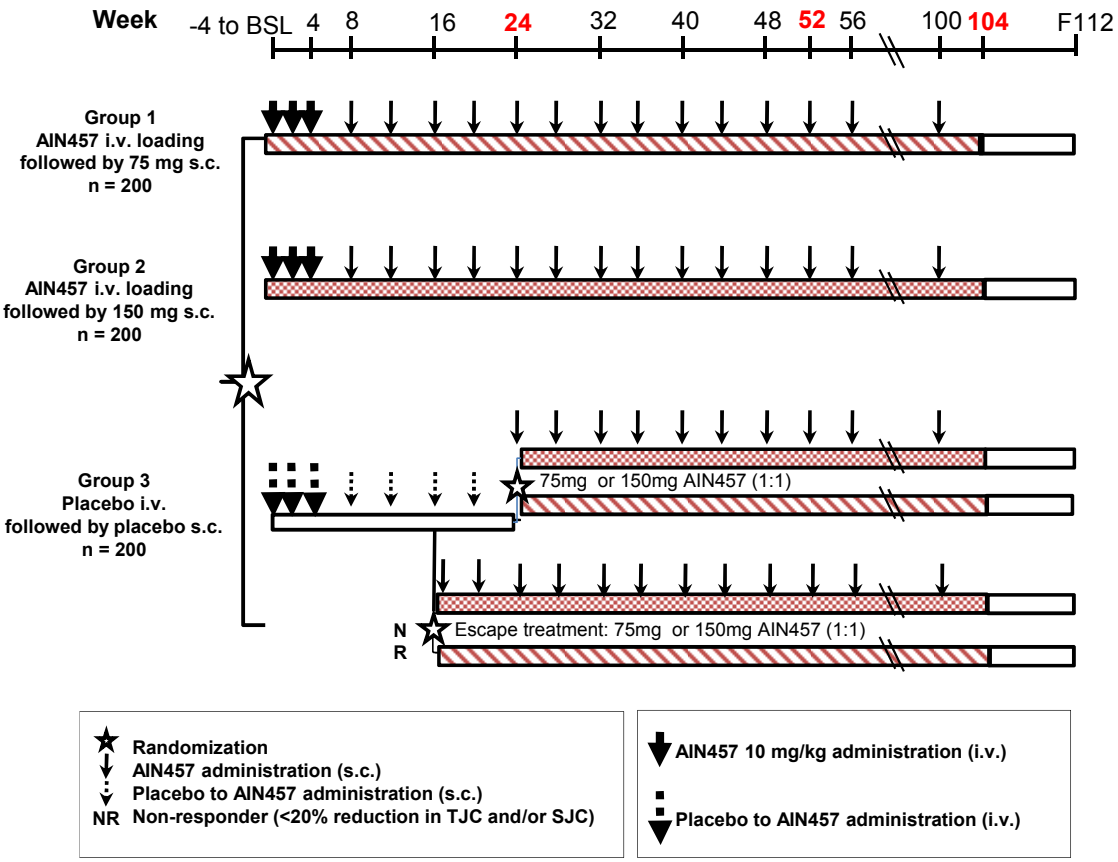
The subjects were stratified as either TNFα inhibitor incomplete responders (TNF-IR) or TNFα inhibitor naïve subjects. Approximately 30% of subjects were TNF-IR to ensure a representative population for the assessment of efficacy and safety.

At Week 16 (Visit 8), subjects were classified as responders (≥20% improvement from baseline in both tender and swollen joint counts) or non-responders. Subjects who were randomized to placebo at baseline were re-randomized by IRT to receive double blind treatment up to 2 years, as follows

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

[redacted]

Figure 13-1 Core Study (CAIN457 F2306) Design



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