NOVARTIS

Clinical Development

AIN457/ secukinumab

Clinical Trial Protocol CAIN457A2304E1 /NCT01640951

A multicenter, double-blind and open label, 4 year extension study of subcutaneous secukinumab in prefilled syringes, assessing long-term safety, tolerability and efficacy in subjects with moderate to severe chronic plaque-type psoriasis treated with either a fixed dose regimen or on a retreatment at start of relapse regimen

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CHMP	the European Union Committee for Medicinal Products for Human Use
CRF	Case Report/Record Form (paper or electronic)
CPO	Country Pharma Organization
CRO	Contract Research Organization
CS	Corticosteroid (s)
DLQI	Dermatology Life Quality Index©
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D	Euro-QoL 5-Dimension Health© Questionnaire
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnaire-Disability Index
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IGA mod 2011	Novartis Invetigator's global assessment modified 2011
IG	Immunogenicity
IIS	Integrated Information Sciences
IRB	Institutional Review Board
IRT	Interactive Response Technology
i.v.	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
OC/RDC	Oracle Clinical/Remote Data Capturing
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic (s)
PFS	Pre-filled syringe

PK	Pharmacokinetic (s)
PsA	Psoriatic Arthritis
PUVA	Psoralen+UVA treatment
SAE	serious adverse event
s.c.	Subcutaneous
SoR	Start of Relapse
VAS	visual analog scale

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
Rebound	A subject experiences a rebound, if PASI increases to > 125% of baseline PASI, or if new pustular psoriasis, or new erythrodermic psoriasis, or more inflammatory psoriasis occurs within 8 weeks after the last dose of study treatment has been received.

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

Amendment 2

Amendment rationale

FDA has requested the following post marketing commitment be applied to this study: *"Complete the treatment and evaluation of subjects enrolled in the ongoing CAIN457A2304E1 trial for a duration of 4 years, unless a safety signal is identified that indicates the potential risks of such continued long-term treatment outweigh the benefits. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration). Subjects will be followed for the occurrence of serious infection, tuberculosis, opportunistic infections, malignancy, hypersensitivity reactions, autoimmune disease, neurologic or demyelinating disease, cardiovascular, gastrointestinal or hematologic adverse events".*

Subjects who complete treatment period and follow-up period are evaluated for 4 years regarding respective adverse events. However, patient who prematurely discontinue treatment are evaluated for less than 4 years.

Therefore, this amendment extends the evaluation of subjects who prematurely discontinue treatment regarding respective adverse events and concomitant medications in order to achieve a 4 year evaluation period. Evaluation of subjects should continue when achievable even if treatment is not continued for the duration. All subjects who prematurely discontinue treatment should complete all assessment of Week 260 (end of treatment visit) and of the follow-up period visits (Weeks 264 and 268). Subsequently, adverse events and use of concomitant medication will be evaluated by the investigator through telephone calls every 3 months for a duration of 4 years from the time when subject has been enrolled into CAIN457A2304E1 study. If deemed necessary by the investigator unplanned assessments at site might be scheduled during this time.

In addition, the study will NOT be terminated in selected countries where the drug is commercially available.

Changes to the protocol

The protocol introduces a follow-up 2 period to assess adverse events and concomitant medications through telephone calls for all subjects who have prematurely discontinued treatment.

Section 3.1, Figure 3-1, Section 6 and Table 6-1 were updated to introduce follow-up 2 period

Section 3.1 and Section Section 5.5.11 were updated to reflect that the study will NOT be terminated in selected countries where the drug is commercially available.

Section 3.5 was updated to specify the impact of follow-up 2 period on final database lock

Section 5.5.9 was updated to specify that subjects who prematurely discontinue treatment should enter follow-up 2 period after completion of follow-up period assessments

Section 5.5.10 was updated to reflect that subjects who are prematurely unblinded and discontinued from treatment should also enter follow-up 2 period.

Section 7.2 was updated to reflect that SAE reporting is extended for subjects who enter follow-up 2 period

Table 6-1 was updated to align dosing schedule with the text of the protocol section

Section 9.2 was updated to reflect that the test of baseline balance is not considered as appropriate use of significance test and may cause misinterpretation of the data

Section 9.5.2 was updated to specify the data collection within the follow-up 2 period

Other minor corrections, clarifications, and editing changes of the protocol text were made in various sections

All 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.

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, and sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1, 25-Apr-2014

Amendment rationale

The results of protocol CAIN457A2304 showed that the re-treatment at start of relapse maintenance regimen (SoR) was not non-inferior to a fixed interval regimen (FI) with treatment every four weeks and that patients experienced better maintenance of effect with secukinumab 300 mg compared to secukinumab 150 mg; therefore, this amendment introduces an opportunity at week 156 for blinded subjects to 1) switch off of the SoR treatment regimen to treatment every four weeks and 2) to increase the secukinumab dose to 300 mg. All subjects will be unblinded at Week 156 and the investigator may switch to the subject one of these open label treatment option(s) depending on the current treatment assignment:

Previous treatment arm through Week 152 (Unblinded at Week 156)	Treatment options, as decided by the investigator	Office visit frequency after Week 156
Secukinumab 300 mg FI	**Continue** secukinumab 300 mg FI	Every 12-16 weeks
Secukinumab 300 mg SoR	**Continue** secukinumab 300 mg SoR for remainder of the study	Every 4 weeks
	OR Switch to secukinumab 300 mg dosed every 4 weeks	Every 12-16 weeks
Secukinumab 150 mg FI	**Continue** secukinumab 150 mg FI	Every 12-16 weeks
	OR Switch to secukinumab 300 mg dosed every 4 weeks	Every 12-16 weeks
Secukinumab 150 mg SoR	**Continue** secukinumab 150 mg SoR for remainder of the study	Every 4 weeks
	OR Switch to secukinumab 300 mg dosed every 4 weeks	Every 12-16 weeks

Additionally, this amendment extends the treatment duration for an additional 104 weeks (for a total of 5 years, one year in the core study or studies and four years in the extension study) and the opportunity for home administration of the study drug. In case secukinumab becomes commercially available in a participating country, the study might be discontinued in the respective country. This extension of treatment will allow for safety, tolerability, and efficacy data to be collected from the participating subjects for up to a total of 5 years.

At the time of this amendment, recruitment is complete with 675 subjects randomized into the trial across 15 countries and 112 sites and approximately 108 subjects have discontinued from the study. Since recruitment is complete and there is no change to protocol-mandated discontinuation, it is not expected that this amendment will have an impact on the study population or have a significant impact on the primary objective of the trial.

Changes to the protocol

The main changes throughout the protocol introduce an opportunity for subjects to switch to treatment with open label secukinumab 300 mg s.c. and to extend the treatment duration for an additional 104 weeks (two years) with the option for home administration in patients receiving secukinumab every four weeks.

These specific changes were made to the protocol:

- The length of the trial was changed from 2 to 4 years and visit names were updated as appropriate throughout the document:
  - Final treatment visit changed from Week 152 to Week 256
  - End of Treatment period changed from Week 156 to Week 260
  - First Treatment-Free Follow-Up visit was changed from Week 160 to Week 264
  - End of Study changed from Week 164 to Week 268.
- The synopsis was updated to reflect the changes in the main protocol text.
- Section 3.1 was updated to introduce unblinding of blinded patients at Week 156, the subsequent option to switch to open label treatment with secukinumab 300 mg s.c. every four weeks, and to allow the subjects to self-inject at home.
- Figure 3-1 was updated to reflect the new study design.
- Section 3.2 was updated to reflect when combined with the core studies the trial will provide data on patients treated with secukinumab for five years.
- Section 3.3 was updated with the primary conclusion of trial CAIN457A2304.
- The risks and benefits of secukinumab were updated in Section 3.6 according to the increased experience and data reported in the Investigators Brochure Edition 13.
- Section 3.6 refers to the Investigator Brochure for the most updated risk/benefit profile.
- The section on treatment (Section 5) was updated throughout to reflect the unblinding of patients at Week 156 and the subsequent option to switch to treatment with open-label secukinumab 300 mg s.c. every four weeks, and to allow the subject to self-inject at home. Details of the treatment options are included in Section 5.2 and Table 5-1. Table 5-3 was added to summarize the overview of treatment and frequency of office visits between Week 156 and Week 256. Details on instructions for home administrations are introduced in Section 5.5.4.
- Section 5.5.8 and Table 5-4 were updated to further clarify the use of prohibited concomitant treatment given the increased experience with the study drug.
- Section 5.5.10, Section 6.5.4.4, and Section 6.6.4 were updated to remove reference to the defunct position Clinical Trial Head
- Section 5.5.11 was updated to specify that in case secukinumab becomes commercially available in a participating country prior to all patients completing the study in that country, the study might be discontinued in the respective country.
- Section 6 and Table 6-1 were updated with assessments for Week 160 through Week 268
- Section 9 was updated to include the secukinumab 300 mg open-label switch group for analysis
- Section 9.4.3 was updated to define how data for the patients who switch to secukinumab 300 mg open-label will be analyzed with respect to endpoints.
- Appendix 3 was updated with the increased duration of the study.

Other minor corrections, clarifications, and editing changes of the protocol text were made in various sections

Protocol synopsis

Protocol number	*CAIN457A2304E1*
Title	*A multicenter, double-blind and open label, 4 year extension study of subcutaneous secukinumab in prefilled syringes, assessing long-term safety, tolerability and efficacy in subjects with moderate to severe chronic plaque-type psoriasis treated with either a fixed dose regimen or on a retreatment at start of relapse regimen*
Brief title	*4 year Extension Study of efficacy and safety of secukinumab in Patients with moderate to severe chronic plaque-type psoriasis*
Sponsor and Clinical Phase	Novartis *Phase 3*
Investigation type	*Drug*
Study type	*Interventional*
Purpose and rationale	To assess long-term safety and maintenance of efficacy in two different treatment regimens, a “fixed dose” regimen and a “retreatment at start of relapse” regimen. This four year (208 weeks), multicenter, double-blind and open label, extension study will collect long-term efficacy, safety and tolerability of secukinumab in the fixed dose and start of relapse treatment regimens.
Primary Objective(s) and Key Secondary Objective	*Objective:* To assess long-term safety and tolerability of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis who completed treatment in the core studies CAIN457A2304 and CAIN457A2307.

Secondary Objectives	• To evaluate the long-term efficacy of secukinumab administered at the start of relapse versus fixed interval regimens, in subjects with moderate to severe chronic plaque-type psoriasis who are PASI 75 responders at Week 12, with respect to PASI 75 response:
	  • at Weeks 104 and 156, for subjects in the fixed interval regimens, or
	  • at Weeks 92 and 144, for subjects in the retreatment at start of relapse regimen who do not require active treatment at Week 92 or 144, respectively, or
	  • at Weeks 104 and 156, for subjects in the retreatment at start of relapse regimen who do require active treatment at Week 92 or 144, respectively.
	• To evaluate the efficacy of secukinumab treatment regimens in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 50/75/90/100 and IGA 0 or 1 response over time.
	• To evaluate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque type psoriasis with respect to PASI score and IGA mod2011 score over time
	• To assess the effects of secukinumab treatment regimens with respect to EQ-5D score over time

	• To investigate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to changes in DLQI over time • To investigate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to DLQI 0 or 1 achievement over time • To investigate the potential development of immunogenicity against secukinumab
Study design	This is a multicenter, double-blind and open label, trial in subjects with moderate to severe chronic plaque-type psoriasis who completed treatment in the maintenance period of studies CAIN457A2304 or CAIN457A2307. This extension study consists of three to four periods: the screening period, the treatment period, the treatment- free follow-up period (for all subjects), and the follow-up 2 period (only for subject who prematurely discontinued treatment).
Population	All subjects who complete treatment in the maintenance period of studies CAIN457A2304 or CAIN457A2307 and meeting inclusion & exclusion criteria are eligible for this study. Approximately 740 subjects are expected to be recruited in this study. When recruitment was complete, 675 subjects had been enrolled at 112 sites.
Inclusion criteria	Subjects eligible for inclusion in this study have to fulfill all of the following criteria: • 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 related activity is performed. Where relevant, a legal representative will also sign the informed consent according to local laws and regulations. • Subjects who complete Week 52 of study CAIN457A2304 or complete Week 40 of study CAIN457A2307 • Subjects expected to benefit from participation in the extension study, as assessed by the subject and investigator
Exclusion criteria	Subjects fulfilling any of the following criteria are NOT eligible for inclusion in this study: • A protocol deviation in the core studies which according to the investigator will prevent the meaningful analysis of the extension study for the individual subject • Ongoing use of prohibited psoriasis or non-psoriasis treatments. Time period from last use of prohibited treatments in the core study to first dose of study drug in this extension study detailed in Table 5-4 must be adhered to. • Subjects expected to be exposed to an undue safety risk if participating in the trial • Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the subject unsuitable for the trial • Plans for administration of live vaccines during the study period • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the

	termination of gestation, confirmed by a positive hCG laboratory test (>10 mIU/mL). • Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for a minimum of 16 weeks after stopping treatment.
Investigational and reference therapy	Secukinumab Prefilled Syringes for s.c. administration Placebo Secukinumab Prefilled Syringes for s.c. administration
Efficacy assessments	Investigator's Global Assessment (IGA mod 2011; scale from 0 – 4) Psoriasis Area and Severity Index (PASI; score from 0 – 72) Rebound assessment
Safety assessments	Evaluation of all AEs and SAEs including injection site reactions Physical examination Vital signs Laboratory evaluations Hematology Clinical chemistry Urinalysis Immunogenicity (assessment of anti-secukinumab antibody development) Electrocardiogram Pregnancy and assessments of fertility
Other assessments	Fasting laboratory evaluations, Health-related quality of life assessments such as DLQI EQ-5D HAQ-DI (only in subjects with psoriatic arthritis from study CAIN457A2304, not CAIN457A2307) PK assessments
Data analysis	Treatment groups for analysis will include: Secukinumab 150 mg fixed interval Secukinumab 300 mg fixed interval Secukinumab 150 mg start of relapse Secukinumab 300 mg start of relapse Secukinumab 300 mg open-label Secukinumab 300 mg open-label switch The primary analysis will focus on safety variables. All safety evaluations will be performed on the Safety set (all subjects who took at least one dose of study treatment during the treatment period.)

	Maintenance of response will be defined analogously as in the primary endpoint in CAIN457A2304, but for week 104 and 156, i.e. PASI 75 response at Weeks 104 and 156, for subjects in the fixed interval regimens, or at Weeks 92 and 144, for subjects in the retreatment at start of relapse regimen who do not require active treatment at Week 92 or 144, respectively, or at Weeks 104 and 156, for subjects in the retreatment at start of relapse regimen who do require active treatment at Week 92 or 144, respectively.
Key words	*4 year Extension Study, in Patients with moderate to severe chronic plaque type psoriasis*

1 Introduction

1.1 Background

CAIN457A2304E1 is an extension study to two phase III studies, CAIN457A2304 and CAIN457A2307 (core studies). Study CAIN457A2304 compares the maintenance of efficacy and safety over time in two different treatment regimens: a fixed dose regimen and a retreatment at start of relapse regimen. Efficacy is measured with PASI response rates; a PASI 75 is defined as a responder whereas a PASI 50 to less than PASI 75 is a partial responder. In study CAIN457A2304, PASI 75 responders at Week 12 continued to the end of the study but partial responders were offered either participation in study CAIN457A2307 or entering the treatment-free follow-up period in CAIN457A2304. Study CAIN457A2304 non-responders at week 12 (PASI response less than 50) were discontinued from treatment and entered the treatment-free follow-up period in CAIN457A2304.

Study CAIN457A2307 evaluates whether a partial responder can be converted to a responder when treated for longer periods of time and/or when treated with a higher dose of the drug via either the s.c. or the i.v. route of administration. Please refer to the protocols of the core studies for full details.

This extension study is planned to collect up to four years of long-term safety, tolerability and efficacy data of secukinumab in both the fixed interval regimen and the retreatment at start of relapse regimen. All subjects completing Week 52 of CAIN457A2304 and Week 40 of CAIN457A2307 will be eligible to participate in this extension study. Week 40 of the CAIN457A2307 study is the end of maintenance visit (EOM) and is equivalent to the Week 52 (EOM) of the CAIN457A2304 core study. Therefore, all subjects entering the CAIN457A2304E1 study will have received 52 weeks of treatment in their previous study / studies. The Week 52 (CAIN457A2304) and Week 40 (CAIN457A2307) of the two core studies will together be referred to as “the EOM visit” (end of maintenance visit for the core studies) in this protocol.

In this extension study, the prefilled syringe (PFS) liquid formulation of secukinumab will be used.

This study may be affected by agency review or potential product approval considerations, whereby if the product is approved during study conduct dose groups in this proposed extension trial may be amended (via a future protocol amendment) based on eventual agency recommendations for product usage in this indication.

1.2 Purpose

The purpose of this extension study is to assess long-term safety and maintenance of efficacy in two different treatment regimens, a “fixed dose” regimen and a “retreatment at start of relapse” regimen. Within each regimen, two different doses are used: 150 and 300 mg s.c. secukinumab. A successful response is defined as a PASI 75, and subjects who meet this criterion are referred to as “responders”. A PASI 75 responder is a subject achieving $\geq$ 75% improvement (reduction) in PASI score compared to baseline of the core study.

Subjects who complete the extension study will provide up to approximately 4 years of additional data to the CAIN457A2304 and CAIN457A2307 core studies, which will be submitted as supplemental information to support the appropriate individualized use of secukinumab for the treatment of moderate to severe, chronic, plaque-type psoriasis.

Subjects who finished the treatment period in studies CAIN457A2304 or CAIN457A2307 and show a meaningful response (as assessed by the investigator and subject) will be enrolled into this extension study to allow them to continue treatment with secukinumab, which will not yet be commercially available at the time of enrollment.

2 Study objectives

2.1 Primary and key secondary objectives

To assess long-term safety and tolerability of secukinumab in subjects with moderate to severe chronic plaque-type psoriasis who completed treatment in the core studies CAIN457A2304 and CAIN457A2307.

2.2 Secondary objectives

- To evaluate the long-term efficacy of 150 mg and 300 mg of secukinumab administered at the start of relapse versus fixed interval regimens of 150 mg and 300 mg of secukinumab respectively, in subjects with moderate to severe chronic plaque-type psoriasis who are PASI 75 responders at Week 12, with respect to PASI 75 response:
    - at Weeks 104 and 156, for subjects in the fixed interval regimens, or
    - at Weeks 92 and 144, for subjects in the retreatment at start of relapse regimen who do not require active treatment at Week 92 or 144, respectively, or
    - at Weeks 104 and 156, for subjects in the retreatment at start of relapse regimen who do require active treatment at Week 92 or 144, respectively.
- To evaluate the efficacy of secukinumab treatment regimens in subjects with moderate to severe chronic plaque-type psoriasis with respect to PASI 50/75/90/100 and IGA 0 or 1 response over time.
- To evaluate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque type psoriasis with respect to PASI score and IGA mod 2011 score over time
- To assess the effects of secukinumab treatment regimens with respect to EQ-5D score over time
- To investigate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to changes in DLQI over time
- To investigate the effects of treatment regimens with secukinumab in subjects with moderate to severe chronic plaque-type psoriasis with respect to DLQI 0 or 1 achievement over time

- To investigate the potential development of immunogenicity against secukinumab
- To investigate the occurrence of relapses (achieved maximal PASI improvement from baseline in core study is reduced by >50%) and rebounds in subjects on secukinumab therapy

2.3 Exploratory objectives

- [redacted]
- To explore the effects of secukinumab with respect to the HAQ-DI in subjects from core study CAIN457A2304 with psoriatic arthritis (PsA) at baseline over time
- [redacted]

3 Investigational plan

3.1 Study design

This is a multicenter, double-blind and open label, trial in subjects with moderate to severe chronic plaque-type psoriasis who completed treatment in the maintenance period of studies CAIN457A2304 or CAIN457A2307. It was expected that approximately 740 subjects would be enrolled at approximately 130 study sites worldwide. When recruitment was complete, 675 subjects had been enrolled at 112 sites.

This extension study consists of four periods: the screening period, the treatment period, and two follow-up periods (follow-up and follow up 2). An outline of the visits is presented in Figure 3-1, while a detailed visit schedule can be found in Table 6-1.

Screening Period

The screening period for the extended maintenance portion of the study is the duration between the signing of the informed consent form and enrollment registered with the interactive response technology (IRT). There are no additional requirements for the treatment period other than subjects are required to complete year 1 of the core studies and all assessments at the end of maintenance visit (Week 52) of core study CAIN457A2304 or end of maintenance visit (Week 40) of core study CAIN457A2307. Subjects who complete the EOM visit and assessments of the core studies and consent to the extension will continue directly into the treatment period of this extension study. Subjects must sign the informed consent form (ICF) for the treatment period once the core assessments have been completed for Week 52 of the core studies and the IRT called to register that the subject completed the core study (CAIN457A2304 or CAIN457A2307). For the purpose of reading and understanding, the ICF can be provided to subjects anytime during the core studies, for example, between Week 48 and prior to the dose at Week 52 of study CAIN457A2304 (Weeks 36 and 40 from study CAIN457A2307 are equivalent to Weeks 48 and 52 of CAIN457A2304). However, subjects will NOT sign the ICF before completing the core studies' EOM assessments.

Note: subjects from CAIN457A2307 started their visits in that study after completing 12 Weeks of the CAIN457A2304 core study; therefore, Week 40 of the CAIN457A2307 study is equivalent to Week 52 of the CAIN457A2304 and CAIN457A2304E1 studies as regards previous treatment duration (i.e., 52 weeks).

The dose administered at Week 52 is the first dose of the CAIN457A2304E1 treatment period.

Treatment Period

The treatment period is defined as Weeks 52 through 260.

Subjects from the CAIN457A2304 maintenance period will continue the treatment regimen and dose that they were assigned to (Fixed interval regimen or Retreatment at start of relapse regimen) during the maintenance treatment period of the core study and return for visits every four weeks up until Week 156. Subjects and study personnel will remain blinded during the first two years of the treatment period (except for patients in the open label part of the study). The last blinded dose of the treatment period is administered at Week 152.

At Week 156, subjects will be unblinded and will have the option (based on investigator judgment) to switch dosing regimens, with the specific options depending on the blinded treatment assigned until that point. Generally, subjects may switch off of the SoR treatment regimen to active secukinumab treatment every four weeks, and subjects may switch from secukinumab 150 mg s.c. to secukinumab 300 mg s.c. After Week 156, office visits will only be required every 12-16 weeks until Week 260 (End of Treatment period for CAIN457A2304E1) unless a subject continues with the SoR treatment regimen. Specific details of the open-label treatment options for unblinded subjects starting at Week 156 are described in Section 5.2 and in Table 5-1.

Subjects from the CAIN457A2307 maintenance period will continue in the treatment regimen and dose that they received during the CAIN457A2307 maintenance treatment period (i.e., 300 mg sc secukinumab every four weeks), and return for visits every four weeks up until Week 156. After Week 156, subjects will continue being treated every four weeks, but will only be required to come in for office visits every 12-16 weeks. These subjects were treated open-label during the core study, and will continue to be treated open-label during the treatment period of CAIN457A2304E1. The last dose of secukinumab is provided at Week 256, four weeks prior to the end of the treatment period.

Please refer to Section 5.2 for a more detailed description of the treatment arms.

Subjects who discontinue study treatment prematurely during the treatment period should have all Week 260 protocol assessments (EOT) performed approximately four weeks after their last dose of secukinumab/secukinumab placebo and then enter the treatment-free follow-up periods (follow-up period and follow-up 2 period).

Follow-up period (for all subjects)

Subjects who complete the treatment period (the end of the treatment phase visit is at Week 260) will enter the treatment free follow-up period with the following visits: Week 264 (Follow-up visit 4, F4), which is 4 weeks post end of treatment period and 8 weeks post last dose), and Week 268 (Follow-up visit 8, F8 or End of Follow-up, EOF) which is 8 weeks post end of

treatment period and 12 weeks post last dose). Subjects who prematurely discontinue treatment should complete all assessment of Week 260 (end of treatment visit) and then enter follow-up period with Weeks 264 and 268 visits.

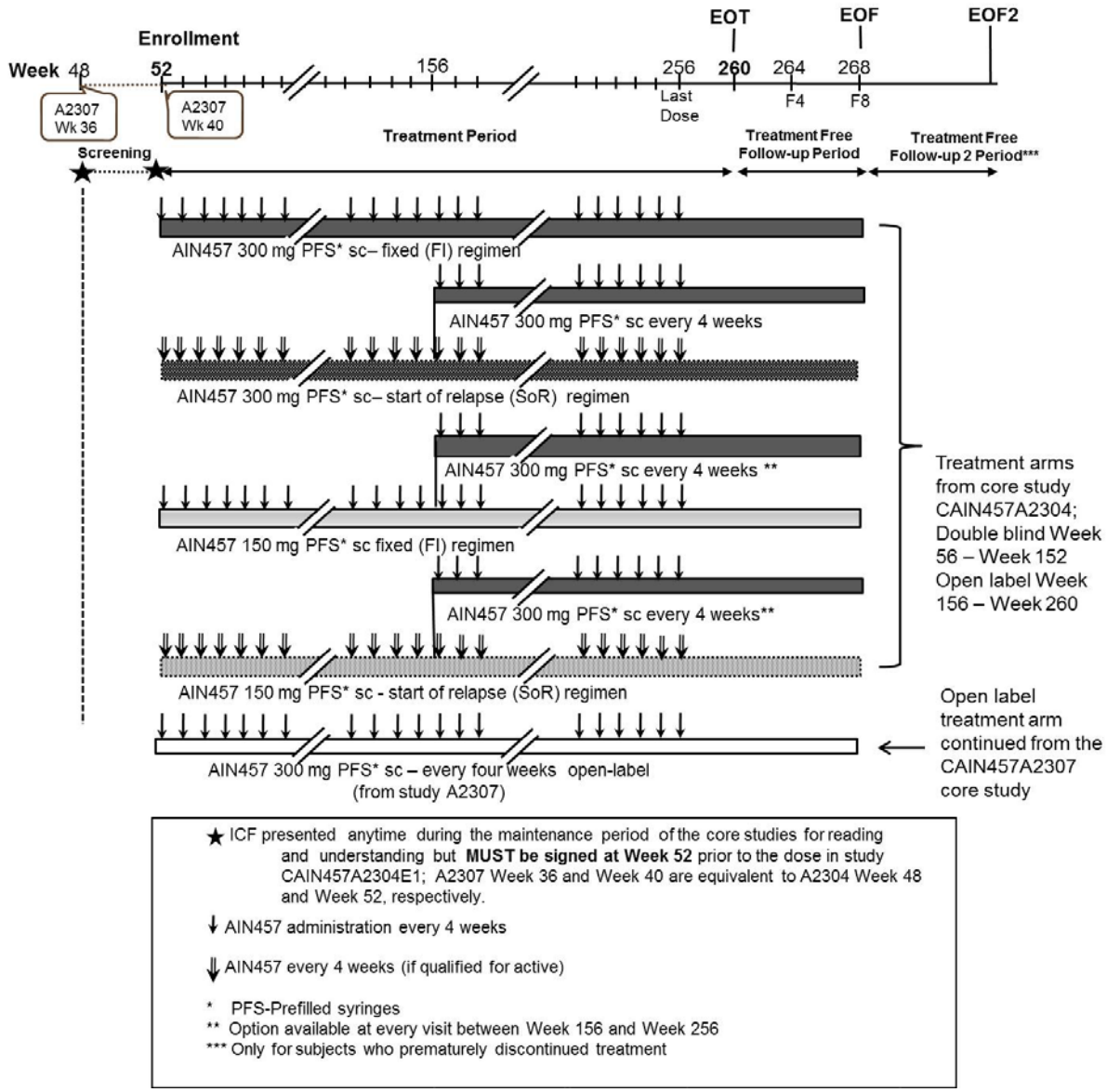
Subjects within the follow-up period who withdraw from study should perform Week 268 assessments (EOF).

Follow-up 2 period (only for subjects who prematurely discontinued treatment)

Subjects who have prematurely discontinued treatment prior to the end of treatment phase (Week 260), and completed the Week 260 visit and the subsequent follow-up period visits (Weeks 264 and 268) should enter the treatment-free follow-up 2 period. Follow-up 2 period consists of telephone calls every 3 months and unplanned assessments e.g. unscheduled physical examinations, vital signs and laboratory assessments at the site if investigator considers this necessary. The end of Follow-up 2 period (EOF2) for an individual subject will be after 4 years from the time when subject has been enrolled into the CAIN457A2304E1 study (Figure 3.1).

Subjects within the follow-up 2 period who withdraw from study will be recorded in the End of Follow-up 2 (EOF2) completion eCRF page.

Figure 3-1 Study design



3.2 Rationale of study design

This four year (208 weeks), multicenter, double-blind and open label, extension study will collect long-term efficacy, safety and tolerability of secukinumab in the fixed dose and start of relapse treatment regimens. The randomization to the treatment arms occurred in the core studies and is carried over into this extension study.

The total study duration of four years will allow for assessment of long term safety and efficacy in subjects treated for up to five years when combined with data from the core studies. The regular assessments of disease activity and clinical status ensure that safety is monitored closely, and that both subject and investigator have the opportunity to assess if the continued

participation of the subject in the study is to the subject's benefit. If the subject's participation is deemed not to be of benefit to the subject, the subject can discontinue study treatment at any time.

Subjects who complete the extension study will provide up to approximately 4 additional years of long-term safety, tolerability and efficacy data, to the CAIN457A2304 core study.

Subjects who finished the treatment period in studies CAIN457A2304 or CAIN457A2307 and show a meaningful response (as assessed by the investigator and subject) will be enrolled into this extension study to allow them to continue treatment with secukinumab, which is not yet commercially available at the time of enrollment.

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

The doses and regimens selected for the secukinumab phase III program were based on phase II trial data. As of the trial initiation, there has not been any data to date to indicate that the doses used in the core studies should be modified. Therefore, this extension study will continue treatment with secukinumab s.c. doses of 150 mg and 300 mg administered every four weeks, and/or at start of relapse (following the randomization that was done during the core studies) for an additional 208 weeks. This will provide long-term secukinumab efficacy and safety data pertaining to the treatment of subjects suffering from chronic plaque-type psoriasis for up to a total of 5 years when combined with the core studies data.

The pivotal phase III trials were analyzed while this extension trial was ongoing and results of protocol CAIN457A2304 showed that the re-treatment at start of relapse maintenance regimen (SoR) was not non-inferior to a fixed interval regimen (FI) with treatment every four weeks and subjects experience better efficacy with 300 mg secukinumab s.c. every four weeks compared to 150 mg secukinumab s.c. every four weeks with similar safety profile between the two doses. Therefore, at Week 156 all patients treated with the SoR treatment regimen are given the option to switch to treatment with active secukinumab every four weeks, and patients treated with secukinumab 150 mg s.c. are given the option to switch to treatment with secukinumab 300 mg s.c. Any switches in treatment regimen or dose are to be made according to the investigator's judgment as the investigator will have three years of experience with the subject and the subject's individual response to secukinumab.

The switch from the lyophilisate to the more convenient prefilled syringe (PFS) is supported by the results of the clinical study CAIN457A2106, which has shown that the exposure and safety profiles of both formulations are highly comparable.

3.4 Rationale for choice of comparator

This extension study uses the same treatments that were assigned during the core CAIN457A2304 and CAIN457A2307 studies. Therefore, no comparators are used.

3.5 Purpose and timing of interim analyses/design adaptations

One interim analysis is planned for this study. At time of marketing authorization submission of the AIN457A project, the safety data of this extension study will be reported. Since the core studies have been unblinded at that stage, this interim analysis will also be unblinded. Of note,

investigators, subjects and site staff will remain blinded to individual treatment group assignments.

Further interim analyses, as regarded appropriate, might be conducted (e.g., to provide additional data for regulatory or publication purposes).

When each subject in the study has either completed treatment period and follow-up period, or discontinued treatment and completed follow-up and follow-up 2 periods (last telephone contact), or withdrawn from study, the final database lock occurs.

3.6 Risks and benefits

Non-clinical studies have not shown any impediment to using secukinumab administered subcutaneously in man. Study CAIN457A2304E1 will use secukinumab drug substance solution in a PFS formulation; biocomparability of secukinumab in PFS and lyophilized formulations has been demonstrated (study CAIN457A2106), with highly comparable pharmacokinetic properties.

At the time of Amendment 1, over 6200 subjects with a variety of autoimmune diseases have received secukinumab. Details of the risk and benefits are outlined in the current version of the Investigator Brochure.

The risk to subjects in this trial will be minimized by compliance with the inclusion/exclusion criteria, proper study design, and close clinical monitoring.

In this extension study, CAIN457A2304E1, all subjects will receive active treatment, either every four weeks regardless of clinical symptoms, or after they have experienced start of relapse. To ensure a double-blind design, some subjects will receive placebo at certain visits, according to their treatment group. For example, patients in the core study CAIN457A2304 who were randomized to and continue on the retreatment at start of relapse regimen who have not experienced a start of relapse will continue on placebo medication until they meet the start of relapse criteria.

All quality, non-clinical pharmacology and toxicology data, as well as the available clinical efficacy and safety data, are considered sufficient to expect a positive benefit / risk ratio for the treatment of psoriasis with secukinumab, and therefore to initiate this extension study CAIN457A2304E1.

4 Population

The study population will consist of a representative group of male and female outpatients (≥ 18 years old) with moderate to severe chronic plaque-type psoriasis who completed the full study treatment period (52 weeks) in the core studies CAIN457A2304 or CAIN457A2307 (Week 40 in study CAIN457A2307 is equivalent to a total of 52 weeks of treatment with secukinumab).

Study CAIN457A2304 randomized 970 subjects. Assuming that 5% of the subjects drop-out up to Week 12, and further 15% drop-out in CAIN457A2304 or CAIN457A2307 it is estimated that about 740 subjects will be eligible to enter this study. When recruitment was complete, 675 subjects had been enrolled at 112 sites.

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 related activity is performed. Where relevant, a legal representative will also sign the informed consent according to local laws and regulations.
2. Subjects who complete Week 52 of study CAIN457A2304 or complete Week 40 of study CAIN457A2307
3. Subjects expected to benefit from participation in the extension study, as assessed by the subject and investigator

4.2 Exclusion criteria

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

1. A protocol deviation in the core studies which according to the investigator will prevent the meaningful analysis of the extension study for the individual subject
2. Ongoing use of prohibited psoriasis or non-psoriasis treatments. Time period from last use of prohibited treatments in the core study to first dose of study drug in this extension study detailed in Table 5-4 must be adhered to.
3. Subjects expected to be exposed to an undue safety risk if participating in the trial
4. Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the subject unsuitable for the trial
5. Plans for administration of live vaccines during the study period
6. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (>10 mIU/mL).
7. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 16 weeks after stopping treatment. Effective contraception is defined as either:
   - Barrier method: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Spermicides alone are not a barrier method of contraception and should not be used alone

   The following methods are considered more effective than the barrier method and are also acceptable:
   - 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 a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male partner sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomised male partner should be the sole partner for that subject
- Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device (IUD) or intrauterine system (IUS)

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had:

- 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or
- six months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL [for US only: and estradiol <20 pg/mL] or
- 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 is she considered not of child bearing potential.

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

5 Treatment

The blind will be maintained for subjects rolling over from the core CAIN457A2304 study into the CAIN457A2304E1 extension study until Week 156. At Week 156, all patients who rolled over from the core CAIN457A2304 study will be unblinded and subjects treated according to the SoR regiment will have the option to switch to treatment with active secukinumab every four weeks, and subjects treated with secukinumab 150 mg s.c. are given the option to switch to treatment with secukinumab 300 mg s.c. Details of these switch options are provided in Section 5.2.

Subjects from CAIN457A2307 are treated open label and will continue to receive the same treatment (300 mg s.c. every four weeks) in the CAIN457A2304E1 extension study.

All of the packaging for the treatments in this study will be packaged to maintain the blind. There will not be any syringes or boxes labeled in an open-label manner as the IRT will be responsible for assigning the appropriate medication numbers to each subject. Although the labels on the treatments will not indicate active, the investigator and subjects from the CAIN457A2307 core study will know that the content of the PFSs that are assigned to these subjects during the CAIN457A2304E1 study are active since the subjects will receive the same treatment that they were assigned to during the maintenance period of the core studies. Also, after Week 156, although the labels on the treatment assigned to the subjects from the CAIN457A2304 will not indicate active or placebo treatment, the investigator and subjects will know what they are being treated with due to the unblinding at Week 156.

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will supply the following study treatment:

1. Investigational treatment: Secukinumab 150 mg/1 mL solution for injection is provided in PFS for s.c. administration. The 150 mg/1 mL solution in PFS is used for both the s.c.150 mg dose (1 syringe) and s.c. 300 mg dose (2 syringes). For blinding purposes the subjects in the 150 mg treatment group will also receive one syringe of placebo 150 mg.
2. Placebo secukinumab 150 mg/1 mL solution for injection is provided in PFS for s.c. administration. It contains a mixture of inactive excipients, matching the composition of secukinumab 150 mg.

Secukinumab 150 mg/1 mL and placebo secukinumab 150 mg/1 mL is labeled as AIN457 150 mg/1 mL/Placebo.

5.1.2 Additional study treatment

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

5.2 Treatment arms

Subjects will continue in the treatment arm that they were assigned to during the CAIN457A2304 core study or the CAIN457A2307 core study until Week 156. At Week 156, subjects who rolled over from the CAIN457A2304 core study will be unblinded and may switch to one of the treatment options described below according to investigator judgment; subjects who rolled over from the CAIN457A2307 core study will continue being treated with secukinumab 300 mg s.c. every four weeks. Treatment arms in this study may be affected by agency review or potential product approval considerations, whereby if the product is approved during study conduct, dose groups in this proposed extension trial may be amended (via a future protocol amendment) based on eventual agency recommendations for product usage in this indication.

The study treatment will be provided in individual boxes that contain secukinumab or placebo PFS sealed in a plastic wrapper. Each study treatment box consists of actual PFS and a safety device type X100L [redacted]. The safety syringe is provided with a needle guard system that will aid protection from accidental needle sticks.

Double-blind treatment arms for subjects entering from the CAIN457A2304 core study

During the core study CAIN457A2304, within each treatment regimen, subjects were assigned to either the 150 or 300 mg s.c. secukinumab in PFS, thus resulting in four treatment arms overall which will be maintained until Week 156:

Fixed-time interval regimen – “FI”: either 150 or 300 mg s.c. secukinumab in PFS: In the treatment period subjects will receive the same dose they received during the maintenance period of the CAIN457A2304 core study. Thus, secukinumab 150 mg subjects will continue to

receive 150 mg secukinumab every four weeks, and secukinumab 300 mg subjects will continue to receive 300 mg secukinumab every four weeks, from Week 52 up to and including Week 152.

Retreatment at start of relapse regimen – "SoR" "start of relapse": either 150 or 300 mg s.c. secukinumab in PFS: "Start of relapse" will be defined as a loss of ≥20% of the maximum PASI gain achieved during the CAIN457A2304 or CAIN457A2304E1 study, compared to baseline of the CAIN457A2304 study, *and* a loss of PASI 75 response. Whenever a subject fulfills the start of relapse criteria, active secukinumab will be administered at their scheduled visits (i.e., every four weeks) until the subject is back to PASI 75 response, at which point in time they will start receiving placebo again. The dose administered in the treatment period of this extension study (secukinumab 150 mg or 300 mg in PFS) will be identical to the dose that these subjects received during the maintenance period of the CAIN457A2304 core study. If a subject does not fulfill the criteria of a start of relapse or is back to PASI 75 response after a start of relapse, they will receive placebo PFS injections (two injections per dose) to maintain the blind. This treatment regimen is applied every four weeks, from Week 52 up to and including Week 152.

At Week 156, patients from the maintenance period of the CAIN457A2304 core study will be unblinded and continue in the study on one of the treatment options in Table 5-1 according to investigator judgment for their assigned treatment arm.

Table 5-1 Open-label treatment options starting at Week 156

Previous treatment arm through Week 152 (Unblinded at Week 156)	Treatment options, as decided by the investigator	New office visit frequency
Secukinumab 300 mg FI	**Continue** secukinumab 300 mg FI	Every 12-16 weeks
Secukinumab 300 mg SoR	**Continue** secukinumab 300 mg SoR for remainder of the study	Every 4 weeks
	OR Switch to secukinumab 300 mg dosed every 4 weeks	Every 12-16 weeks
Secukinumab 150 mg FI	**Continue** secukinumab 150 mg FI	Every 12-16 weeks
	OR Switch to secukinumab 300 mg dosed every 4 weeks	Every 12-16 weeks
Secukinumab 150 mg SoR	**Continue** secukinumab 150 mg SoR for remainder of the study	Every 4 weeks
	OR Switch to secukinumab 300 mg dosed every 4 weeks	Every 12-16 weeks

Open-label treatment arm for subjects entering from the CAIN457A2307 core study

Secukinumab 300 mg s.c. in PFS regimen arm: Each subject to continue receiving two s.c. injections of 150 mg secukinumab in PFS every four weeks. Doses will be administered from Week 52 up to and including Week 256.

Overview of treatment schedule according to treatment arm

The treatment details for each treatment arm for Week 52 through Week 152 are highlighted in Table 5-2 below. The treatment details for each treatment assignment for Week 156 through Week 256 are highlighted in Table 5-3 below.

Table 5-2 Overview of treatment between Week 52 and Week 152

Treatment arm	Double-blinded A2304 subjects: Week 52 to Week 152	Open-label A2307 subjects: Week 52 to Week 152
secukinumab 150 mg fixed interval	1 s.c. secukinumab 150 mg PFS injection + 1 s.c. PBO secukinumab PFS injection	N/A
secukinumab 300 mg fixed interval	2 s.c. secukinumab 150 mg PFS injections	2 s.c. secukinumab 150 mg PFS injections
secukinumab 150 mg at start of relapse	At start of relapse and until PASI 75 is regained: 1 s.c. secukinumab 150 mg PFS injection + 1 s.c. PBO secukinumab PFS injection	N/A
	Otherwise: 2 s.c. PBO secukinumab PFS injections	N/A
secukinumab 300 mg at start of relapse	At start of relapse and until PASI 75 is regained: 2 s.c. secukinumab 150 mg PFS injections	N/A
	Otherwise: 2 s.c. PBO secukinumab PFS injections	N/A

PBO = placebo; PFS=pre-filled syringe

Table 5-3 Overview of treatment between Week 156 and Week 256

Assigned treatment	Treatment delivered and frequency of office visits
secukinumab 150 mg fixed interval	1 s.c. secukinumab 150 mg PFS injection every four weeks Office visits required every 12-16 weeks
secukinumab 300 mg fixed interval/ every four weeks	2 s.c. secukinumab 150 mg PFS injections every four weeks Office visits required every 12-16 weeks
secukinumab 150 mg at start of relapse	1 s.c. secukinumab 150 mg PFS injection every four weeks upon meeting SoR criteria and until PASI 75 is regained; no treatment otherwise Office visits required every 4 weeks
secukinumab 300 mg at start of relapse	2 s.c. secukinumab 150 mg PFS injection every four weeks upon meeting SoR criteria and until PASI 75 is regained No treatment otherwise

Assigned treatment	Treatment delivered and frequency of office visits
	Office visits required every 4 weeks

5.3 Treatment assignment

Patients will continue receiving study treatment as per their treatment arm in the core studies (i.e., CAIN457A2304 or CAIN457A2307) until Week 156. The randomization numbers will be generated using the following procedure to ensure that treatment assignment is concealed from patients and investigator staff. A randomization list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio.

At the end of Week 52 of CAIN457A2304 (or Week 40 of CAIN457A2307), the investigator will complete core study assessments, enter the PASI response into the eCRF and register the completion of core study visit in the IRT. The Week 52 of CAIN457A2304 (or Week 40 of CAIN457A2307) visit in the core study is the randomization visit for CAIN457A2304E1. Based on the fulfillment of inclusion/exclusion criteria by the subject and IRT notification from the database of core studies at Week 52 (explained above), the investigator (or designee) will call the IRT set up of CAIN457A2304E1. The randomization number will be adopted from core study (CAIN457A2304 and CAIN457A2307) in this extension study and IRT will only specify a unique medication number for the first package of investigational treatment to be dispensed to the patient. The randomization number will not be communicated to the caller and the treatment assignment will be unbiased and concealed from patients and investigator staff.

The randomization list from the core study CAIN457A2304 or CAIN457A2307 will be adopted for this extension study. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

At Week 156, all subjects will be unblinded and will continue with one of the treatment options described in Section 5.2 based on their previous treatment arm and the investigator's judgment. The investigator should select the best option from the options based on the assigned treatment up to that point. This selection should be based on knowledge of and experience with the patient.

5.4 Treatment blinding

Subjects, investigator staff and persons performing the assessments will remain blind to the identity of the treatment, for subjects who participated in the core CAIN457A2304 study, from the time of enrollment in the extension study until Week 156, using the following methods:

(1) Randomization data from the core study are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study

(2) The identity of the treatments will be concealed by the use of investigational treatments that are identical in packaging, schedule of administration and appearance. Unblinding will only occur in the case of subject emergencies (see Section 5.5.11).

In order to maintain the blind for the subjects coming from study CAIN457A2304, placebo PFSs are used.

Subjects participating from the CAIN457A2307 core study, as well as investigator staff, persons performing the assessments and data analysts will be unblinded to the treatment that these subjects are receiving throughout the duration of this extension study.

In addition, the bioanalyst will have access to the randomization lists from the core study to facilitate analysis of pharmacokinetic samples. The bioanalyst will keep the information confidential.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient 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 patient, the Subject Number will not be reused. The Subject Number is maintained from the core study/ studies in the extension.

Upon signing the informed consent form, the investigator or his/her staff will contact the IRT and provide the requested identifying information for the patient to register them into the IRT. The site should select the CRF book with a matching Subject Number from the EDC system to enter data.

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

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 two-part label. A unique randomization number is printed on each part of this label which corresponds to one of the 5 treatment arms and a specific visit. Investigator staff will identify the investigational treatment package(s) to dispense to the patient by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, 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 patient's unique subject number.

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.

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

information about the patient except for the medication number. The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. 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.

Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking study treatment

Prefilled syringes are packaged as one syringe per box. Until Week 156, each subject will require two boxes of PFSs per dose.

- One secukinumab 150 mg PFS and one placebo secukinumab PFS (150 mg dose) OR
- Two secukinumab 150 mg PFS (300 mg dose) OR
- Two placebo secukinumab 150 mg PFS (Placebo dose for subjects in the SoR regimen, who have not relapsed)

After Week 156, subjects with site visits every 12-16 weeks will be expected to perform home administrations at the protocol specified time points (every 4 weeks) when there is no correlated office visit. In these cases, the investigator will dispense, via IRT, the appropriate number of investigational treatment packages for the planned home administrations until the next expected site visit and detach the outer part of the label from the packaging prior to giving the package to the subject. The subjects will record the date(s) of administration at home and will return the used medication and packaging at their next site visit. Subjects will be asked to return all unused medication and packaging at the latest by the completion of the study or discontinuation of investigational treatment. Site staff will record the dates of administration on the appropriate documents.

All study treatment kits assigned to the subject during the study will be recorded / databased in the IRT.

The syringes with the ready-to-use study treatment solution (PFS) will be provided by the site staff during the study visit.

The first study treatment administration will occur at Week 52 (enrollment into the extension) after all study scheduled assessments have been performed (and inclusion / exclusion criteria confirmed) and only after the scheduled blood samples have been drawn. It is preferred that the subject self-inject the treatment during the site visit, however, if a subject is not able or not willing to self-administer, administration will be performed by study site staff. If the subject is not able or not willing to self-administer the PFS at home, he/she may come into the site for dosing every 4 weeks.

For subjects willing to self-inject, the first use at enrollment visit (Week 52) will take place under guidance and the supervision of one site staff member. At the enrollment visit (Week 52) the site staff will walk subjects through the "Instructions For Use" on how to self-inject via PFS. At the following visits, subjects will receive the PFS and instructions at the study site to follow on their own.

NOTE: The needle cover of the syringe contains dry rubber (latex), which should not be handled by persons sensitive to this substance.

During the treatment period from Week 52 until Week 256, subjects will receive a maximum of 104 study treatment injections (2 injections of secukinumab 150 mg PFS and/or placebo PFS at each visit). The actual number of study treatment injections will depend on the treatment assigned. All subjects will receive 52 study treatment injections between Week 52 and Week 152 (2 injections of secukinumab 150 mg PFS and/or placebo PFS at each visit); between Week 156 and 256 subjects could receive as many as 52 study treatment injections (2 injections of secukinumab 150 mg PFS every four weeks) or as few as 0 study treatment injections (SoR treated subjects who do not meet start of relapse criteria at any point).

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

At each visit, all study assessments, including the completion of Patient Reported Outcomes (PROs), should be completed prior to the self injection of study treatment.

After Week 256, no further study treatment will be administered during the treatment period. In addition, no study treatment is administered during the follow-up period and follow-up 2 period.

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

All dates, times of injections, mode of injection (self or by study site staff) during the study must be recorded on the Dosage Administration Record eCRF. Immediately before dispensing the package for injection, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

The investigator should promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity of the study.

Administration

Secukinumab solution for s.c. injection or placebo secukinumab solution (active or placebo, respectively) will be provided in a PFS.

The study treatment solution must be injected in non-affected areas of the skin. If possible, throughout the trial administer the study treatment to one of the following body regions, changing the injection site from visit to visit: right thigh, left thigh, right stomach, left stomach, upper outer arm (when assisted by attendant).

Prior to administration the boxes containing the PFS with study treatment solution should be allowed to come to room temperature unopened for about 20 minutes before administration. Used PFS should be disposed immediately after use in a sharps container OR according to the regulatory needs of the respective countries.

Home administration

After Week 156 (two years of self-administered study treatment under the supervision of site staff), subjects will be expected to self-administer the PFS at home when they are not visiting the site for any other trial related procedure. Subjects must be instructed to contact the investigator/site staff prior to any self-administration if they have any AEs or SAEs to report. The subjects will be allowed to self-administer treatment at home only if they have exhibited correct self-administration of the PFS at the site. If the subject is not able or not willing to self-administer the PFS, he or she should visit the site every 4 weeks, according to the visit schedule, and the staff or subject will administer the study drug at the site. However, during those visits no other assessments will be performed other than checking vitals (recorded in source) and checking for AEs or SAEs.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Other than the protocol-specified dosing-changes at Week 156, no dose adjustments or interruptions are permitted.

A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, the subject must be discontinued from the trial.

5.5.6 Rescue medication

Rescue medication is not permitted in this study.

5.5.7 Concomitant treatment

The investigator must consider the baseline and ongoing concomitant treatment in the core studies CAIN457A2304 or CAIN457A2307 at Week 52 before a subject enrolls in the extension study (CAIN457A2304E1).

The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of study treatment. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject started study treatment must be listed on the Concomitant medications eCRF or Surgeries and Medical Procedures eCRF. Start date, end date, unit, frequency, route and reason for administration or change are to be recorded.

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

5.5.8 Prohibited Treatment

The use of concomitant medication for psoriasis in all body regions (except face, scalp, and/or genitoanal area as noted below) is restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions. Use of bland emollients must be recorded on the Concomitant medications eCRF.

The definition of "bland" excludes all topical medications that contain pharmacologically active ingredients such as (but not limited to) lactic acid, salicylic acid, urea, α-hydroxy acids or fruit acids.

The use of bland emollients should be avoided during the 12 hours preceding a scheduled study visit.

Topical corticosteroid (CS) treatment, or use of other topical treatment that is likely to impact signs and symptoms of psoriasis, is not allowed for treatment of psoriasis, except when applied to the face, scalp, and/or genitoanal area for ≤14 consecutive days. Topical corticosteroid use for indications other than psoriasis not on an area affected with psoriasis is allowed for ≤14 consecutive days.

Subjects need to be advised to limit exposure to ultraviolet (UV) light (including sunbathing and/or use of UV tanning devices) during the study to avoid possible effect on psoriasis.

The investigator should instruct the subject to notify the study site about any new treatments he/she takes after the start of the study treatment. All prohibited medications and significant non-drug therapies administered after the subject starts treatment with study treatment must be listed on the Concomitant medications eCRF or the Surgeries and Medical Procedures eCRF.

Use of any treatments displayed in Table 5-4 that could confound the efficacy is NOT allowed for any indication during the study excluding treatment-free follow-up 2 period.

Table 5-4 Prohibited treatment

Prohibited treatments[†,‡]
Alefacept, briakinumab, efalizumab, ustekinumab
Biological immunomodulating agents other than above (e.g., adalimumab, etanercept, infliximab)
Other systemic immunomodulating treatments[§] (e.g., MTX, cyclosporine A, corticosteroids[§], cyclophosphamide)
Other systemic psoriasis treatments* (e.g. retinoids, fumarates)
Photochemotherapy (e.g., PUVA)
Phototherapy (e.g., UVA, UVB)
Use of topical treatment that is likely to impact signs and symptoms of psoriasis for > 14 consecutive days* (e.g., corticosteroids [CS], vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)
Live virus vaccinations during extension study

Prohibited treatments†,‡
Any investigational treatment or participation in any interventional clinical trial during extension trial

†If a subject inadvertently used the prohibited treatment in the core study (e.g. CAIN457A2304 or CAIN457A2307) without undue safety risk till completion of Week 52, eligibility will need to be discussed with the global clinical team.

‡In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

§Inhalative CS with only a topical effect (e.g., to treat asthma) are not considered "systemic immunomodulating treatments" and are therefore acceptable as co-treatment

*There is no restriction on the use of anti-histamines or the use of corticosteroids in the eye or ear.

5.5.9 Discontinuation of study treatment and premature patient withdrawal

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

Discontinuation from a treatment period

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 end of treatment (EOT) eCRF (Week 260).

Study treatment *must* be discontinued under the following circumstances:

- Withdrawal of informed consent
- Emergence of the following adverse events: adverse events that in the judgment of the investigator, taking into account the subject's overall status, prevent the subject from continuing participation in the study (for example, sepsis or serious infection).
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study.
- Pregnancy (see Section 6.5.6 and Section 7.4)
- Continued use of prohibited treatment as per recommendations in Table 5-4.
- Any other 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, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

Subjects who discontinue study treatment should NOT be considered withdrawn from the study. These subjects should have all Week 260 protocol assessments performed approximately four weeks after their last dose of secukinumab and then enter the treatment-free follow-up period (Weeks 264 and 268). Subsequently, these subjects should enter the follow-up 2 period. On the EOT eCRF (Week 260), the site staff must record the date and primary reason for stopping study treatment.

The investigator must contact the IRT when the subject completes the assessments on Week 260 due to study treatment discontinuation.

Study treatment must be discontinued after emergency unblinding.

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

See Section 6 for the required assessments of these subjects after study treatment discontinuation.

Withdrawal from a treatment-free period

If premature withdrawal occurs for any reason in the treatment-free follow up period or follow-up 2 period, 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 applicable end of study period eCRF (Follow-up period completion eCRF [Week 268] or Follow-up 2 period completion eCRF, respectively).

Patients who withdraw from the follow-up period should perform the Week 268 assessments (see Table 6-1).

Premature subject withdrawal

Subjects who state an intention to withdraw prematurely from the study will be asked to return for follow-up visits to assess safety after cessation of therapy and, if willing, to assess duration of effect (e.g. rebound assessments). If the subject returns to the study site to have his/her follow-up visits, the investigator will follow the study treatment discontinuation procedures.

The investigator must contact the IRT when the subject completes the assessments on visit of Week 260 to register the subject's early completion of the study due to subject withdrawal.

Lost to follow-up

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

5.5.10 Emergency breaking of treatment assignment

Emergency treatment code breaks should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient 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 patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system

will automatically inform the Novartis monitor for the site and the global study lead that the code has been broken.

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

Study treatment must be discontinued after emergency unblinding.

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

Subjects who are prematurely unblinded will be discontinued from the study treatment and requested to return for the end of the treatment period visit (Week 260) , two follow-up visits and follow-up 2 period as described in Section 3.1.

5.5.11 Study completion and post-study treatment

- A subject entering into CAIN457A2304E1 will be said to have completed the extension study after he/she has completed all visits and assessments as defined in Table 6-1 and received all doses of the study treatment in accordance with the protocol.
- The extension study as a whole will be considered complete when all eligible subjects rolled over from the core study (e.g., CAIN457A2304 or CAIN457A2307) have completed as per protocol the visits and assessments defined in Table 6-1 for study CAIN457A2304E1.

The investigator also must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. Subjects who complete CAIN457A2304E1 may be eligible to enter another planned extension trial.

5.5.12 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and properly managed for a prematurely withdrawn patient. 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 patient'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 Assessment Schedule lists all of the assessments and indicates with an "x" when the visits are performed.

Subjects should be seen for all visits on the designated day within the allowed "visit window" specified below or as close to it as possible.

During the treatment period, subjects may be seen at an unscheduled visit, e.g. if they experience deterioration of psoriasis, 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. A visit window of "±5" will be allowed for Week 52 to Week 260 during the treatment period during the follow-up period or as close to it as possible.

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 (Week 260) will be performed (see Section 5.5.10). Subjects will return to the study site for further assessments as indicated under the follow-up visits (Weeks 264 and 268) (see Section 3.1).

Only subjects who prematurely discontinued study treatment should enter follow-up 2 period after completion of follow-up visits (Weeks 264 and 268). Follow-up 2 period includes telephone calls every 3 months until 4 years from the time subjects have been enrolled into CAIN457A2304E1 as well as potential unplanned assessments e.g physical examinations, vital signs and laboratory assessments during this time.

If they refuse to return for the needed assessments in the follow-up period 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 dose of study treatment, including final contact at the 12-week point. Documentation of attempts to contact the subject should be recorded in the subject record.

Order of assessments:

- Subject to complete QoL tools prior to any investigator assessments. Order of QoL tools is: DLQI, EQ-5D, HAQ-DI (subjects with history of PsA only but not applicable to subjects from the CAIN457A2307 core study)
- Investigator to complete investigator assessments. Order is:
  1. IGA
  2. PASI
- All remaining study visit procedures (e.g., laboratory sample collection, vital signs measurements) must be completed prior to study treatment dosing.
- Enter PASI and IGA assessments into eCRFs BEFORE contacting IRT at any scheduled visit
- Contact IRT to register the subject visit and receive study drug assignment.

Table 6-1 Assessment schedule

	Treatment Period (Years 1 and 2)																																Unscheduled visit
Week (Relative to Baseline of core studies)	52[a] Core	52[a] Ext	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156		
Visit window (in days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5		
Day	365	365	393	421	449	477	505	533	561	589	617	645	673	701	729	757	785	813	841	869	897	925	953	981	1009	1037	1065	1093		
In office visit- all subjects	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x
Obtain informed consent		x																											Continue with Week 160	
Inclusion/exclusion criteria[1]		x																												
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		x
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		(x)
Weight	x				x			x			x				x			x			x			x				X		
Vital signs	x		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		x
Urinalysis (local)	x				x			x			x				x			x			x			x				X		
Lab analysis: chemistry and hematology[2]	x		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		x
Fasting Labs: lipid panel[2]	x							x							x						x							X		
Fasting Labs: plasma glucose [2]	x				x			x			x				x			x			x			x				X		
Serum pregnancy test[3]	x																													x[3]
Urine pregnancy test (local)[4]	x				x			x			x				x			x			x			x				X		
ECG (standard 12 lead)	x				x			x			x				x			x			x			x				X		
Blood sample for IG[5,6]	x							x							x						x							X		x[5,6]
Blood sample for PK[5,6]	x				x			x							x			x			x							X		x[5,6]
PASI	x		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		x
IGA mod 2011	x		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		x
Adverse event (AE) assessment	x		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		x
EQ-5D	x				x			x			x				x			x			x			x				X		

	Treatment Period (Years 1 and 2)																																Unscheduled visit
Week (Relative to Baseline of core studies)	52[a] Core	52[a] Ext	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144	148	152	156					
Visit window (in days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5					
Day	365	365	393	421	449	477	505	533	561	589	617	645	673	701	729	757	785	813	841	869	897	925	953	981	1009	1037	1065	1093					
DLQI	x				x			x			x				x			x			x			x				X				
HAQ-DI[8]	x				x			x			x				x			x			x			x				X				
Serious AE assessment	x		x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X		x			
Completion call for core study	x																																
Complete PASI and IGA eCRF and call IRT		x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	X					
Dispense Investigational Treatment		x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	x	x	x	x	x	x	x	x					

	Treatment Period (Years 3 and 4)																											Unscheduled visit[11]	Follow-up period		Follow-up 2 Period
Week (Relative to Baseline of core studies)	160	164	168	172	176	180	84	188	192	196	200	204	208	212	216	220	224	228	232	236	240	244	248	252	256	260		264 /F4	268 /F8	Phone call every 3 months
Visit Window (in days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5	±5	
Days	1121	1149	1177	1205	1233	1261	1289	1317	1345	1373	1401	1429	1457	1485	1513	1541	1569	1597	1625	1653	1681	1709	1737	1765	1793	1821		1849	1877	
In office visit if every 4 wks dosing			x			x			x				x			x			x			x						x	x	
Home administration if every 4 wks dosing	x	x		x	x		x	x		x	x	x		x	x		x	x		x	x		x	x	x					
In office visit if SoR dosing	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x		x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Physical examination			x			x			x				x			x			x			x				x	(x)	x	x	
Weight																										x			x	
Vital signs	O	O	x	O	O	x[1]	O	O	x	O	O	O	x	O	O	x	O	O	x	O	O	x	O	O	O	x	x	x	x	
Urinalysis (local)			x			x			x				x			x			x			x				x			x	
Lab analysis: chemistry and hematology[2]						x							x						x							x	x	x	x	
Fasting Labs: lipid panel[2]																										x			x	
Fasting Labs: plasma glucose[2]						x							x						x							x			x	

	Treatment Period (Years 3 and 4)																										Unscheduled visit[11]	Follow-up period		Follow-up 2 Period
Week (Relative to Baseline of core studies)	160	164	168	172	176	180	84	188	192	196	200	204	208	212	216	220	224	228	232	236	240	244	248	252	256	260		264 /F4	268 /F8	Phone call every 3 months
Visit Window (in days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5	±5	
Days	1121	1149	1177	1205	1233	1261	1289	1317	1345	1373	1401	1429	1457	1485	1513	1541	1569	1597	1625	1653	1681	1709	1737	1765	1793	1821		1849	1877	
Serum pregnancy test[3]																											x[3]			
Urine pregnancy test (local)[4]			x			x			x				x			x			x			x				x			x	
ECG (standard 12 lead)						x							x						x							x			x	
Blood sample for IG[5,6]													x													x	x[5,6]			x	
Blood sample for PK[5,6]													x													x	x[5,6]			x	
PASI	O	O	x	O	O	x	O	O	x	O	O	O	x	O	O	x	O	O	x	O	O	x	O	O	O	x	x	x	x	
Assessment of rebound symptoms[7]																										x	x[7]	x	x	
IGA mod 2011			x			x			x				x			x			x			x				x	x	x	x	
Adverse event (AE) assessment	O	O	x	O	O	x	O	O	x	O	O	O	x	O	O	x	O	O	x	O	O	x	O	O	O	x	x	x	x	x
DLQI			x			x			x				x			x			x			x				x				
HAQ-DI[8]			x			x			x				x			x			x			x				x				
Serious AE assessment	O	O	x	O	O	x	O	O	x	O	O	O	x	O	O	x	O	O	x	O	O	x	O	O	O	x	x	x	x	x
Complete PASI (and IGA[9]) eCRF and call IRT	O	O	x	O	O	x	O	O	x	O	O	O	x	O	O	x	O	O	x	O	O	x	O	O	O	x				

	Treatment Period (Years 3 and 4)																										Unscheduled visit[11]	Follow-up period		Follow-up 2 Period
Week (Relative to Baseline of core studies)	160	164	168	172	176	180	84	188	192	196	200	204	208	212	216	220	224	228	232	236	240	244	248	252	256	260		264 /F4	268 /F8	Phone call every 3 months
Visit Window (in days)	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5	±5		±5	±5	
Days	1121	1149	1177	1205	1233	1261	1289	1317	1345	1373	1401	1429	1457	1485	1513	1541	1569	1597	1625	1653	1681	1709	1737	1765	1793	1821		1849	1877	
Dispense Investigational Treatment [10]	O	O	x	O	O	x	O	O	x	O	O	O	x	O	O	x	O	O	x	O	O	x	O	O	O	x				
End of Treatment Period (EOT) eCRF and call IRT																										x				
Follow-up Period completion eCRF																													x	
Follow-up 2 Period completion eCRF																														x

eCRF:electronic case report form; PK:pharmacokinetics; IG:immunogenicity

O: assessment completed for subjects with protocol-mandated in-office visits in between Week 160 and 256.

*The screening period will be the duration between signing the informed consent form and enrollment registered with Interactive response technology (IRT). Subjects must sign the informed consent form after completing the core study Week 52 assessments.

[a] Enrollment into the extension study occurs on the same day (Week 52) as the end of maintenance period of the core study CAIN457A2304 or CAIN457A2307 (±5 days). The column for Week '52 core' represents assessments that will be done during the CAIN457A2304 core Week 52 visit or the CAIN457A2307 Week 40 visit. These assessments will be entered in the core study eCRFs. The column Week '52 ext' represents assessments that will be done for the CAIN457A2304E1 study.

[1]These assessments are supported by and are stored with the source documentation. However, data regarding to which Inclusion/Exclusion criteria are not met are captured on the Inclusion/Exclusion Screen eCRF.

[2] Samples will be shipped to and analyzed by the central laboratory.

[3] To be done for female subjects of childbearing potential for whom local urine pregnancy test at end of maintenance period (Week 52) of core study is positive. The study drug treatment should not be given until the results confirm that subject is not pregnant.

[4] If there is a positive urine pregnancy test, study treatment must be withheld and a serum pregnancy test must be done at the same visit.

[5] Samples will be shipped by the sites and stored by the central laboratory. Samples will be shipped to reference laboratories for analysis. Each PK and IG sample is to be collected pre-dose for visits from Week 52 to Week 256.

[6] An unscheduled IG and or PK sample is collected only to replace an IG or PK sample not taken at a regular scheduled visit. (If an IG sample is taken, a PK sample must accompany the IG sample.)

[7] Unscheduled rebound assessment only to be done for an unscheduled visit that occurs during the treatment free follow-up period following a study drug discontinuation.

[8] During this extension study, the HAQ-DI is completed only by subjects from core study CAIN457A2304 who have a history of psoriatic arthritis at the core baseline visit.

[9] IGA eCRF only needs to be completed at visits when IGA is required

[10] In subjects treated per SoR regiment, investigational treatment should only be dispensed and administered to patients meeting protocol-defined SoR treatment criteria

[11] During follow-up 2 period unscheduled visits may include unplanned assessments like physical examinations, vital signs and laboratory assessments if investigator considers this necessary.

6.1 Information to be collected on screening failures

All subjects who have signed an informed consent but who cannot or chose not to enter the CAIN457A2304E1 treatment period will be considered screen failures. If the subject discontinues before enrollment, the IRT must be called within two days and the reason for not being enrolled will be entered on the Screening Phase Disposition electronic Case Report Form (eCRF). The Screening visit date, Informed Consent eCRF, Inclusion/Exclusion Criteria eCRF must be completed. If the subject has any SAE in the screening period (between signing the ICF and being enrolled), the Adverse Event eCRF and a paper SAE form must be completed.

If a subject fails to be treated in the extension study, the subject completes the follow-up visits in the respective core study.

The Withdrawal of consent eCRF should be completed if consent was withdrawn during the screening period before the subject was enrolled. The Death eCRF should be completed in the case of a death during the screening period.

6.2 Patient demographics/other baseline characteristics

The following information will be based on information derived from core study CAIN457A2304 or CAIN457A2307. This information will not be reentered into the CAIN457A2304E1 eCRFs.

Subject demographic and baseline characteristic data to be collected on all subjects include: date of birth, age, sex, race, ethnicity, source of subject referral, and on-going concomitant medications (relative to core studies) present before signing informed consent for this extension study.

6.3 Treatment exposure and compliance

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

Compliance will be assessed by Novartis study personnel at each visit using vials counts and information provided by the pharmacist or the qualified site personnel.

6.4 Efficacy

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

It is important to **perform the IGA before the PASI,** as the knowledge of PASI scoring can potentially influence how the evaluator scores the IGA. Therefore, the following order should be applied when performing the efficacy assessments during study visits:

- Investigator's Global Assessment (IGA mod 2011; scale from 0 – 4)
- Psoriasis Area and Severity Index (PASI; score from 0 – 72)
- Rebound assessment

6.4.1 Investigator's global assessment (IGA mod 2011)

IGA mod 2011 will be conducted for overall psoriatic disease as indicated in Table 6-1. It is recommended that the same evaluator conducts the assessment throughout the study whenever possible.

The IGA mod 2011 rating scale for overall psoriatic disease is shown in Table 6-2 The IGA mod 2011 rating scale.

The IGA mod 2011 scale has been used in the core studies CAIN457A2304 and CAIN457A2307, and is a modified version of the scale used in secukinumab phase II studies; it was developed in collaboration with health authorities.

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

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

Table 6-2 The IGA mod 2011 rating scale

Score	Short description	Detailed description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.
1	Almost clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling
2	Mild	Pink to light red coloration; just detectable to mild thickening; predominantly fine scaling
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe / coarse scaling covering almost all or all lesions

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

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

6.4.2 Assessment of the psoriasis area and severity index (PASI)

The investigator or qualified designee will complete the PASI assessment as indicated in Table 6-1. Whenever possible, the same evaluator should perform this assessment at all visits.

A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 6-3. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

1. The neck is assessed as part of the head.

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

Table 6-3 The PASI scoring system

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

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

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

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

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

Because the head and neck, upper limbs, trunk and lower limbs correspond to approximately

10%, 20%, 30% and 40% of the body surface area, respectively, the PASI score is calculated using the formula:

PASI = 0.1(EH+IH+DH)AH + 0.2(EU+IU+DU)AU + 0.3(ET+IT+DT)AT + 0.4(EL+IL+DL)AL

The keys for the letters are provided in Table 6-3.

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0.

The **investigator** is only responsible for collecting the **components** or scoring signs and total regional area. PASI calculations, including changes over time will be done by Novartis via the PASI Score eCRF. At Week 52 and every visit throughout the extension study, the investigator or qualified designee should ensure that all the information required for the PASI calculation was entered into the PASI Score eCRF and that a PASI score is available prior to contacting IRT. The start of relapse status will be automatically calculated in the PASI score eCRF for the specific visit. Based on the start of relapse status, IRT will assign a medication number. This will be transmitted to the pharmacist for the preparation of the appropriate study treatment to be administered to the subject.

Definitions of efficacy variables based on PASI

The following definitions are used in this study (see CHMP guidelines for psoriasis (CHMP/EWP/2454/02 2004)), baseline referring to randomization visit in CAIN457A2304:

- **PASI 50 response:** subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders
- **PASI 75 response:** subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders
- **PASI 90 response:** subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders
- **PASI 100 response/remission:** complete clearing of psoriasis (PASI=0)
- **Relapse**: when the achieved maximal PASI improvement from baseline is reduced by >50%
- In addition to the above, the following definition is also used in this protocol:
- **Start of relapse:** loss of ≥20% of the maximum PASI gain in CAIN457A2304 or CAIN457A2304E1 (compared to baseline of the core study) achieved at any time before the visit at which the assessment is made and loss of PASI 75 response
- **PASI Partial response:** Subjects achieving at least 50%, but less than 75% reduction of PASI compared to baseline (i.e PASI 50 but not a PASI 75 response)
- **PASI Non response:** Subjects achieving less than 50% reduction of PASI compared to baseline

6.4.2.1 Assessment of rebound

Rebound of disease will be assessed as indicated in Table 6-1.

In addition, to the assessment of PASI, the investigator will assess whether new pustular psoriasis, or new erythrodermic psoriasis, or more inflammatory psoriasis occurred (yes/no).

6.4.3 Appropriateness of efficacy assessments

PASI scores outcome measures, the assessment of the severity of the psoriasis symptoms and the extent to which the subject's body area is affected by the disease, is mandated by the EMA for psoriasis (CHMP guideline on the treatment of psoriasis-CHMP/EWP/2454/02 2004).

6.5 Safety

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

- Evaluation of all AEs and SAEs including injection site reactions
- Physical examination
- Vital signs
- Laboratory evaluations
- Hematology
- Clinical chemistry
- Urinalysis
- Immunogenicity (assessment of anti-secukinumab antibody development)
- Electrocardiogram
- Pregnancy and assessments of fertility

For frequency of assessments, see Table 6-1

6.5.1 Physical examination

A physical examination, including general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological systems will be performed as indicated in Table 6-1.

If possible, assessments for an individual subject should be performed by the same member of the study site staff throughout the study.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to the signing of the informed consent form will have been already entered during core study in the Medical History screen on the subject's eCRF. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the subject's eCRF (Section 7).

6.5.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be assessed at every scheduled visit as indicated in Table 6-1.

After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured twice (measurements separated by 1 to 2 minutes) using a validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used (Mancia et al 2007). On the Vital Signs eCRF, the average of the two measurements will be entered. If possible, assessments should be performed by the same study site staff member throughout the study.

Normal blood pressure will be defined as a systolic pressure of 90 to <120 mmHg, and a diastolic blood pressure of 60 to <80 mmHg under the measurement conditions outlined above. Notable blood pressure will be hypertension (systolic ≥140 mmHg and/or diastolic ≥ 90 mmHg) or hypotension (systolic <90 mmHg and/or diastolic <60 mmHg). A blood pressure indicative of prehypertension (systolic 120 to < 140 mmHg and/or diastolic 80 to < 90 mmHg) will not be regarded as notable (Chobanian et al 2003). A normal pulse rate will be defined as a rate of 60 to 100 beats per minute under the measurement conditions outlined above. Notable pulse rates are a rate below 60 bpm (bradycardia) or above 100 bpm (tachycardia).

The investigator will decide whether action needs to be taken to address notable vital signs, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol.

6.5.3 Height and weight

Height and weight will be based on information derived from core study CAIN457A2304 or CAIN457A2307. This information will not be reentered into the CAIN457A2304E1 eCRFs at Week 52 (enrollment) and body weight will be measured as listed in Table 6-1. Body weight will be measured in indoor clothing, but without shoes. If possible, body weight assessments should be performed by the same study site staff member and using the same scale throughout the study.

6.5.4 Laboratory evaluations

Subjects should avoid smoking within the hour preceding the blood draws. A central laboratory will be used for analysis of all specimens listed below, unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual. Refer the Laboratory Manual for identification of laboratory reference range values and the schema for notification of site staff and Novartis for out of range values.

Appendix 1 shows the extended laboratory ranges that are considered clinically notable.

Whether action needs to be taken to address notable laboratory values will be decided by the investigator, taking into account the overall status of the subject. No specific action is foreseen as part of the study protocol.

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils including bands, lymphocytes, monocytes, eosinophils, basophils) and platelet count will be measured at all scheduled study visits, within the visit window specified in Table 6-1.

6.5.4.2 Clinical chemistry

Serum chemistries will include urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT),GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid. Serum chemistries will be measured at all scheduled study visits within the visit window specified in Table 6-1.

6.5.4.3 Urinalysis

Dipsticks will be provided by the central laboratory to the study sites for local urinalysis assessments. The sites will record the results in the appropriate eCRF page for each subject.

Standard dipstick measurements for specific gravity, protein, glucose, pH, blood, urine blood dipstick (non-hemolyzed), urine blood dipstick (hemolyzed), bilirubin, ketones and WBC will be done at scheduled visits as indicated in Table 6-1.

6.5.4.4 Immunogenicity (IG)

Blood samples for IG (anti-secukinumab antibodies) will be taken pre-dose at the scheduled timepoints as indicated in Table 6-1 and Table 15-2. Blood samples (approximately 2 mL) will be collected into serum separator tubes (SST). The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2500 revolutions per minute (rpm) for 10 minutes.

Serum samples will be placed on ice, split into 2 aliquots (labeled plain barrier polypropylene tubes) and then stored (within 30 minutes of collection) at approximately -70°C to -20°C prior to shipment on dry ice to the central laboratory. Shipment of stored aliquots from the site to the central lab should be on a monthly basis. To the extent possible, the site should send each aliquot to the central laboratory separately. If a study site does not have the facility to store aliquots at the conditions specified, then they will maintain the sample on dry ice at the site and ship on dry ice on the day of collection. The central lab will ship one aliquot of the samples on dry ice to the analytical laboratory. The remaining aliquots must be kept at the central lab as a backup sample. Remaining samples will only be disposed of after approval by the global study lead (typically 6 to 12 months after the clinical study report [CSR] is published).

All blood samples will be taken by direct venipuncture. The actual sample collection date and exact time of collection will be entered on the Blood collection for IG eCRF or the unscheduled blood collection for IG eCRF, as appropriate. Sampling problems will be noted in the ‘Reason sample not taken’ section of the eCRF.

A laboratory manual 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 and sample number preprinted on the label.

Further details on labeling of the IG samples can be found in Appendix 4, Section 16.1.1

6.5.5 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed as indicated in Table 6-1. At each visit when an ECG is done, the investigator must review and initial the tracing. The tracing must then be stored with the subject's source documents.

All ECGs must be performed on the ECG machines provided to the study site. All ECGs will be independently reviewed by a central reader. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

Even though there is no exclusion criterion specifically based on the ECG, clinically significant findings from the ECG assessment made at Week 52 of the core study must be discussed with the Novartis Medical Monitor prior to enrolling the subject in the extension study.

If the ECG findings are clinically relevant and would prevent the subject from participating in the study (taking into account the subject's overall status as well as the medication profile), the subject should not receive study treatment.

6.5.6 Pregnancy and assessments of fertility

A serum β-hCG test will have already been performed on all women of child-bearing potential who entered studies CAIN457A2304 and CAIN457A2307.

All women of child-bearing potential who are eligible to participate in this extension study will have a local urine pregnancy test as indicated in Table 6-1. If positive, they will undergo a serum pregnancy evaluation conducted at the Central Laboratory

Any woman whose resulting pregnancy test is positive (based on serum β-hCG as defined by the Central Laboratory) at the Enrollment Visit Week 52 will have to discontinue from this extension study and return to the follow-up assessments in the core study.

A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, the subject must be discontinued from the trial (as per Section 5.5.10)

6.5.7 Appropriateness of safety measurements

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

6.6 Other assessments

These include (as indicated in Table 6-1)

- Fasting laboratory evaluations,
- Health-related quality of life assessments such as
  1. DLQI

2. EQ-5D
3. HAQ-DI (only in subjects with psoriatic arthritis from study CAIN457A2304, not CAIN457A2307)

- PK assessments will be done as indicated in Table 6-1.

[redacted]

6.6.1 Fasting laboratory evaluations

Fasting (8 hour duration with water *ad libitum*) laboratory tests will be assessed as indicated in Table 6-1.

Subjects should avoid smoking within the hour preceding the blood draws.

A central laboratory will be used for analysis of all fasting laboratory specimens. Details of the collections, shipment of samples and reporting of results by the central laboratory are provided to the investigators in the Laboratory Manual.

6.6.1.1 Plasma glucose

Fasting plasma glucose will be taken as a fasting blood sample at scheduled visits as indicated in Table 6-1.

6.6.1.2 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol, triglycerides, lipoprotein (a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be measured from a fasting blood sample at scheduled visits as indicated in Table 6-1.

6.6.2 Resource utilization

Not applicable

6.6.3 Health-related Quality of Life

The impact of psoriasis on various aspects of subject's health-related quality of life will be assessed by the following validated instruments:

- Dermatology Life Quality Index (DLQI©)
- EuroQOL 5-Dimension Health Status Questionnaire (EQ-5D©)
- Health Assessment Questionnaire- Disability Index (HAQ©-DI) (subjects with PsA from study CAIN457A2304 only)

At the appropriate scheduled visits (see Table 6-1), questionnaires are to be completed by each subject in the language with which she/he is most facile, and **before** she/he sees the Investigator for clinical assessments. Responses will be collected using digitized paper with a digital pen. The digitized paper will serve as source documentation; the pen will be transferred to its docking station for transmittal of the subject's responses to the vendor's database. Subjects are to complete the "Patient Reported Outcome (PRO) - Completion confirmation by the patient" page after completing all the questionnaires of a visit. This document will not be sent to the sponsor but kept at site in source documents.

The subject is to be given sufficient space and time to complete the questionnaires. The study coordinator is to 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 source documentation.

Completed questionnaires will be reviewed and examined by a blinded staff member at the site (not the Investigator or evaluator of the subject for the physician assessments), before the clinical examination, for responses that may indicate potential AEs or SAEs. The Investigator is to review not only the responses to the questions in the questionnaires but also to look for unsolicited comments written by the subject. If AEs or SAEs are confirmed by the Investigator, then she/he must record the events as per instructions given in Section 7 of the protocol.

Investigators and study coordinators are not to encourage subjects to change the responses reported in the completed questionnaires. Study coordinators are to complete the header information at the top of the questionnaire prior to distributing it to the subjects.

6.6.3.1 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay and Khan, 1994). The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school. The measure is widely used: it has been tested across 32 different skin conditions and is available in 55 languages. The recall period is the last week, and the instrument requires 1 to 2 minutes for completion. Each item has four response categories, ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI total score is a sum of the 10 questions. Scores range from 0 to 30 and higher scores indicate greater health-related quality-of-life impairment. Additionally, each subscale of the DLQI may be analyzed separately.

The DLQI questionnaire (date of publication 1994) will be completed by the subject as indicated in Table 6-1.

6.6.3.2 EuroQOL 5-Dimension (EQ-5D©) Health Status Questionnaire

EQ-5D© is a generic instrument to assess each subject's health status. It provides a simple descriptive profile and a single index value for health status. The instrument essentially consists of 2 pages – the EQ-5D© descriptive system and the EQ visual analog scale (VAS). The EQ-5D© descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Each dimension has 3 response levels: no problems, some problems, severe problems. The subject is asked to indicate her/his health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

The VAS records the respondent's self-rated health on a vertical scale where the endpoints are labeled 'Best imaginable health state' and 'Worst imaginable health state'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

The EQ-5D© questionnaire (date of publication 1990) is to be completed by the subject at the visits indicated in Table 6-1.

6.6.3.3 Health Assessment Questionnaire- Disability Index (HAQ©-DI) (subjects with PsA only)

The Health Assessment Questionnaire (HAQ©) was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. Although originally developed for use in subjects with rheumatic disease, the HAQ has been employed across a large variety of disease areas. The disability assessment component of the HAQ (Health Assessment Questionnaire© – Disability Index), the HAQ-DI, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 items in eight categories of functioning including dressing & grooming, arising, 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 (without any difficulty [0]), with some difficulty (1), with much difficulty (2), and unable to do (3). The HAQ-DI also includes questions about the use of 'aids or devices' and aid from other people to supplement the answers given to the 20 items.

The purpose of the HAQ-DI in this study is to provide long-term information on the functional ability of psoriasis subjects that also suffer from psoriatic arthritis.

The HAQ-DI questionnaire will be completed by the subject as indicated in Table 6-1 by all subjects with a medical history of PsA recorded on the Psoriatic Arthritis History eCRF during the screening period of the CAIN457A2304 core study (subjects from the CAIN457A2307 study will not participate in the HAQ-DI questionnaire).

6.6.4 Pharmacokinetics

At all study sites, blood samples will be collected for PK at the scheduled visits as indicated in Table 6-1.

For a detailed description of the blood sampling schema, including time points, refer to the Blood Log in Appendix 3, Table 15-1.

All blood samples will be taken by direct venipuncture. Blood samples (approximately 2 mL, not less than 1.5 mL) will be collected into SST tubes. The blood sample will be allowed to clot over a minimum of 30 minutes at room temperature prior to harvesting of the serum. The serum will be obtained by centrifugation at approximately 2,500 rpm for 10 minutes.

Serum samples will be placed on ice, split into 2 aliquots (polypropylene tubes) and then stored (within 30 minutes of collection) at -70°C to -20°C (approximately) prior to shipment to the central laboratory. Shipment of stored aliquots from the site to the central lab should be on a monthly basis. To the extent possible, the site should send each aliquot to the central laboratory separately. If a study site does not have the facility to store aliquots at the conditions specified, then samples must be stored on dry ice at the site and shipped on dry ice on the day of collection. The central lab will ship one aliquot of the samples on dry ice to the analytical laboratory. The remaining aliquots must be kept at the central lab as a backup sample. Remaining samples will

only be disposed of after approval by the global study lead (typically 6 to 12 months after the Clinical study report (CSR) is published).

The actual sample collection date and exact time of collection will be entered on the Blood collection for PK eCRF or the Unscheduled blood collection for PK eCRF, as appropriate. Sampling problems will be noted in the 'Reason sample not taken' section of the eCRF.

PK sample handling, labeling and shipment instructions

A laboratory manual 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 and sample number preprinted on the label.

Further details on labeling of the pharmacokinetics samples can be found in Appendix 4, Section 16.1.1

PK sample stability

AIN457 is stable in serum samples for 4 months at -20°C or at -80°C. Longer stability assessment is ongoing.

PK analytical methods

An ELISA method will be used for bioanalytical analysis of AIN457 in serum, with an anticipated lower limit of quantification (LLOQ) of 80 ng/mL. The detailed method description to assess AIN457 concentration will be described in the bioanalytical raw data of the study and in the respective BDR.

[redacted]

6.6.6 Other biomarkers

Not applicable.

7 Safety monitoring

7.1 Adverse events

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

The occurrence of adverse events should be sought by non-directive questioning of the patient at each office visit or each telephone call during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Subjects must be instructed to contact the investigator/site staff prior to any self-administration of study drug if they have any AEs or SAEs to report.

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 patient 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 *(select what is applicable)*
  study treatment (no/yes), or
  investigational treatment (no/yes), or
  the other study treatment(non-investigational) (no/yes), or
  both or indistinguishable,
- 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 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 patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient 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); [study/investigational] *(select)* 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 patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient'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 patient safety, every SAE, regardless of causality, occurring during following time periods must be reported to Novartis within 24 hours of learning of its occurrence:

- after the subject has provided informed consent and until 12 weeks after the last administration of study treatment or 30 days after the subject has stopped the study participation (defined as last visit of the study at Week 268) for subjects who don't enter follow-up 2 period
- after the subject has provided informed consent and until the last telephone contact for patients who enter follow-up 2 period

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

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

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

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

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

Follow- up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or

progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

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

7.3 Liver safety monitoring

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

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of LFTs elevations
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

Please refer to Table 14-1 in Appendix 2 for complete definitions of liver events.

Any liver event which meets the criteria for "**medically significant**" event as outlined in Table 14-1 of Appendix 2 should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Every liver event as defined in Table 14-1 of Appendix 2 should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in Table 14-2 in Appendix 2.

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

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

7.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be

followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

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

7.5 Prospective suicidality assessment

Not applicable.

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 patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

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 patients will be disclosed.

8.2 Data collection

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

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed

or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

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

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

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

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

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) may review the safety data of this trial at selected time intervals. If needed, details regarding the DMC process will be available in relevant secukinumab DMC charter.

8.5 Adjudication Committee

Not required.

9 Data analysis

Treatment groups for analysis will include:

- Secukinumab 150 mg fixed interval

- Secukinumab 300 mg fixed interval
- Secukinumab 150 mg start of relapse
- Secukinumab 300 mg start of relapse
- Secukinumab 300 mg open-label
- Secukinumab 300 mg open-label switch

9.1 Analysis sets

Randomized set: The randomized set will be defined as all subjects who were randomized in core studies and who entered this extension study.

Full analysis set (FAS): The FAS will be comprised of all subjects entered the study. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization in core study. If the actual stratum is different to the assigned stratum in IRT, the actual stratum will be used in analyses.

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

9.2 Patient demographics and other baseline characteristics

Demographics and baseline characteristics

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

Medical history

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

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

Psoriasis specific medical history will be summarized by treatment group. Previous treatments for psoriasis and whether or not response was achieved will be summarized by treatment group.

All the medical history information will be retrieved from the core studies.

9.3 Treatments

Study treatment

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

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

Prior and concomitant medication

Prior and concomitant medications will be summarized in separate tables by treatment group.

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

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

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

The number and percentage of subjects receiving different classes of prior psoriasis therapy (biologic systemic therapy, non-biologic systemic therapy, topical, phototherapy, photochemotherapy) will be presented by treatment group as well as the reasons for stopping their previous prior psoriasis therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other) and the total duration of exposure to psoriasis therapies previously.

Prior concomitant medications will be retrieved from the core studies.

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

The primary analysis will focus on safety variables, please refer to Section 9.5.2. There are no other key secondary variables assessed in this study.

9.4.1 Variable(s)

Not Applicable

9.4.2 Statistical model, hypothesis, and method of analysis

Not applicable

9.4.3 Handling of missing values/censoring/discontinuations

Missing values in efficacy analyses, except for maintenance of response will not be imputed. All analyses will be based on observed values only.

For maintenance of response, please see definition below, missing values with respect to response variables based on PASI score score will be imputed with non-response regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). Following the intent-to-treat principle for subjects who prematurely discontinue treatment, but who are observed in the follow-up period, efficacy data collected in follow-up periods will be linked to planned but missed study visits as well, following imputation schemes described in the analysis plan.

Subjects who opt to change treatment regimen or dose level and move into open-label treatment with 300 mg s.c. secukinumab every four weeks for the remainder of the trial will be considered as non-responders in the analysis of maintenance of response.

For other efficacy analyses they will not be considered after the timepoint of switching.

9.4.4 Supportive analyses

Not applicable

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Maintenance of response

Maintenance of response will be defined analogously as in the primary endpoint in CAIN457A2304, but for week 104 and 156, i.e. PASI 75 response

- at Weeks 104 and 156, for subjects in the fixed interval regimens, or
- at Weeks 92 and 144, for subjects in the retreatment at start of relapse regimen who do not require active treatment at Week 92 or 144, respectively, or
- at Weeks 104 and 156, for subjects in the retreatment at start of relapse regimen who do require active treatment at Week 92 or 144, respectively.

Summary statistics for maintenance of response at Week 104 and 156 will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe 1998).

PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response over time

Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response by visit will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals for response rates will be derived as well based on the score method including continuity correction (Newcombe, 1998).

PASI score over time

Summary statistics will be provided for absolute PASI scores as well as for percent change from baseline by visit and treatment group. Figures will also be provided.

IGA mod 2011 score over time

Summary statistics for the IGA mod 2011 score over time will be presented by visit and treatment group in contingency tables.

Relapse

The number and percentage of subjects experiencing relapse will be presented by visit and treatment group.

Rebound

Rebound is defined as a worsening of PASI of > 125% of the value at baseline (core study), or new pustular, erythrodermic or more inflammatory psoriasis occurring within 8 weeks of stopping therapy (i.e., if this definition is fulfilled at more than 8 weeks after last study treatment administration, this is not defined as rebound). The number and percentage of subjects experiencing rebound will be presented by visit and treatment group.

9.5.2 Safety variables

All safety evaluations will be performed on the Safety set.

Adverse events

Treatment emergent adverse events are defined as any events started after the first dose of study treatment and within 84 days after the last study treatment, or events present prior to the first dose of study treatment, but increased in severity based on preferred term within 84 days after the last study treatment.

With the exception of adverse events that qualify as "treatment emergent" (see definition above), data collected from telephone visits and unscheduled visits in follow-up period 2 will only be included in individual patient listings, but not in summary tables.

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

Confidence intervals for relative frequencies will be derived as well according to the score method including continuity correction by Newcombe, 1998.

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, if appropriate, will be presented.

For infections, time-to-event analysis will be done. Results will be tabulated and the Kaplan-Meier estimates for the cumulative rate will be plotted.

Additional analyses will be provided for adjudicated adverse events.

In supplementary analyses, exposure (or observation)-time adjusted analyses in terms of incidence rate and event rate will be provided.

Laboratory data

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

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

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

Immunogenicity

Summary statistics for baseline, each post-baseline visit and change from baseline to each visit will be provided. Summary statistics will be provided for the percent of subjects with immunogenicity. If appropriate, shift tables will also be presented.

Vital signs

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

ECG

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

9.5.3 Resource utilization

Not applicable

9.5.4 Health-related Quality of Life

Summaries will be based on the FAS and will be presented separately for study periods (i.e., treatment period and follow-up period) if not specified otherwise.

EQ-5D

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

DLQI©

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

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

In addition, summary statistics will be provided for number of subjects achieving DLQI 0 or 1.

HAQ©-DI (for subjects with PsA at baseline of the core study)

Summary statistics will be derived for HAQ©-DI score over time for all subjects with psoriatic arthritis recorded on the Psoriatic Arthritis History eCRF at screening visit of the core study. Absolute and relative frequencies for HAQ©-DI response will also be presented. HAQ©-DI response is defined by an improvement of 0.3 score points compared to baseline.

9.5.5 Pharmacokinetics

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

[redacted]

[redacted]

9.5.7 Biomarkers

Not applicable.

9.5.8 PK/PD

Not applicable.

9.6 Interim analyses

One interim analysis is planned for this study. At time of marketing authorization submission of the AIN457A project, the safety data of this extension study will be reported. Since the core studies have been unblinded at that stage, this interim analysis will also be unblinded. Of note, investigators, subjects and site staff will remain blinded to individual treatment group assignments.

Further interim analyses, as regarded appropriate, can be conducted (e.g., for regulatory or publication purposes).

9.7 Sample size calculation

Study CAIN457A2304 planned to randomize 918 subjects. Assuming that 5% of the subjects drop-out up to Week 12, and further 15% drop-out in CAIN457A2304 or CAIN457A2307 it is estimated that about 740 subjects will be eligible to enter this study. Assuming that the PASI 75 response rate at Week 12 in CAIN457A2304 is 80% and under the assumed drop-out rates above, about 148 subjects of each of the four treatment groups of CAIN45A2304 will be eligible to enter this extension study.

With 148 subjects per treatment group the likelihood to observe at least one occurrence of an AE with a crude incidence of 0.1% is about 14% and with a crude incidence of 1% is about 77%.

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 patients 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 patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

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

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.

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 patient 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 patient 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

References are available upon request

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13 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. Notable values for blood pressure and pulse are presented in Section 6.5.2 Whether action needs to be taken to address notable laboratory or vital signs values will be decided by the investigator, taking into account the overall status of the subject. No specification is foreseen as part of the study protocol.

Liver Function and Related Variables

Alanine transaminase (ALT) (SGPT):	> 3 x Upper Limit of Normal (ULN)
Aspartate transaminase (AST) (SGOT):	> 3 x ULN
Total bilirubin:	> 2 x ULN
Alkaline phosphatase:	> 2.5 x ULN

Renal Function and Electrolyte Variables

Creatinine (serum):	> 1.5 x ULN
Potassium:	> 6 mmol/L or < 3 mmol/L
Sodium:	> 160 mmol/L or < 115 mmol/L

Hematology Variables

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

Urinalysis Variable

Protein urine dipstick:	++*

* ++ is ≥ 100 mg/dL

14 Appendix 2: Liver event definitions and follow-up requirements

Table 14-1 Liver Event Definitions

	Definition/ threshold
Adverse event of special interest	
Laboratory values	ALT or AST > 3 x ULN
	ALP > 2 x ULN
	TBL > 1.5 x ULN
Medically significant event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction])
	TBL > 3 x ULN
	Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN)
Adverse events	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

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

Table 14-2 Liver Event Follow Up Requirements

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for *more than 2 weeks*, discontinue the study drug Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms[b]	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to ≤5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Event type	Actions required	Follow-up monitoring
		Repeat LFT once or twice in the weekIf elevation persists, establish causality	
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the weekIf elevation persists, establish causality	investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)
"Drug-related hepatic disorders - severe events only" SMQ AE	Medically significant	Discontinue the study drug hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

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

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

15 Appendix 3: Blood collection log for pharmacokinetics (PK) and immunogenicity (IG)

Table 15-1 Blood collection log for PK

Visit Name	Time point	Volume (approx.)	Analyte	Sample number	Dose Reference ID/ PK collection number**
Week 52[1]	Pre-dose	(2 mL)	AIN457 for PK	(5)	(5)
Week 64	Pre-dose	2 mL	AIN457 for PK	7	7
Week 76	Pre-dose	2 mL	AIN457 for PK	8	8
Week 104	Pre-dose	2 mL	AIN457 for PK	9	9
Week 116	Pre-dose	2 mL	AIN457 for PK	10	10
Week 128	Pre-dose	2 mL	AIN457 for PK	11	11
Week 156	Pre-dose	2 mL	AIN457 for PK	12	12
Week 208	Pre-dose	2 mL	AIN457 for PK	13	13
Week 260	672 hours*	2 mL	AIN457 for PK	14	14
Week 268 (F8)	2016 hours*	2 mL	AIN457 for PK	15	14

[1]The data and sample numbering for Week 52 visit (enrollment) will have been collected as part of the end of maintenance visit (Week 52) from core study CAIN457A2304 or CAIN457A2307

* Scheduled post-dose time points for sample numbers 14 and 15 (672 hours and 2016 hours post-dose, respectively) refer to the last dose given at Week 256 as time 0.

** If a PK sample is collected at an unscheduled visit, the sample numbers will follow the pattern, 1001, 1002, etc.

Table 15-2 Blood collection log for IG

Visit Name	Time point	Volume (approx.)	Analyte	PK collection number**
Week 52[1]	Pre-dose	(2 mL)	anti-AIN457 for IG	(504)
Week 76	Pre-dose	2 mL	anti-AIN457 for IG	506
Week 104	Pre-dose	2 mL	anti-AIN457 for IG	507
Week 128	Pre-dose	2 mL	anti-AIN457 for IG	508
Week 156	Pre-dose	2 mL	anti-AIN457 for IG	509
Week 208	Pre-dose	2 mL	anti-AIN457 for IG	510
Week 260	672 hours*	2 mL	anti-AIN457 for IG	511
Week 268(F8)	2016 hours*	2 mL	anti-AIN457 for IG	512

[1]The data and sample numbering for Week 52 visit (enrollment) will have been collected as part of the end of maintenance visit (Week 52) from core study CAIN457A2304 or CAIN457A2307

* Scheduled post-dose time points for sample numbers 511 and 512 (672 hours and 2016 hours post-dose, respectively) refer to the last dose given at Week 256 as time 0.

** If an IG sample is collected at an unscheduled visit, the sample numbers will follow the pattern, 3001, 3002, etc.

16 Appendix 4: Pharmacokinetics (PK) and immunogenicity (IG) sample labeling information

16.1.1 PK sample handling

The samples must be labeled as in the following example and as provided by the central laboratory

Study code:	CAIN457A2304**E1**
Site:	cccc (4 digits for the current site number)
Subject:	Ccccrrr (4 digits for the site number where the subject was enrolled concatenated with 3 digits for the assigned subject number. Add '0' ahead of the numbers if needed to obtain the correct number of total digits)
Sample number:	As indicated in Table 15-1
Analyte:	AIN457 for PK

Labels will be provided by the central laboratory with all information preprinted.

As PK samples are managed by a central laboratory, no added label should cover the original label.

16.1.2 IG sample handling

The samples must be labeled as in the following example and as provided by the central laboratory

Study code:	CAIN457A2304**E1**
Site:	cccc (4 digits for the current site number)
Subject:	Ccccrrr (4 digits for the site number where the subject was enrolled concatenated with 3 digits for the assigned subject number. Add '0' ahead of the numbers if needed to obtain the correct number of total digits)
Sample number:	As indicated in Table 15-2
Analyte:	anti-AIN457 for IG

Labels will be provided by the central laboratory with all information preprinted.

As IG samples are managed by a central laboratory, no added label should cover the original label.