NOVARTIS

Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol for Study CAIN457A2302E1 / NCT01544595

A multicenter, double-blind, randomized withdrawal extension study of subcutaneous secukinumab in prefilled syringes to demonstrate long-term efficacy, safety and tolerability up to 4 years in subjects with moderate to severe chronic plaque-type psoriasis completing preceding psoriasis phase III studies with secukinumab

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List of abbreviations

AE	adverse event
ALT	alanine aminotransferase/glutamic pyruvic transaminase/GPT
ANCOVA	analysis of covariance
AST	aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT
ATC	anatomical therapeutic classification
CHMP	the European Union Committee for Medicinal Products for Human Use
CPO	country pharma organization
CRF	case report/record form (paper or electronic [e])
CRO	contract research organization
CS	corticosteroid (s)
CSR	clinical study report
DS&E	Drug Safety & Epidemiology
DLQI	Dermatology Life Quality Index©
DMC	data monitoring committee
ECG	electrocardiogram
EDC	electronic data capturing
EQ-5D	EuroQOL 5-Dimension© Health Questionnaire
FAS	full analysis set
FDA	United States Food and Drug Administration
HAQ	Health Assessment Questionnaire©
HAQ-DI	Health Assessment Questionnaire© – Disability Index
HDL	high density lipoprotein
HRQoL	health-related quality of life
IA&R	Integrated Analytics & Reporting
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ICF	informed consent form
IGA	investigator's global assessment
IGA mod 2011	Novartis investigator's global assessment modified 2011
IIS	Integrated Information Sciences

IG	immunogenicity
IL	interleukin
IRB	institutional review board
IRT	interactive response technology
IVRS	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
OC/RDC	oracle clinical/remote data capturing
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamic(s)
PFS	prefilled syringe
PK	pharmacokinetic (s)
PMDA	Pharmaceutical and Medical Devices Agency (Japan)
PsA	psoriatic arthritis
PUVA	psoralen + UVA treatment
REB	research ethics board
s.c.	subcutaneous
SAE	serious adverse event
VAS	visual analog scale

Glossary of terms

Term	Definition
Assessment	A procedure used to generate data required by the study
Control treatment	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.
Core studies	Refers to the secukinumab phase III studies (e.g., CAIN457A2302 or CAIN457A2303 and other secukinumab phase III studies) from which subjects meeting the inclusion/exclusion criteria will potentially enter the extension study CAIN457A2302E1
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Epoch	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 treatment	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study treatment administration and assessments; at this time all study treatment administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Stop study participation	Point/time at which the subject came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Any treatment administered to the subject as part of the required study procedures; includes investigational treatment and any control treatments
Study treatment discontinuation	Point/time when subject permanently stops taking study treatment for any reason; may or may not also be the point/time of premature subject withdrawal
Subject Number	A number assigned to each subject who enrolls in the study. When combined with the site number, a unique identifier is created for each subject in the study.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 3

Amendment rationale

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 CAIN457A2302E1 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 mediations through telephone calls for all subjects who have prematurely discontinued treatment.

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

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 5.5.12 was updated to reflect that the study will NOT be terminated in selected countries where the drug is commercially available.

Section 7.1 was updated to reflect that AE evaluation is done at each telephone call during follow-up 2 period as well.

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

Section 6.5.4 and Table 6-1 were updated to add Amylase and Lipase to the Chemistry analysis panel to collect additional safety information [redacted]

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 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 2, 09-Sep-2014

Amendment rationale

The purpose of this amendment is to clarify the wording for countries not selected for early trial termination when the drug is commercially available, this study will continue up to the end of additional 104 weeks of treatment. It also clarifies a discrepancy in the Assessment Schedule that PK samples at Week 140 are collected for all subjects and at Week 144 in case of relapse. This is consistent with Appendix 2.

Changes to the protocol

These changes were made to the protocol:

- Section 5.5.12 was updated to reflect the clarification to early study termination.
- Table 6-1 included a correction that PK samples are collected for all subjects at Week 140 and at Week 144 in case of relapse.

At the time of this amendment, recruitment is complete with 1146 patients randomized into the trial. It is not expected that this amendment will influence the study population or have a significant impact on the primary objective of the trial

Amendment 1, 08-April-2014

Amendment rationale

The purpose of this amendment is to provide continued treatment for patients in the trial for an additional 104 weeks (or overall up to four years) or until the drug is commercially available in the market in the country of participation, whichever occurs first. This extension of treatment will allow for safety, tolerability, and efficacy data to be collected from the participating patients for a longer time period.

All subjects will be unblinded and start open label at week 156. Subjects on secukinumab 150 mg may continue on 150 mg every 4 weeks or switch to 300 mg at Week 156 or any other regular site visit if the investigator feels the subject would benefit from the higher dose. Patients on 300 mg will continue on 300 mg. Patients who were on placebo during the randomized withdrawal period will start secukinumab 150 mg or 300 mg if the investigator decides the subject would benefit from the higher dose.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions. The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Changes to the protocol included:

- Synopsis was updated to reflect the changes in the main protocol text.
- Added one study figure to describe the updated study design (Fig 3-1).
- Section 1.1 was updated to reflect the purpose of extending the study for additional 2 years to obtain safety data.
- Study design (Section 3.1) was updated to include the open label period of the study and to allow the subjects to self-inject at home. It will also allow the subjects receiving 150mg secukinumab to switch to a higher 300 mg dose of secukinumab during this period of the study.
- Rationale of the study design (Section 3.2) was updated to clarify that the added open label period is primarily designed to collect additional safety data.
- Section 3.5 was updated to allow possible Interim Analysis in the future if needed
- Section 3.6 refers to Investigator Brochure for the most updated Risk/Benefit profile
- Inclusion criteria (Section 4.1) were updated to specify the eligibility for the subjects to enter the extension maintenance period.
- Treatment groups (Section 5.2) were updated to include the extension maintenance period.
- Treatment blinding (Section 5.4) was updated to include the open label period, which is an unblinded study period.
- Dispensing the investigational treatment (Section 5.5.2) describes that investigator will dispense via IRT, treatment packages for self-injection at home.
- Section 5.5.4 was updated with the Home Administration instructions

- Prohibited treatment (Section 5.5.8) was updated to further clarify the use of prohibited concomitant medications to allow the use of antihistamines and topical corticosteroids
- Section Discontinuation from treatment period (Section 5.5.9) clarifies the procedures for patient who discontinue during the withdraw treatment /treatment period vs. the open label period
- Section 5.5.12 clarifies that the study treatment might be discontinued in those countries when the study drug becomes commercially available
- Visit schedule (Section 6) was updated with assessments for the extension maintenance period
- PK sample stability was clarified in Section 6.6.5
- Section 9.6 clarifies that additional interim analyses may be conducted at various time points for publications or health authority request

Protocol synopsis

Title of study: A multicenter, double-blind, randomized withdrawal extension study of subcutaneous secukinumab in prefilled syringes to demonstrate long-term efficacy, safety, and tolerability up to 4 years in subjects with moderate to severe chronic plaque-type psoriasis completing preceding psoriasis phase III studies with secukinumab.

Purpose and rationale: This extension study (CAIN457A2302E1) is planned to collect an additional four years of long-term efficacy, safety, and tolerability data of secukinumab in either continuous or interrupted therapy (randomized withdrawal period) in subjects completing either one of the two phase III studies CAIN457A2302 or CAIN457A2303 (and potentially other secukinumab phase III studies) and showing at least partial response to secukinumab at Week 52 of the core study .

An interim analysis on safety data only at time of submission and a primary endpoint analysis (PEA) up to Week 68 will be conducted. The data collected in this study up to the time of the interim analysis may be part of the submission package. The data collected beyond the time of the interim analysis will deliver important long-term information on the effect of long-term treatment of chronic plaque-type psoriasis with secukinumab. Additional interim analyses may be conducted at various time points for publications or health authority requests.

The double-blind randomized withdrawal period will allow assessing whether continuation of treatment with secukinumab is of benefit to subjects after having been treated with secukinumab for up to 52 weeks in the preceding phase III studies, compared to stopping treatment with secukinumab. In addition, this treatment period will deliver important information on the effect of stopping treatment with secukinumab, including time to relapse (i.e., loss of ≥50% of previous gain in PASI reduction) and frequency of rebounds, and therefore addresses the needs brought forward by Health Authorities.

Objectives:

Primary objective

To demonstrate the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis, who were PASI 75 responders at Week 52 of the core study, with respect to loss of PASI 75 up to Week 68, compared to placebo.

Secondary objectives

- To assess the efficacy of secukinumab 150 mg or 300 mg with respect to PASI 50/75/90/100 response and IGA 0 or 1 response, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg with respect to PASI score and IGA mod 2011 score, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To assess time to PASI 75 response **for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg**.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to loss of IGA 0 or 1 response, compared to placebo **in subjects who were PASI 75 responders and IGA 0 or 1 responders at Week 52.**
- To assess time to IGA 0 or 1 response for subjects who were IGA 0 or 1 responders at re-randomization, and who lost IGA 0 or 1 response during randomized withdrawal, and **who were re-treated after relapse with secukinumab 150 mg or 300 mg.**
- To assess the clinical safety of secukinumab 150 mg or 300 mg as assessed by vital signs, clinical laboratory values, electrocardiograms (ECGs), and adverse events (AEs) monitoring,

compared to placebo in subjects who were PASI 75 responders at Week 52, in subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and in subjects who were partial responders at Week 52.

- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to changes in Dermatology Life Quality Index© (DLQI©), compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to DLQI 0 or 1 achievement, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to EuroQOL 5-Dimension© Health Questionnaire (EQ-5D©) score, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To investigate the effects of treatment with secukinumab 150 mg or 300 mg on the occurrence of rebound following cessation of therapy, in subjects who were PASI 75 responders at Week 52, for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to relapse, compared to placebo **in subjects who were PASI 75 responders at Week 52.**
- To investigate the development of immunogenicity (IG) against secukinumab over time.

Exploratory objectives

- [redacted]
- [redacted]
- To explore the effects of treatment with secukinumab with respect to the Health Assessment Questionnaire©– Disability Index (HAQ©-DI) in subjects with psoriatic arthritis (PsA) at baseline of core study over time.

Study design:

CAIN457A2302E1 is a four year multicenter, double-blind, randomized withdrawal extension study of two ongoing phase III studies CAIN457A2302 and CAIN457A2303 and will potentially include subjects rolling over from other secukinumab phase III studies (preceding studies collectively referred as core studies). About 1,220 subjects from approximately 300 sites in studies CAIN457A2302 and CAIN457A2303 are rolling over to this extension study.

In this extension study, the prefilled syringe (PFS) liquid formulation of secukinumab will be used. In order to maintain double-blind in this study, matching placebo is used.

This 4 year extension study will include a 2-year double blind period (between Week 52 and Week 156), during which randomized withdrawal analysis will be performed, followed by an additional 2-year open label period (between Week 156 to Week 260). The subjects will receive the last blinded treatment at Week 152. At Week 156, after performing the scheduled study assessments, the site will contact IRT

to unblind the study treatment. Therefore Week 156 is the end of blinded withdrawal treatment/treatment period (EoT) and the beginning of the open label period. Week 156 will be the first open label treatment. Subject will receive the last dose of the study drug at Week 256. Week 260 will be the end of open label treatment period (OL-EoT).Subjects completing the maintenance period (52 weeks) in the core studies (e.g., CAIN457A2302 and CAIN457A2303) will be classified based on Week 52 PASI response as **PASI 75 responders** (achieving at least PASI 75) or **partial responders** (achieving at least PASI 50, but not PASI 75) or **non-responders** (not achieving at least a PASI 50 response). This Week 52 visit in the core studies is the randomization visit for CAIN457A2302E1 (extension study).

For the subjects classified as PASI 75 responders at Week 52 the study consists of 5 or 6 periods

(i) screening period: is the duration between signing the informed consent form (ICF) and randomization registered with Interactive Response Technology (IRT).

(ii) randomized withdrawal period: the duration of randomized withdrawal period for each subject is different i.e., starting from Week 52 until the subject experiences the relapse or up to Week 156.

(iii) treatment period: A placebo subject experiencing a relapse during the withdrawal period will receive four doses of secukinumab s.c. at weekly intervals followed by secukinumab s.c. every four weeks. Subjects on secukinumab in the randomized withdrawal period who have a relapse, will be given four weekly doses of placebo s.c. Following the loading doses, subjects will continue on secukinumab treatment at 4 week intervals. Any subject, whether randomized to placebo or active treatment, will only be treated once with the weekly loading dose regimen. For subsequent relapses, patients will continue on secukinumab at 4 week intervals. Week 152 will be the last dose of the blinded treatment period. At Week 156 subjects will enter the open label period. The site must call IRT in order to unblind the subject to enter the open label period prior to performing the dosing.

(iv) open label period: The treatment will be unblinded at Week 156 and the subjects will enter the open label period. During this period, the subjects will be given pre-filled syringes and instructed to perform self-injection at home every 4 weeks and return to the site every 12 or 16 weeks (please see Table 6-1 Assessment schedule). The first open label dose will be given at the site at Week 156. Subjects previously randomized to receive 150 mg secukinumab may continue with 150 mg secukinumab open label or may switch to 300 mg s.c. at the discretion of the investigator. Subjects previously randomized to 300 mg secukinumab will continue with 300 mg secukinumab open label. Subjects receiving placebo during randomized withdrawal period will start secukinumab 150 mg or 300 mg at the discretion of the investigator. Any subject on 150 mg s.c. may be switched to 300 mg s.c. at the discretion of the investigator at a regularly scheduled visit. Note: the Week 244 visit will be the last scheduled visit at which the subjects will be allowed to switch to 300 mg dose. Decreasing the dose from 300 mg to 150 mg is not allowed.

Placebo patients who enter the open label period will be given once weekly s.c. injections of secukinumab for 4 consecutive weeks and then s.c. injections every 4 weeks. Patients who choose not to switch from placebo to secukinumab will be allowed to exit the study. For subjects, who will not enter the open label period, Week 156 will be the EoT visit at which no treatment will be administered. After completing the Week 156 EoT visit, these subjects will enter the follow up period. For all the subjects who enter the open label period, the last dose of the study medication will be administered at Week 256. Week 260 is the end of the open label treatment period (OL- EoT).

(v) follow-up period (for all subjects): treatment free period (Week 264 to Week 268).

(vi) follow-up 2 period: treatment free period only for patients who prematurely discontinued treatment 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 CAIN457A2302E1 study

For the subjects classified as partial responders at Week 52 the study consists of 4 or 5 periods

(i) screening period: is the duration between signing the informed consent form (ICF) and randomization registered with IRT.

(ii) treatment period: starting from the randomization visit at Week 52 continuing through Week 156. The patients will receive secukinumab s.c. every 4 weeks at the dose which they were originally assigned in the core study. At Week 156 they will enter the open label period. For subjects who don't enter the open label period, Week 156 visit is the EoT.

(iii) open label period: At Week 156, the subjects will be given pre-filled syringes and starting Week 160 the subjects will be asked to perform self-injection at home every 4 weeks and return to the site every 12 or 16 weeks (please see Table 6-1 Assessment schedule). Also, at Week 156 subjects receiving 150 s.c. may be switched to 300 mg s.c. if the subject and the PI agree that the subject would benefit from the higher dosage at a regularly scheduled visit. The subjects will receive the last dose of the study medication at Week 256.

(iv) follow-up period (for all subjects): treatment free period (Week 264 to Week 268).

(v) follow-up 2 period: treatment free period only for patients who prematurely discontinued treatment 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 CAIN457A2302E1 study.

NOTE: *Partial responders **DO NOT** participate in the randomized withdrawal and **DO NOT** receive any loading dose even if they experience a full relapse (a loss of >50% of the maximum PASI gain compared to baseline of the core study).*

Subjects classified as **partial responders** at Week 52 of the core studies will continue the same treatment dose in PFS (secukinumab s.c. 150 mg or 300 mg) that they were receiving at the time of completing the maintenance period (Week 52) in the core study.

In the **follow-up period** (Week 264 to Week 268) all subjects will visit the study site for safety and efficacy assessments while being off-treatment.

In the **follow-up 2 period** safety 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 CAIN457A2302E1 study for patients who have prematurely discontinued treatment only.

Population: All subjects from study CAIN457A2302 or CAIN457A2303 (and potentially rolling over from other secukinumab phase III studies) who were randomized to and have been receiving secukinumab treatment during the maintenance period of the core studies (e.g., CAIN457A2302 or CAIN457A2303), and who completed the full study treatment period (52 weeks) in the core studies, and who have at least a partial response at Week 52 of the core studies, and who comply with the inclusion and exclusion criteria of this study, are eligible to enter into this extension study.

Inclusion/Exclusion criteria:

Inclusion criteria

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

1. Subjects who completed the full study treatment period (52 weeks) in the core studies (e.g., CAIN457A2302 or CAIN457A2303), and after randomization have been receiving

secukinumab treatment during the maintenance phase of the core studies, and show at least a partial response (PASI 50 or better) at Week 52 of the core studies.

2. Written informed consent must be obtained before any assessment is performed.
3. For inclusion in the open label period, written informed consent for protocol amendment 1 must be obtained.
4. For inclusion in the open label period, the subject must be deemed to benefit from the study drug based on the investigator's clinical judgment.

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 to use of prohibited treatments in the core study detailed in the **Table** below have to be adhered.

Prohibited treatments†,‡	**Time period before randomization visit at Week 52**
Alefacept, briakinumab, efalizumab, ustekinumab	6 months
Biological immunomodulating agents other than above (e.g., adalimumab, etanercept, infliximab)	12 weeks
Other systemic immunomodulating treatments§ (e.g., MTX, cyclosporine A, corticosteroids§, cyclophosphamide)	4 weeks
Other systemic psoriasis treatments* (e.g., retinoids, fumarates)	4 weeks
Photochemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Use of topical treatment ** that is likely to impact signs and symptoms of psoriasis for >14 days* (e.g., corticosteroids [CS], vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)	2 weeks
Live virus vaccinations during extension study	6 weeks
Any investigational treatment or participation in any interventional clinical trial during extension trial	4 weeks or 5 half-lives (whichever Is longer)

†If a subject inadvertently used the prohibited treatment in core study (e.g., CAIN457A2302 or CAIN457A2303) without undue safety risk till completion of Week 52, he/she must have completed the time period as defined in the table above. Subjects who have not completed an adequate time period (table above) will not be eligible for the current extension study.

‡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

**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

3. Subjects not expected to benefit from participation in the extension study, as assessed by the subject and investigator
4. Subjects expected to be exposed to an undue safety risk if participating in the study
5. Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the subject unsuitable for the study
6. Plans for administration of live vaccines during the study period
7. 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)
8. 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 vasectomized 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.

Investigational and reference therapy:

Novartis will provide the following study treatments

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 s.c.150 mg dose (1 syringe) and s.c. 300 mg dose (2 syringes). For blinding purpose the subject in 150 mg treatment group will also receive one syringe of placebo secukinumab 150 mg.
2. Reference therapy: 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.

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

Other assessments:

- Safety assessments:
  - Evaluation of all AEs and SAEs including injection site reactions, physical examination; vital signs; weight and height, laboratory assessments including hematology, clinical chemistry, local urinalysis, immunogenicity (IG) (assessment of anti-secukinumab antibody development), ECG ,pregnancy and assessments of fertility
- [redacted]
- Fasting laboratory evaluations; plasma glucose, lipid panel
- PK
- Health-related Quality of life (HRQoL): 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 psoriatic arthritis [PsA] at baseline of the core study)

Data analysis:

Treatment groups for analysis will include:

- Subjects who were PASI 75 responders at Week 52
  - Secukinumab 150 mg
  - Secukinumab 300 mg
  - Placebo (secukinumab 150 mg in core studies)
  - Placebo (secukinumab 300 mg in core studies)
- Subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg
  - Secukinumab 150 mg
  - Secukinumab 300 mg
- Subjects who were partial responders at Week 52
  - Secukinumab 150 mg
  - Secukinumab 300 mg

The following hypotheses will be tested for 52 weeks≤ t ≤68 weeks

- H1: Secukinumab 150 mg is not different from placebo with respect to the cumulative rate for subjects who lost PASI 75 response up to Week 68
- H2: Secukinumab 300 mg is not different from placebo with respect to the cumulative rate for subjects who lost PASI 75 response up to Week 68

The familywise error will be set to α=2.5% (one-sided). The two hypotheses H1 (referring to 150 mg) and H2 (referring to 300 mg) will be tested at α/2=1.25% one-sided. In case, a null hypothesis has been

rejected for one dose, but not for the other dose, the alpha can be shifted to the other dose and the null hypotheses can be retested at level α=2.5% (one-sided).

For loss of PASI 75 response, between-treatment differences will be evaluated using a log-rank test, stratified by geographical region and body weight stratum, to compare the survival functions between secukinumab treatment groups versus placebo. The hazard ratios for these comparisons for loss of PASI 75 response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group, core study and baseline PASI of core study and baseline (at Week 52) PASI of extension study as explanatory variable and stratified by geographical region and body weight stratum. The primary analysis will be the log-rank test. Subjects who have not lost PASI 75 response up to Week 68 will be considered as censored observations.

Separate analyses will be performed for comparison of 150 mg secukinumab with placebo and 300 mg secukinumab with placebo. The two placebo groups will not be pooled for this analysis.

1 Introduction

1.1 Background

CAIN457A2302E1 is an extension study to two ongoing phase III studies CAIN457A2302 and CAIN457A2303, and will potentially include subjects from other secukinumab phase III studies (preceding studies collectively referred as core studies). Study CAIN457A2302 and study CAIN457A2303, each, is multicenter, randomized, controlled trial to investigate the efficacy of secukinumab after twelve weeks of treatment, and safety, tolerability and long-term efficacy up to one year in subjects with moderate to severe chronic plaque-type psoriasis. Both the studies are planned to demonstrate superiority of secukinumab compared with placebo. In addition, the study CAIN457A2303 aims also to show the non-inferiority versus etanercept. Please refer to the protocols of the respective studies for full details.

At the end-of-phase-II meetings with several Health Authorities (FDA, EMA, and PMDA) in the first quarter of 2011, it was agreed to submit data from core studies along with interim data from at least one extension study to show long-term efficacy, safety, and tolerability of secukinumab in subjects with psoriasis. This study will also provide information from a randomized withdrawal period for subjects who have shown a PASI 75 response to secukinumab at Week 52 of the core studies (e.g., CAIN457A2302 or CAIN457A2303) for 2 years until Week 156. The long-term efficacy, safety, and tolerability data (open label) will be collected for an additional 2 years. The overall treatment period (core study [52 weeks] plus extension [268 weeks]) is 320 weeks.

Subjects (PASI 75 responders and partial responders) randomized to and completing Week 52 of the core studies (e.g., CAIN457A2302 or CAIN457A2303) on secukinumab treatment will be eligible to join this extension study, which is planned to collect up to- four years of long-term efficacy, safety, and tolerability data of secukinumab in either continuous or interrupted therapy (randomized withdrawal period). Subjects on placebo treatment or etanercept in the maintenance phase of the core studies, as well as subjects on secukinumab, but not showing at least a partial response, will not be eligible to enter this extension study.

The study design, objectives, and other procedures of this extension study are applicable to other secukinumab phase III studies from which subjects meeting the inclusion/exclusion criteria will potentially enter the extension study CAIN457A2302E1.

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

1.2 Purpose

This extension study (CAIN457A2302E1) is planned to collect an additional four years of long-term efficacy, safety, and tolerability data of secukinumab in either continuous or interrupted therapy (randomized withdrawal period) in subjects completing either one of the two phase III studies CAIN457A2302 or CAIN457A2303 (and potentially other secukinumab phase III studies) and showing at least partial response to secukinumab at Week 52 of the core study. An interim analysis on safety data only and a primary endpoint analysis (PEA) up to Week 68 will be conducted.

The data collected in this study up to the time of the interim analysis will be part of the submission package. The data collected beyond the time of the Week 68 interim analysis will deliver important information on the effect of long-term treatment of chronic plaque-type psoriasis with secukinumab. Additional interim analyses may be conducted at various time points for publications or health authority requests.

The two year double-blind randomized withdrawal period will allow assessing whether continuation of treatment with secukinumab is of benefit to subjects after having been treated with secukinumab for up to 52 weeks in the preceding phase III studies, compared to stopping treatment with secukinumab. In addition, this treatment period will deliver important information on the effect of stopping treatment with secukinumab, including time to relapse (i.e., loss of ≥50% of previous gain in PASI reduction) and frequency of rebounds, and therefore addresses needs brought forward by Health Authorities. The two year double–blind period of the study will be followed by a two year open label period. During the open label treatment period, subjects initially on the lower dose (150 mg) will be offered to switch to the higher dose (300 mg), at the discretion of the investigator. This allows all subjects in the study to receive the most efficacious dose of secukinumab.

2 Study objectives

For study treatments and description of treatment subgroups refer **Section 3.1**.

2.1 Primary objective

To demonstrate the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis, who were PASI 75 responders at Week 52 of the core study, with respect to loss of PASI 75 up to Week 68, compared to placebo.

2.2 Secondary objectives

- To assess the efficacy of secukinumab 150 mg or 300 mg with respect to PASI 50/75/90/100 response and IGA 0 or 1 response, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52
- To assess the efficacy of secukinumab 150 mg or 300 mg with respect to PASI score and IGA mod 2011 score, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52
- To assess time to PASI 75 response **for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg**.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to loss of IGA 0 or 1 response, compared

to placebo **in subjects who were PASI 75 responders and IGA 0 or 1 responders at Week 52.**

- To assess time to IGA 0 or 1 response for subjects who were IGA 0 or 1 responders at re-randomization, and who lost IGA 0 or 1 response during randomized withdrawal, and **who were re-treated after relapse with secukinumab 150 mg or 300 mg.**
- To assess the clinical safety of secukinumab 150 mg or 300 mg as assessed by vital signs, clinical laboratory values, electrocardiograms (ECGs), and adverse events (AEs) monitoring, compared to placebo in subjects who were PASI 75 responders at Week 52, in subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to changes in Dermatology Life Quality Index© (DLQI©), compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to DLQI 0 or 1 achievement, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to EuroQOL 5-Dimension© Health Questionnaire (EQ-5D©) score, compared to placebo over time in subjects who were PASI 75 responders at Week 52, over time for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and over time in subjects who were partial responders at Week 52.
- To investigate the effects of treatment with secukinumab 150 mg or 300 mg on the occurrence of rebound following cessation of therapy, in subjects who were PASI 75 responders at Week 52, for subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg, and in subjects who were partial responders at Week 52.
- To assess the efficacy of secukinumab 150 mg or 300 mg in subjects with moderate to severe chronic plaque-type psoriasis with respect to relapse, compared to placebo **in subjects who were PASI 75 responders at Week 52**.
- To investigate the development of immunogenicity (IG) against secukinumab over time.

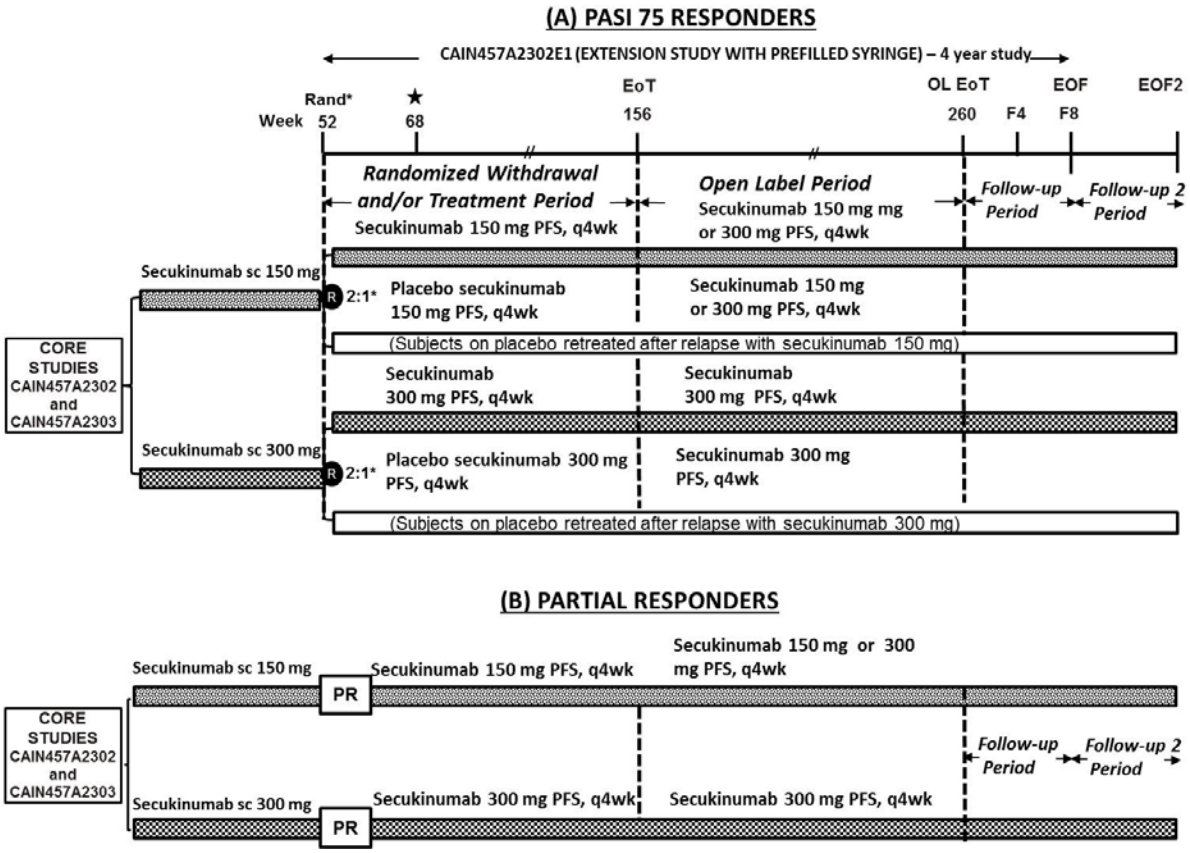
2.3 Exploratory objectives

- [redacted]
- [redacted]
- To explore the effects of treatment with secukinumab with respect to the Health Assessment Questionnaire© – Disability Index (HAQ©-DI) in subjects with psoriatic arthritis (PsA) at baseline of core study over time.

3 Investigational plan

3.1 Study design

Figure 3-1 Study design



PFS: prefilled syringe; Week 52 – end of maintenance period in core studies (e.g., CAIN457A2302 or CAIN457A2303) which is randomization (Rand*) visit for CAIN457A2302E1 (extension study); The screening period will be the duration between signing the informed consent form and randomization registered with Interactive Response Technology (IRT); s.c.: subcutaneous; Week 156 end of treatment period (EoT); Week 260 – open label end of treatment (OL-EoT) period; q4wk – every four weeks; end of follow up (EOF)

★Primary endpoint analysis (PEA) at Week 68; R PASI 75 Responders: subjects with PASI 75 at Week 52 of core study; PR Partial responders: subjects with PASI 50, but not PASI 75 response at Week 52 of core study; first full relapse – a loss of > 50% of the maximum PASI gain compared to the baseline of core study

(A) PASI 75 Responders entering randomized withdrawal period

Subjects who were PASI 75 **responders** at Week 52 visit of the core studies (e.g.,CAIN457A2302 or CAIN457A2303) and have been on secukinumab s.c. 150 mg or 300 mg in the core studies will be randomized to continue same s.c. doses of secukinumab in PFS or receive placebo every 4 weeks up to Week 152. Randomization in each group will be 2:1 (refer protocol text for details)

a. Secukinumab 150 mg PFS group: One s.c. injection of secukinumab 150 mg in PFS plus s.c. injection of placebo secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week 152 (or until first relapse). Subjects with **first full relapse** will be treated with two s.c. injections of placebo secukinumab 150 mg in PFS once weekly for three weeks (1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 150 mg regimen every 4 weeks dosing is continued thereafter. Subjects who enter the open label period to continue beyond Week 152 will receive one injection of 150 s.c. every 4 weeks. Starting Week 156, subjects on 150 mg s.c. will have the option to switch to 300 mg s.c.at regularly scheduled visits.

b. Placebo secukinumab 150 mg PFS: Two s.c. injections of placebo secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week 152 (or until first relapse). Subjects with **first full relapse** will be treated with one s.c. injection of secukinumab 150 mg in PFS plus one s.c. injection of placebo secukinumab 150 mg in PFS once weekly for four weeks (at the visit where the relapse was diagnosed, 1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 150 mg regimen every 4 weeks dosing is continued thereafter. Subjects on placebo who enter the open label period to continue beyond Week 152 will be treated with one injection of secukinumab 150 mg s.c. in PFS once weekly for four weeks and then one injection s.c. every 4 weeks. Starting Week 156, subjects on 150 mg s.c. will have the option to switch to 300mg s.c.(two injections of 150 s.c.) at regularly scheduled visits.

c. Secukinumab 300 mg PFS group: Two s.c. injections of secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week 152 (or until first relapse). Subjects with **first full relapse** will be treated with two s.c. injections of placebo secukinumab 150 mg in PFS once weekly for three weeks (1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 300 mg regimen every 4 weeks dosing is continued thereafter. Subjects who enter the open label period to continue beyond Week 152 will receive two injections of 150 s.c. every 4 weeks.

d. Placebo secukinumab 300 mg PFS : Two s.c. injections of placebo secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week152 (or until first relapse). Subjects with **first full relapse** will be treated with two s.c. injection of secukinumab 150 mg in PFS plus once weekly for four weeks (at the visit where the relapse was diagnosed, 1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 300 mg regimen every 4 weeks dosing is continued thereafter. Subjects on placebo who enter the open label period to continue beyond Week 152 will be treated with two s.c. injections of secukinumab 150 mg in PFS once weekly for four weeks and then two s.c. injections of secukinumab 150 mg s.c. every 4 weeks.

● Refer protocol text for details and for treatment at relapse.

(B) Partial responders not entering the randomized withdrawal period

● Subjects who were **partial responders** at Week 52 visit in core studies (e.g., CAIN457A2302 or CAIN457A2303) and have been on secukinumab s.c. 150 mg or 300 mg in core studies **do not** participate in the randomized withdrawal. These subjects will continue same treatment s.c. dose in PFS (secukinumab s.c. 150 mg or 300 mg) as they were receiving at the time of completing the maintenance period (Week 52) in the core studies. Subjects continuing beyond week 152 will be given open label secukinumab. Starting Week 156, subjects on 150 mg s.c. will have the option to switch to 300 mg s.c.at regularly scheduled visits.

● NOTE: Subjects who are **non-responders** at Week 52 of the core studies (e.g., CAIN457A2302 or CAIN457A2303) are not eligible to enter this extension study, and will complete follow-up visits in the core studies.

Follow-up 2 period: treatment free period only for patients who prematurely discontinued treatment

An outline of the study design is presented in Figure 3-1, while a detailed visit and assessment schedule can be found in Table 6-1. The study design is applicable to other secukinumab phase III studies from which subjects meeting the inclusion/exclusion criteria will potentially enter the extension study CAIN457A2302E1.

This 4 year extension study will include a 2-year double blind period (between Week 52 and Week 156) during which randomized withdrawal analysis will be performed, followed by an additional 2-year open label period (between Week 156 to Week 260). The subjects will receive the last blinded treatment at Week 152. At Week 156, after performing the scheduled study assessments and prior to receiving the first unblinded dose of the study drug, the site will be asked to contact IRT to unblind the study treatment. For subjects who will continue into the open label period, Week 156 will be the beginning of the open label period. The subjects who will not continue into the open label period Week 156 will be the end of blinded withdrawal treatment/treatment period (EoT) at which no study drug will be administered. During the open label period, subjects will receive the last dose of the study drug at Week 256. Week 260 will be the end of open label treatment period (OL-EoT).

Subjects completing the maintenance period (52 weeks) in the core studies (e.g., CAIN457A2302 or CAIN457A2303) will be classified based on Week 52 PASI response as "PASI 75 responders" or "partial responders" or "non-responders". This Week 52 visit in the core studies is the randomization visit for CAIN457A2302E1 (extension study).

- **PASI 75 Responders:** subjects with a PASI 75 response (subjects achieving ≥ 75% improvement [reduction] in PASI score compared to baseline of the core study) at Week 52 of core study
- **Partial responders:** subjects with a PASI 50 response (subjects achieving ≥ 50% improvement [reduction] in PASI score compared to baseline of the core study, but not PASI 75 response) at Week 52 of core study
- **Non-responders:** not achieving at least a PASI 50 response at Week 52 of core study

For the subjects classified as PASI 75 responders at Week 52 the study consists of 5 or 6 periods

At Week 52 of the core studies subjects enrolling in the extension trial will go through a screening period, a randomized withdrawal period, a treatment period, a two year secukinumab open label period and a follow up period.

(i) screening period: is the duration between signing the informed consent form (ICF) and randomization registered with interactive response technology (IRT).

(ii) randomized withdrawal period (double blind): Subjects will be randomized to either secukinumab or placebo. The subjects will continue on either secukinumab or placebo until there is a relapse or up to Week 156. If there is a relapse the patient will enter the treatment period.

In randomized withdrawal period (between Week 52 and Week 156), subjects in the group of **PASI 75 responders** who have been receiving secukinumab s.c. 150 mg dose during the maintenance period of core studies will be randomized 2:1 to **continue** same s.c. doses of secukinumab in PFS from the core studies or receive s.c. placebo secukinumab in PFS. Similarly, those subjects who were receiving secukinumab s.c. 300 mg dose during the maintenance period of core studies will be randomized 2:1 to **continue** same s.c. doses of secukinumab in PFS from the core studies or receive s.c. placebo secukinumab in PFS. Randomization will be stratified by geographical region and by body weight (< 90 kg or ≥90 kg) collected at Week 52. In order to maintain double-blind in this study, matching placebo is

used. Therefore subjects classified as PASI 75 responders and entering the randomized withdrawal period will be randomized (as explained above) at Week 52 in either of four treatment groups (Figure 3-1). Subjects who were on s.c. secukinumab 150 mg in the core study will be randomized to (a) or (b) treatments and subjects who were on s.c. secukinumab 300 mg in the core study will be randomized to (c) or (d) treatments, as explained below:

a. Secukinumab 150 mg PFS group: One s.c. injection of secukinumab 150 mg in PFS plus s.c. injection of placebo secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week 152 (or until first full relapse).
b. Placebo secukinumab 150 mg PFS: Two s.c. injections of placebo secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week 152 (or until first full relapse).
c. Secukinumab 300 mg PFS group: Two s.c. injections of secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week 152 (or until first full relapse).
d. Placebo secukinumab 300 mg PFS: Two s.c. injections of placebo secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks up to Week 152 (or until first full relapse).

Subjects in the randomized withdrawal period experiencing a **first full relapse** (a loss of >50% of the maximum PASI gain compared to baseline of the core study) at any scheduled visit after Week 52 during the randomized withdrawal period, will enter the **treatment period**. The dose regimen in treatment period (**loading dose and treatment thereafter**) is described in Table 3-1.

Table 3-1 Loading dose regimen at time of first full relapse* and treatment thereafter (treatment period) between Week 52 and Week 156

Groups at time of randomization (Week 52)	Treatment period
	Loading dose regimen at time of first full relapse* and treatment thereafter
Secukinumab 150 mg PFS	Two s.c. injections of placebo secukinumab 150 mg in PFS once weekly for three weeks (1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 150 mg regimen every 4 weeks dosing is continued thereafter.
Placebo secukinumab 150 mg PFS	One s.c. injection of secukinumab 150 mg in PFS plus one s.c. injection of placebo secukinumab 150 mg in PFS once weekly for four weeks (at the visit where the relapse was diagnosed, 1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 150 mg regimen every 4 weeks dosing is continued thereafter.
Secukinumab 300 mg PFS	Two s.c. injections of placebo secukinumab 150 mg in PFS once weekly for three weeks (1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 300 mg regimen every 4 weeks dosing is continued thereafter.
Placebo secukinumab 300 mg PFS	Two s.c. injection of secukinumab 150 mg in PFS plus once weekly for four weeks (at the visit where the relapse was diagnosed, 1 week, 2 weeks and 3 weeks later). After 4 weeks following relapse the routine dosing with secukinumab 300 mg regimen every 4 weeks dosing is continued thereafter.

*first full relapse: (a loss of >50% of the maximum PASI gain compared to baseline of the core study)

Those subjects experiencing a **second relapse** will **NOT** receive any loading dose regimen, regardless of the group they are randomized at Week 52 of the core studies. However, they will continue secukinumab s.c. 150 mg (one s.c. injection of secukinumab 150 mg in PFS with matching placebo) or 300 mg (two s.c. injections of secukinumab 150 mg) dose given every four weeks through Week 152 and at Week 156 they will enter the open label period.

Subjects who do not experience first full relapse will continue the treatment to which they were randomized at Week 52 through Week 152 at Week 156 they will enter the open label period.

(iii) treatment period (double blind): A placebo subject experiencing a relapse during the withdrawal period will receive four doses of secukinumab s.c. at weekly intervals followed by secukinumab s.c. every four weeks. Subjects on secukinumab in the randomized withdrawal period who have a relapse, will be given four weekly doses of placebo s.c. Following the loading doses subjects will continue on secukinumab treatment at 4 week intervals. Any subject, whether randomized to placebo or active treatment, will only be treated once with the weekly loading dose regimen. For subsequent relapses patients will continue on secukinumab at 4 week intervals. At Week 152 subjects will receive the last treatment of the blinded treatment period. Week 156 will be the end of the treatment period (EoT).

(iv) open label period: The treatment will be unblinded at Week 156 and the subjects will enter the open label period. During this period, the subjects will be given pre-filled syringes and instructed to perform self-injection at home every 4 weeks and return to the site every 12 or 16 weeks (see Table 6-1 Assessment schedule). The first open label dose will be given at the site at Week 156. Subjects on 150mg s.c may continue on 150mg s.c. and subjects on 300 mg s.c. will continue on 300 mg s.c secukinumab. Subjects who were on placebo during the randomized withdrawal period will start on secukinumab 150 mg s.c. or 300 mg s.c. if the investigator decides the subject would benefit from the higher dose. Placebo subjects who enter the open label period will be given once weekly s.c. injections of secukinumab for 4 consecutive weeks and then s.c. injections every 4 weeks. Any subject starting on secukinumab 150 mg may continue on 150 mg every 4 weeks or switch to 300 mg at Week 156 or any other regular site visit if the investigator decides the subject would benefit from the higher dose. Note: the Week 244 visit will be the last scheduled visit at which the subjects will be allowed to switch to 300mg dose. Decreasing the dose from 300 mg to 150 mg is not allowed. For all subjects, who will not enter the open label period, Week 156 will be the EoT visit at which no treatment will be administered. After completing the Week 156 EoT visit, these subjects will enter the follow up period. For all subjects who enter the open label period, the last dose of the study medication will be given at Week 256. Week 260 is the end open label treatment period.

(v) follow-up period (for all subjects): treatment free period (Week 264 to Week 268).

(vi) follow-up 2 period: treatment free period for patients who prematurely discontinued treatment. 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 CAIN457A2302E1 study

For the subjects classified as partial responders at Week 52 the study consists of 4 or 5 periods

(i) screening period: is the duration between signing the informed consent form (ICF) and randomization registered with IRT.

(ii) treatment period (double blind): starting from the randomization visit at Week 52 continuing through Week 156 , subjects in the group of **partial responders** who have been receiving s.c. secukinumab150 mg or 300 mg dose during the maintenance period of core studies will continue the same treatment dose in PFS (secukinumab s.c. 150 mg or 300 mg) that they were receiving at the time of completing the maintenance period (Week 52) in the core study (Figure 3-1), i.e., a subject continuing secukinumab s.c. 150 mg will use one s.c. injection of secukinumab 150 mg in PFS plus s.c. injection of placebo secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks until Week 152; and a subject continuing secukinumab s.c. 300 mg will use two s.c. injections of secukinumab 150 mg in PFS at randomization (Week 52) and thereafter every 4 weeks until Week 152. At Week 152 subjects will receive the last treatment of the blinded treatment period. Week 156 will be the end of the treatment period (EoT).

(iii) open label period: The first open label dose will be given at the site at Week 156. At Week 156, the subjects will be given pre-filled syringes and starting Week 160, the subjects will be asked to perform self-injection at home every 4 weeks and return to the site every 12 or 16 weeks (see Table 6-1 Assessment schedule). Also, at regularly scheduled visits at the site, the subject receiving 150 mg s.c. may be switched to 300 mg s.c. if the subject and the PI agree that there would be a benefit from a higher dosage. The last visit at which the subjects may be switched to the higher dosage is Week 244. For all subjects, who will not enter the open label period, Week 156 will be the EoT visit at which no treatment will be administered. After completing the Week 156 EoT visit, these subjects will enter the treatment-free follow up period. For all subjects who enter the open label period, the last dose of the study medication will be given at Week 256. Week 260 is the end open label treatment period.

(iv) follow-up period: treatment free period (Week 264 to Week 268).

(v) follow-up 2 period: treatment free period for patients who prematurely discontinued treatment

NOTE: *Partial responders **DO NOT** participate in the randomized withdrawal and **DO NOT** receive any loading dose even if they experience a full relapse (a loss of >50% of the maximum PASI gain compared to baseline of the core study)*

Subjects on placebo treatment or etanercept in the maintenance phase of the core studies will not be eligible to enter this extension study, and will complete follow-up visits in the core studies.

Follow-up period (Week 264 to Week 268)

The treatment-free follow-up period (no study treatment administered during follow-up period) includes visits at Week 264 (Follow-up visit F4, which is 4 weeks after the EoT/OL-EoT visit, and 8 weeks after last study treatment administration) and Week 268 (follow-up visit F8 [or End of follow-up {EOF}]), which is 8 weeks after the EoT/OL-EoT visit, and 12 weeks after the last study treatment administration.

Follow-up 2 period

Subjects who have prematurely discontinued treatment prior to the end of treatment phase (Week 260), and completed 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. 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 CAIN457A2302E1 study (Figure 3-1).

3.2 Rationale of study design

The first two years (104 weeks), of this multicenter, double-blind, randomized withdrawal extension study is set up to collect the long-term efficacy, safety and tolerability of secukinumab

in either continuous or interrupted therapy (randomized withdrawal/treatment period). The second two years of the study is open label and primarily designed to collect additional safety data.

Since interruptions of treatment for various reasons are common in chronic diseases such as psoriasis, the first two years of this extension study will investigate the effect of treatment interruption as well as re-treatment following treatment interruption in a "randomized withdrawal" design.

In addition, the "randomized withdrawal" period will allow assessing whether continuation of treatment with secukinumab is of benefit to subjects after having been treated with secukinumab for up to 52 weeks, compared to stopping treatment with secukinumab.

The concept of "randomized withdrawal" is in line with recommendations from the EMA as outlined in the guidelines for the development of drugs to treat psoriasis (CHMP/EWP/2454/02), and with feedback received at the end-of-phase-II meetings with the FDA, the EMA, and the PMDA.

Because a relapse can only reasonably be assessed if a subject has a response to start with, only subjects that have a PASI 75 at Week 52 of one of the core studies will be re-randomized into the randomized withdrawal period of this extension study.

The "randomized withdrawal" period does not have a defined end. Instead, retreatment (including loading dose) will be initiated for each subject individually if at any scheduled visit a relapse is experienced. This is considered appropriate, since a subject not suffering from a relapse is not considered in need of active treatment at that time, and hence should not be exposed to treatment until the worsening of the disease (relapse). After two years any subjects on placebo in the randomized withdrawal arm will either be discontinued or started on secukinumab.

Partial responders (i.e., subjects having a PASI 50 response, but not a PASI 75 response) are also allowed to enter the extension study; they will continue the treatment they received during the maintenance of the core study. This is based on the rationale that a subject could have been a responder during most of the core study, but suffered from a minor loss of response at Week 52 (e.g., because of seasonal variation), and could still be regarded to benefit from continuous treatment with secukinumab. In addition, even for a subject responding to secukinumab only with a partial response, continuous treatment with secukinumab might still be the best available treatment option for this subject (e.g., due to intolerance or non-availability of other options). Therefore, at Week 52 of the core study, investigator and subject will perform an assessment of whether the subject is expected to benefit from inclusion in the extension study; if that assessment is positive, the subject is eligible to enter the extension study.

In the last two years of the study during the open label period subjects on 150 mg s.c. will be allowed to switch to 300 mg s.c. at the discretion of the investigator. The switch will be allowed starting Week 156 and only during the scheduled visit. Once subjects switch into the higher dose, they will not be allowed to switch back to the lower dose. Also, subjects initially randomized to 300 mg s.c. will not be allowed to switch to 150 mg sc at any time during the study.Non-responders to secukinumab (i.e., subjects not having at least a PASI 50 response) at

Week 52 of the core studies are not eligible to enter the extension study, since they do not show a meaningful response to the active treatment.

Subjects on placebo in the core studies until Week 52 are not eligible to enter the extension study because they have shown that their disease status is not in need of active treatment. Hence, there is no benefit expected for these subjects from entering the extension study.

Subjects on etanercept in the core study (CAIN457A2303) until Week 52 are not eligible to enter the extension study because the extension study has no objective that would justify comparison of secukinumab against an active comparator; instead, the main focus of the study objectives is to compare different secukinumab regimens against each other. Since etanercept is an approved treatment in the countries where the study CAIN457A2303 is performed in, subjects can receive etanercept by prescription.

3.3 Rationale of dose/regimen, duration of treatment

The doses and regimens selected for secukinumab are projected to deliver high efficacy while at the same time ensuring subject safety. The proposal to continue treatment with s.c. doses of 150 mg and 300 mg administered every four weeks, as well as the additional treatment duration of 208 weeks (leading to an overall treatment period [core plus extension] of 260 weeks) is based on the need for efficacy and safety information during chronic treatment in subjects suffering from chronic plaque-type psoriasis.

The rationale of the dose/regimen for re-treatment after full relapse is supported by model-based considerations. These model-based predictions are subject to caveats and assumptions, but appear to provide plausible guidance. The predictions are considered as extrapolations, as they are made for regimens, time points, subject subsets and withdrawal/re-treatment patterns for which limited or no data is available, as they have not (or not in exactly this way) been studied so far (which is the nature of the current status of development of secukinumab in psoriasis).

The inclusion of a randomized withdrawal treatment period will allow assessing time to relapse and frequency of rebound after cessation of treatment, compared to continuous treatment. This is in line with guidelines for the development of drugs to treat psoriasis (CHMP/EWP/2454/02).

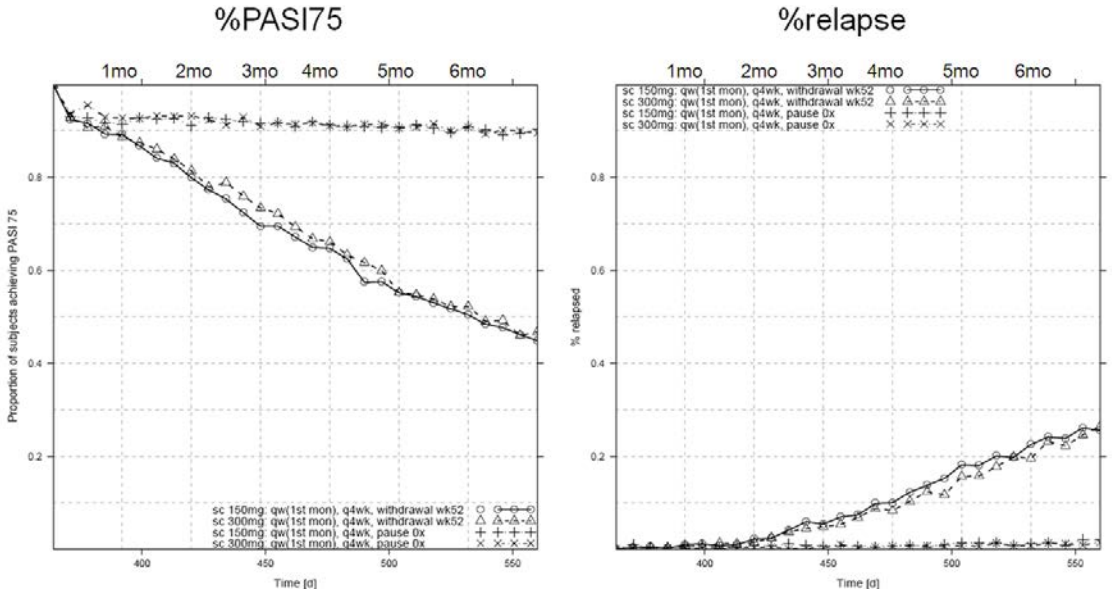
The switch from the lyophilisate to the more convenient prefilled syringe is supported by the results of clinical study CAIN457A2106, which has shown that the exposure profiles of both formulations are virtually identical. This will also remove the need to have unblinded pharmacists involved in the study; these were necessary in the core studies to ensure the double-blind.

Model-based predictions in Figure 3-2 suggest:

- Subjects lose PASI 75 response after withdrawal at an approximate rate of 10% per month (see Figure 3-2 left).

- Substantially less subjects show a full relapse, the predictions reaching 10% after four months (see Figure 3-2 right).

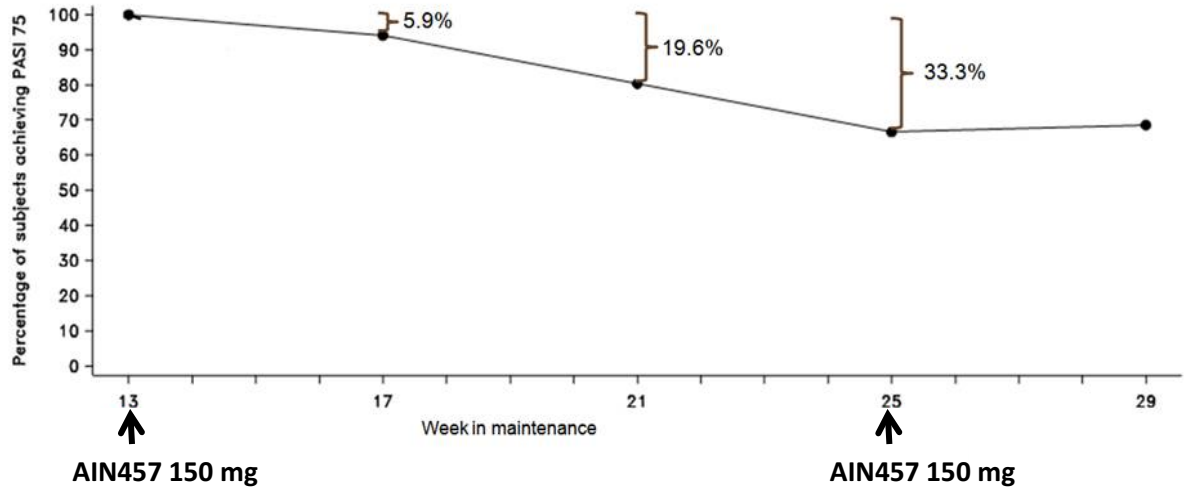
Figure 3-2 Model-based prediction of % PASI 75 responders and % of subjects relapsing during a period of 6 months after either continuous treatment or of withdrawal (based on responders at Week 52)



Model base exploration with high and unquantifiable uncertainty, thus no intervals are provided

The use of loss of PASI 75 as primary objective is supported by results from study CAIN457A2211 wherein a loss of PASI 75 was observed during treatment-free maintenance periods in an increasing number of subjects over time (see Figure 3-3).

Figure 3-3 Observed loss of PASI 75 response during "fixed interval" maintenance treatment of study CAIN457A2211



AIN457: Secukinumab

During each 4-week interval, an additional approximately 10% of subjects lost PASI 75 response; twelve weeks after last administration of secukinumab, 33.3% of the subjects had lost PASI 75 response. While data from Week 16 is not available from that study, since subjects were retreated after 12 weeks, it can reasonably be expected that around 40% of subjects will have lost PASI 75 response 16 weeks after last administration of secukinumab. This percentage is large enough to allow for a meaningful comparison as outlined in the primary endpoint of extension study CAIN457A2302E1.

It is understood that the trough level of secukinumab after 12 weeks of treatment in study CAIN457A2211 might be somewhat different than at Week 52 of studies CAIN457A2302 and CAIN457A2303, but this is expected to have no major impact on the time to loss of PASI 75.

3.4 Rationale for choice of comparator

Use of placebo (i.e. withdrawal of active therapy) in a randomized withdrawal study design until retreatment is necessary (in the case of psoriasis a “relapse”, i.e., loss of >50% of the previous gain in PASI reduction) is in accordance with Health Authority Guidelines on Choice of Control Group in Clinical Trials (e.g., CPMP/ICH/364/96 2001). This is also be supported by the fact that all subjects will have the opportunity to receive active treatment after experiencing a relapse. All patients in the last two years of the trial will be on active treatment.

3.5 Purpose and timing of interim analyses/design adaptations

A PEA will be conducted when all subjects have completed Week 68 of treatment. Data from this PEA will be provided for the Day 120 update during the process of market authorization. Of note, the study procedures will not be modified as a result of this PEA.

Additional interim analyses may be conducted at various time points for publications or health authority requests. The study procedures will not be modified as a result of these interim analyses.

When each subject of 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 either intravenously (i.v.) or s.c. in man. Study CAIN457A2302E1 will use secukinumab drug substance solution in PFS; this formulation has already been used in a biocomparability study, CAIN457A2106, and has shown almost identical properties compared to the lyophilisate.

Secukinumab is expected to show good to excellent efficacy in the treatment of psoriasis, as outlined in Section 1.1.

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 the extension study CAIN457A2302E1, all subjects will receive active treatment, either from the start of the study, or after they have experienced a relapse. To ensure a double-blind design, some subjects will receive placebo up to 156 weeks or until the first relapse, according to the group to which they were randomized.

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 extension study CAIN457A2302E1.

4 Population

All subjects from study CAIN457A2302 and CAIN457A2303 (and potentially rolling over from other secukinumab phase III studies) who were randomized to and have been receiving secukinumab treatment during the maintenance period of the core studies (e.g., CAIN457A2302 or CAIN457A2303), and who completed the full study treatment period (52 weeks) in core studies and who have at least a partial response at Week 52 of the core studies, and who comply with the inclusion and exclusion criteria of this study, are eligible to enter into this extension study.

Assuming drop-outs rates of 5% for secukinumab and 15% for placebo in the induction phases of the core studies, 15% drop-out rate in the maintenance phases of the core studies, and a PASI 50 response rate of about 95%, it is aimed that a total of about 1,220 subjects will be eligible to enter this extension study across approximately 300 sites worldwide.

4.1 Inclusion criteria

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

1. Subjects who completed the full study treatment period (52 weeks) in the core studies (e.g., CAIN457A2302 or CAIN457A2303), and after randomization have been receiving secukinumab treatment during the maintenance phase of the core studies, and show at least a partial response (PASI 50 or better) at Week 52 of the core studies.
2. Written informed consent must be obtained before any assessment is performed.
3. For inclusion in the open label period, written informed consent for protocol amendment1 must be obtained.
4. For inclusion in the open label period, the subject must be deemed to benefit from the study drug based on the investigator's clinical judgment.

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 to use of prohibited treatments in the core study detailed in the protocol have to be adhered to Table 5-1.
3. Subjects not expected to benefit from participation in the extension study, as assessed by the subject and investigator
4. Subjects expected to be exposed to an undue safety risk if participating in the study
5. Current severe progressive or uncontrolled disease which in the judgment of the investigator renders the subject unsuitable for the study
6. Plans for administration of live vaccines during the study period
7. 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)
8. 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 vasectomized 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

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will provide the following study treatments

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 s.c.150 mg dose (1 syringe) and s.c. 300 mg dose (2 syringes). For blinding purpose the subject in 150 mg treatment group will also receive one syringe of placebo 150 mg during the blinded period of the study
2. Reference therapy: 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 study.

5.2 Treatment groups

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 aided with a needle guard system that will aid protection from accidental needle sticks.

For the subjects classified as PASI 75 responders at Week 52 the study consists of 5 or 6 periods

(i) screening period: is the duration between signing the informed consent form (ICF) and randomization registered with IRT.

(ii) randomized withdrawal period: the duration of randomized withdrawal period for each subject is different i.e., starting from Week 52 until the subject experiences the relapse or up to Week 156 (see Section 3.1 on Study Design for additional details)

(iii) treatment period: starting from the visit in randomized withdrawal period at which a subject experiences relapse and continuing through Week 156. During the Week 152 visit subject will receive the last blinded dose of the study treatment. At Week 156 the subjects will enter the open label period. For subject who will not move to the open label period, the Week 156 visit is the EoT. For subjects who will move to the open label period, the Week 156 visit will be the first open label treatment.

(iv) open label period: starting from Week 156 to Week 260 all subjects will be on open label secukinumab. The subjects will receive the last dose of the study medication at Week 256. The Week 260 visit is the OL –EoT.

(v) follow-up period (for all subjects): treatment free period (Week 264 to Week 268)

(vi) follow-up 2 period: treatment free period only for patients who prematurely discontinued treatment. 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 CAIN457A2302E1 study.

For the subjects classified as partial responders at Week 52 the study consists of 4 or 5 periods

(i) screening period: is the duration between signing the informed consent form (ICF) and randomization registered with IRT.

(ii) treatment period: starting from the randomization visit at Week 52 continuing through Week 156 the subjects will receive secukinumab s.c. every 4 weeks at the dose which they were originally assigned in the core study. During the Week 152 visit subject will receive the last blinded dose of the study treatment. At Week 156 the subjects will enter the open label period. For subject who will not move to the open label period, the Week 156 visit is the EoT. For subjects who will move to the open label period, the Week 156 visit will be the first open label treatment.

(iii) open label period: starting from Week 156 to Week 260 all subjects will be on open label secukinumab. The subjects will receive the last dose of the study medication at Week 256. The Week 260 visit is the OL –EoT.

(iv) follow-up period (for all subjects): treatment free period (Week 264 to Week 268).

(v) follow-up 2 period: treatment free period only for patients who prematurely discontinued treatment. 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 CAIN457A2302E1 study.

NOTE: *Partial responders **DO NOT** participate in the randomized withdrawal and **DO NOT** receive any loading dose even if they experience a full relapse (a loss of >50% of the maximum PASI gain compared to baseline of the core study)*

5.3 Treatment assignment, randomization

At the end of Week 52 visit in the core study (e.g., Visit 21 of study CAIN457A2302 or CAIN457A2303) the investigator will complete Week 52 assessments, enter the PASI response into the eCRF and register the completion of Week 52 visit in the IRT.

The IRT system will search (after the PASI response status has been updated by investigator or designee in IRT) the databases of core studies at Week 52 to identify whether or not the subject has been on secukinumab (s.c. 150 mg or 300 mg) at the time of completion of Week 52 visit in the core study.

For the subjects classified as PASI 75 responders at Week 52

Once investigator or designee has entered Week 52 PASI response status in the IRT and also registered with IRT the completion of Week 52 visit of the core studies on secukinumab treatment, a subject will be eligible for randomization in the extension study.

The Week 52 visit in the core study is the randomization visit for CAIN457A2302E1 (extension study).

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 extension study (CAIN457A2302E1).The IRT can be contacted via the Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment groups (secukinumab 150 mg or placebo secukinumab 150 mg or secukinumab 300 mg or placebo secukinumab 300 mg) and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to the caller or any of the site staff members.

The randomization numbers at Week 52 will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment groups, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Randomization will be stratified by geographical region and by body weight (< 90 kg or ≥90 kg) collected at Week 52.

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

For the subjects classified as partial responders at Week 52

The same randomization process used for PASI 75 responders at Week 52 will be followed for partial responders at Week 52.

A randomization numbers will be assigned to partial responders. These randomization numbers will be linked to the two different treatment groups (secukinumab 150 mg, secukinumab 300 mg) which correspond to the treatment received in the core studies. Partial responders at Week 52 will then continue to receive the treatment they were assigned in the core studies.

5.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments, and data analysts will remain blind to the identity of the study treatment from the time of randomization until final database lock, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study.
2. The identity of the treatments will be concealed by the use of investigational treatment that are all identical in packaging, schedule of administration and appearance.

In order to maintain blind in this study, placebo is used.

During the double blinded period of the study, unblinding will only occur in the case of subject emergencies (see Section 5.5.10), at the time of the primary endpoint at Week 68, and when the patients enter the open label part of the study at Week 156After all subjects complete Week 68, designated sponsor team members will be unblinded, whereas the subjects, investigator staff, and persons performing the assessments will remain blinded until Week 156 to ensure reliable efficacy and safety measures. At Week 156 all subjects will enter the open label period and subjects, investigator staff, and persons performing the visit assessments will become unblinded.

In case the results of the core study are published while the extension study is ongoing, the data will be published in groups only, with limited ability to unblind individual subjects (The exception to this might be rare safety events that, if occurring in only one treatment group, would allow unblinding of the affected subjects). However, since this would be relevant to only a very small group of subjects, if any, no impact on the overall validity of the extension study is expected. Nevertheless, the integrity of the primary endpoint is not affected since no unblinding with respect to placebo in the randomized withdrawal is performed.

5.5 Treating the subject

5.5.1 Subject numbering

Subjects in the extension study CAIN457A2302E1 will be assigned a uniquely identified subject number for the extension study. The uniquely identified subject number is composed by the study identifier (CAIN457A2302E1), 4-digit study site identifier assigned by Novartis for the site in the core study and a 3-digit sequential number assigned by the investigator in the core study (e.g.,CAIN457A2302E1_1234001). The last 7 digits of the unique subject identifier will remain the same for the subject in the core study and the extension study.

Subjects will be given the ICF during one of the scheduled visits of the core study (e.g., Week 48 [Visit 20] or at earlier visit in study CAIN457A2302 or CAIN457A2303) **to read and understand** for their participation in this extension study. Subjects will **NOT** be signing the ICF **before** completing the assessments on Week 52 visit of the core study (e.g., Visit 21 of the study CAIN457A2302 or CAIN457A2303) and unless the investigator has entered the Week 52 PASI response in the IRT, and registered the completion of the core study Week 52 visit in the IRT, and the IRT confirms that the subject was on secukinumab in the core study.

Subjects who are eligible (as decided by the investigator or designee) based on the inclusion/exclusion criteria and IRT notification (see Section 5.3) will be asked to sign the ICF. In order to enter data for extension study CAIN457A2302E1, the site is to select a CRF book, add the subject's number from the core study (e.g., CAIN457A2302 or CAIN457A2303) and update the electronic data capturing (EDC) system with this number.

If the subject fails to be treated for any reason, the IRT must be notified immediately and the reason for not being treated will be entered on the Screening Epoch Disposition electronic Case Repot Form (eCRF). The data or information regarding demography for the subjects not randomized will be available as a listing from the core study databases. The Inclusion/Exclusion eCRF for the extension study CAIN457A2302E1 is to be completed for the subjects not randomized (after signing the ICF), along with Adverse Events eCRF (for study CAIN457A2302E1) for any SAE that occurred after signing the ICF. If a subject fails to be treated in the extension study, the subject completes the follow-up visits in the respective core study.

5.5.2 Dispensing the investigational treatment

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

The boxes containing single prefilled syringes with study treatment solution (secukinumab or placebo secukinumab) has a 2-part label. A unique medication number is printed on each part of this label. The blinded qualified study site staff personal will identify the study treatment box to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the box containing PFS with study treatment, blinded qualified study site staff personal will detach the outer part of the label from the boxes and affix it to the source document (Drug Label Form) for that subject's unique subject number.

At Week 160, and once the home administration is operationally set up, subjects will be expected to perform home administrations at the protocol specified time points. For these cases the investigator will dispense, via IRT, an appropriate number of investigational treatment packages for home administrations and detach outer part of the label from the packaging. The subjects will record the date(s) of administration at home and will return the used medication and packaging at their next visit to the site. Subjects will be asked to return all unused medication and packaging the latest at the completion of the study or at the time of discontinuation of the investigational treatment. Site staff will record in the appropriate documents the dates of the administration. Detailed instructions will be provided separately.

5.5.3 Storage of investigational treatment

Single PFS with study treatment solution (secukinumab or placebo) will be packed in individual boxes. The boxes 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, PFS should be stored according to the instructions specified on the treatment labels. PFS and/or clinical supplies are to be dispensed and administered only in accordance with the protocol.

The boxes containing the PFS with study treatment solution should be kept at 2 to 8°C (36°F and 46°F). PFS should be protected from direct exposure to light. Therefore the PFS must be stored protected from light.

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

The investigator (or designee) must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

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

5.5.4 Instructions for prescribing and taking study treatment

Each subject will require two boxes of syringe set (PFS) per dose throughout the study.

- One secukinumab 150 mg PFS and one placebo secukinumab PFS (150 mg group) **OR**
- Two secukinumab 150 mg PFS (300 mg group) **OR**
- Two placebo secukinumab 150 mg PFS (Placebo group)

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.

All doses of study treatment (secukinumab and/or placebo secukinumab) will be injected at the study site after Week 52 assessments for study CAIN457A2302 or CAIN457A2303 have been completed. It is preferred that subject should self-inject, however, if a subject is not able or not willing to self-administer, administration will be performed by study site staff.

The first study treatment administration (self or by study site staff) will occur at randomization visit (Week 52) after inclusion/exclusion criteria have been confirmed, the core study scheduled assessments at Week 52 have been performed, and the scheduled blood samples have been drawn, and only after the investigator has registered the completion of the core study with IRT.

For subjects willing to self-inject, the first use at randomization visit (Week 52) will take place under guidance and the supervision of one site staff member. At the randomization visit (Week 52) the subjects will be instructed through the site staff by walking them through the "Instructions For Use" on how to self-inject via PFS. At the following visits, subjects will receive the PFS at the study site.

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

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

At each visit, all study assessments, including the completion of health-related quality of life (HRQoL) tools (as reported by subjects), should be completed prior to the injection of study treatment.

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

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.

Administration

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

During the open label period, after approximately two years of study of self-administered treatment under the supervision of site staff during the double blinded period, subjects will be expected to self-administer the PFS at home when they are not visiting the site for any other trial related procedures.

The subjects will be allowed to self-administer treatment at home (starting Week 160) only if they have exhibited correct use for self-administering the PFS at the site.

It is important that during the self-administration period at home, subjects contact the investigator / site staff in case they are experiencing any AE/SAEs or have any concerns.

If the subject is not able / not confident to self-administer the PFS, he/she should visit the site every 4 weeks during the open label treatment period, according to the visit schedule, and either the staff or the subject will administer the study drug. However, during those visits no other assessments will be performed.

5.5.5 Permitted dose adjustments and interruptions of study treatment

No dose adjustments or interruptions are permitted.

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 core study (e.g., CAIN457A2302 or CAIN457A2303) Concomitant medications eCRF, Surgeries and Medical Procedures eCRF, and Prior Psoriasis Therapy eCRF page at Week 52 randomization visit before a subject enters the extension study (CAIN457A2302E1). The Week 52 concomitant medication data for the extension study will be the same as the baseline concomitant medication data of the core study for all three eCRFs. All concomitant medications that were ongoing from the core study at the Week 52 randomization visit will be followed in the extension on the applicable Concomitant medications eCRF or Surgeries and Medical Procedures eCRF.

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

5.5.8 Prohibited Treatment

Use of any treatments displayed in Table 5-1 that could confound the efficacy is **NOT** allowed for any indication during the study excluding the treatment-free follow-up 2 period.

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.

Table 5-1 Prohibited treatment

Prohibited treatments[†,‡]	Time period before randomization visit at Week 52
Alefacept, briakinumab, efalizumab, ustekinumab	6 months
Biological immunomodulating agents other than above (e.g., adalimumab, etanercept, infliximab)	12 weeks
Other systemic immunomodulating treatments[§] (e.g., MTX, cyclosporine A, corticosteroids[§], cyclophosphamide)	4 weeks
Other systemic psoriasis treatments* (e.g., retinoids, fumarates)	4 weeks
Photochemotherapy (e.g., PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks

Prohibited treatments[†,‡]	Time period before randomization visit at Week 52
Use of opical treatment ** that is likely to impact signs and symptoms of psoriasis for >14 days* (e.g., corticosteroids [CS], vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)	2 weeks
Live virus vaccinations during extension study	6 weeks
Any investigational treatment or participation in any interventional clinical trial during extension trial	4 weeks or 5 half-lives (whichever Is longer)

[†]If a subject inadvertently used the prohibited treatment in core study (e.g., CAIN457A2302 or CAIN457A2303) without undue safety risk till completion of Week 52, he/she must have completed the time period as defined in the table above. Subjects who have not completed an adequate time period (table above) will not be eligible for the current extension study.

[‡]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

** 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.

5.5.9 Discontinuation of study treatment and premature subject withdrawal

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

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 randomized withdrawal /treatment EoT eCRF (Week 156) or if the subject is discontinued during the open label period on the OL-EoT eCRF (Week 260).

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

- Withdrawal of informed consent
- Emergence of the following AEs: the AEs 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 sections 6.5.6 and 7.3)
- Use of prohibited treatment as per recommendations in Table 5-1.
- 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 discontinued from study treatment should **NOT** be considered withdrawn from the study. If the subject discontinues treatment during the randomized withdrawal/double blinded treatment or open label period then the site staff must record the date and primary reason for stopping study treatment on the appropriate EoT eCRF

When subject discontinues the study treatment, then assessments described at Week 260 should be performed approximately four weeks after their last dose of secukinumab and the subject should then return per appropriate schedule for assessments described at Week 264 and Week 268 (follow-up period). Subsequently, these subjects should enter the follow-up 2 period.

The investigator must contact the IRT when the subject completes the assessments on Week 156 and/or 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).

Subjects who withdraw from follow-up 2 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 (Week 264 and Week 268), the investigator will follow the study treatment discontinuation procedures.

The investigator must contact the IRT when the subject completes the assessments of the EoT/ OL-EoT visit 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 unblinding of treatment assignment

Emergency breaking of the assigned treatment code should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency code breaks are performed using the IRT. When the investigator or his/her blinded designee contacts the system to unblind a subject, he/she must provide the requested subject identifying information and the date, time, and reason for unblinding. The investigator will then receive details of the treatment for the specified subject and a fax confirming this information. The system will automatically inform the Novartis monitor for the study site and the Clinical Trial Head that the code has been broken.

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

Study treatment for the study subject **must** be discontinued after emergency unblinding.

Subjects who are prematurely unblinded will be discontinued from the study treatment and requested to return for the applicable end of period visit (end of randomized withdrawal period visit or the end of the treatment period visit [Week 260], two follow-up visits at Week 264 and Week 268 and follow-up 2 period.

5.5.11 Study completion and post-study treatment

A subject entering into the extension study CAIN457A2302E1 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 eligible subjects rolled over from the core study (e.g., CAIN457A2302 or CAIN457A2303) have completed as per protocol the visits and assessments defined in Table 6-1 for the extension study CAIN457A2302E1.

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 the extension study CAIN457A2302E1 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 subject should be seen as soon as possible and properly managed as described in Section 6 for a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing Institutional Review Boards (IRBs) and/or Independent Ethics Committees (IECs) of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits 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 periods, 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 256 during randomized withdrawal and/or treatment period, the open label period or the follow-up period. Patients are expected to adhere as close as possible to the visit schedule.

Relapse visits (R1, R2, and R3) will have visit window of "±2" days. Time schedule of relapse visits cannot be anticipated and will be different for each subject experiencing first full relapse (a loss of >50% of the maximum PASI gain compared to baseline of the core study).

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 (Week 264 and 268).

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 CAIN457A2302E1 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 HRQoL tools prior to any investigator assessments. Order of HRQoL tools is: DLQI©, EQ-5D©, HAQ©-DI (subjects with history of PsA at baseline of core study). Note: EQ-5D© will not be performed during the open label period.
- 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 during the double blind period
- Contact IRT to register the subject visit.
- Syringe set boxes of study treatment (secukinumab or placebo secukinumab) are made available to the subjects for self-injection or administration by study site staff

Table 6-1 Assessment schedule

	*Randomized withdrawal and/or treatment period (Year 1 and 2)																											Unscheduled visit	Relapse 1 (R1)[b]	Relapse 2 (R2)[b]	Relapse 3 (R3)[b]
Week (Relative to Baseline of core studies)	**52[a]**	**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				
Day	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				
Visit at the site	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																										x[18]				
Inclusion/exclusion criteria[1]	x																										x				
Demography and other characteristics[2]	x																														
Physical examination	x[3]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x				
Height[4]	x																														
Weight	x[3]	x						x						x			x			x							x				
Vital signs	x[3]	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			
[redacted]																															
Urinalysis (local)	x[3]			x			x			x				x			x			x			x				x				
Lab analysis: chemistry and hematology[5]	x[3]	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[5]	x[3]			x			x			x				x			x			x			x				x				
Fasting Labs: plasma glucose[4,5]	x[3]			x			x			x				x			x			x			x				x				
Serum pregnancy test[5]	x[6]													x													x	x[7]				
Urine pregnancy test (local)[6]	x[3]			x			x			x				x			x			x			x				x				
ECG (standard 12 lead)	x[3]			x			x			x				x			x			x			x				x				
Blood sample for IG[8]	x[3]						x							x						x			x				x	x[9]			

	*Randomized withdrawal and/or treatment period (Year 1 and 2)																											Unscheduled visit	Relapse 1 (R1)[b]	Relapse 2 (R2)[b]	Relapse 3 (R3)[b]
Week (Relative to Baseline of core studies)	**52[a]**	**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				
Day	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				
Blood sample for PK[8]	x[3,10]	x	x	x[10]	x	x	x[10]	x	x	x[10]	x	x	x	x[10]	x	x	x[10]	x	x	x[10]	x	x	x[10]	x	x	x	x[10]	x[9]			
PASI	x[3]	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[11]	x[11]	x[11]
Assessment of rebound symptoms[12]	x[3]	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[3]	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[11]	x[11]	x[11]
EQ-5D©	x[3]			x			x			x				x			x			x			x				x				
DLQI©	x[3]			x			x			x				x			x			x			x				x				
HAQ-DI©[14]	x[3]			x			x			x				x			x			x			x				x				
Adverse event (AE) assessment	x[3]	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[11]	x[11]	x[11]
Serious AE assessment	x[3]	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[11]	x[11]	x[11]
Concomitant medications	x[3]	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[11]	x[11]	x[11]
Randomization via IRT[15]	x																														
Administration of study treatment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[20]		x	x	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		x	x	x
End of screening phase completion eCRF	x																														
End of blinded randomized withdrawal/ treatment period (EoT): submit EoT period completion eCRF and call IRT																											x				
End of follow-up period: submit follow-up period completion eCRF																															
Call to subjects from study-coordinator reminding the visit	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

	Open Label treatment period (Year 3 and 4)																										Unscheduled visits [21]	Follow-up period		Follow-up 2 period
Week (Relative to Baseline of core studies)	160	164	168	172	176	180	184	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 three 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	
Day	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	
Visit at the sites[19]			x			x			x				x			x			x			x				x		x	x	
Home administration[17]	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	
Height[4]																														
Weight																										x			x	
Vital signs			x			x			x				x			x			x			x				x	x	x	x	
Urinalysis (local)																										x			x	
Lab analysis: chemistry including amylase and lipase and hematology[5]						x							x						x							x	x	x	x	
Fasting Labs: lipid panel[5]																										x			x	
Fasting Labs: plasma glucose [4,5]						x							x						x							x			x	
Serum pregnancy test[5]																										x	x[7]			
Urine pregnancy test (local)[6]						x							x						x							x			x	

	Open Label treatment period (Year 3 and 4)																										Unscheduled visits [21]	Follow-up period		Follow-up 2 period
Week (Relative to Baseline of core studies)	160	164	168	172	176	180	184	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 three 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	
Day	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	
ECG (standard 12 lead)						x							x						x							x			x	
Blood sample for IG[8]																										x	x[9]		x	
Blood sample for PK[8]																										x[10]	x[9]		x[10]	
PASI			x			x			x				x			x			x			x				x	x	x	x	
Assessment of rebound symptoms[12]																										x		x[13]	x	
IGA mod 2011			x			x			x				x			x			x			x				x	x	x	x	
DLQI©						x							x						x							x				
HAQ-DI©[14]						x							x						x			x				x				
Adverse event (AE) assessment			x			x			x				x			x			x			x				x	x	x	x	x
Serious AE assessment			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
Complete PASI and IGA eCRF and call IRT			x			x			x				x			x			x			x				x				
Administration of study treatment	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x					

	Open Label treatment period (Year 3 and 4)																										Unscheduled visits [21]	Follow-up period		Follow-up 2 period
Week (Relative to Baseline of core studies)	160	164	168	172	176	180	184	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 three 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	
Day	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	
End of open label treatment period (OL-EoT): submit EoT period completion eCRF and call IRT																										x				
End of follow-up period: submit follow-up period completion eCRF																													x	
End of follow-up 2 period: submit follow-up 2 period completion eCRF																														x
Call to subjects from study-coordinator reminding about the visit			x			x			x				x			x			x			x				x		x	x	

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

*For subjects classified as PASI 75 responders at Week 52 of the core study (e.g., CAIN457A2302 or CAIN457A2303), the study consists of 5 or 6 periods – screening period, randomized withdrawal period, treatment period, open label period (OL) ,follow-up period and follow-up 2 period; For subjects classified as partial responders at Week 52 of the core study (e.g., CAIN457A2302 or CAIN457A2303), the study consists of 4 or 5 periods – screening period, treatment period, open label period ,follow-up period and follow-up 2 period; The screening period will be the duration between signing the informed consent form and randomization registered with Interactive Response Technology (IRT).

[a]Subjects would be randomized on the same day (Week 52) which is end of maintenance period of the core study (e.g.,CAIN457A2302 or CAIN457A2303).

[b]Relapse visits (R1, R2 and R3) will have visit window of ±2 days.

[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] Investigator must consider the baseline data of core study (e.g., CAIN457A2302 or CAIN457A2303) Demography eCRF, Smoking History eCRF, Cardiovascular History eCRF, Medical History eCRF, Psoriasis History eCRF, Psoriatic Arthritis History eCRF, and Prior Psoriasis Therapy eCRF at Week 52 before a subject enters the extension study. The data for these assessments at Week 52 visit for extension study will be same as the baseline data of the core study.

[3] Data for these assessments already have been collected at end of maintenance visit (Week 52) of the core study (e.g. CAIN457A2302 or CAIN457A2303). The data on the eCRFs for these assessments in extension study at Week 52 will be same as end of maintenance visit (Week 52) of the core study. AE and SAE data will be again collected after completion of core study Week 52 visit assessments. PASI response status from Week 52 records of the core study to be entered in the IRT by the unblinded site personal from core study for randomization in the extension study.

[4] The data for this assessment to be collected freshly at Week 52 (randomization).

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

[6]To be done for female subjects 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.

[7]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.

[8]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.

[9]An unscheduled IG and or PK sample is collected only to replace an IG or PK sample not taken at a regular scheduled visit.

[10] The PK blood sampling at these scheduled visits must be collected for all subjects. PK blood collections at other time points are “event driven” i.e., PK blood samples will only be collected in case of relapse.

[11]Relapse visits (R1 to R3) are the visits in the treatment period. The time schedule for these 3 relapse visits will be different for each subject. A subject will make these relapse visits **after a full relapse** (a loss of >50% of the maximum PASI gain compared to baseline of the core study) occurred on the previous scheduled visit. PASI and IGA mod 2011 assessments, and data on AEs, SAEs and concomitant medications will be collected during these 3 relapse visits. [12]Rebound assessments to be done during the randomized withdrawal period as well as during the treatment period. Note, the duration of randomized withdrawal period until the subject experiences the relapse is different for each subject and does not have definite end.

[13]Unscheduled rebound assessment only to be done for an unscheduled visit that occurs during the follow-up period.

[14] Only for subjects with psoriatic arthritis (PsA) recorded on the Psoriatic Arthritis History eCRF during screening in core study.

[15] The investigator must complete the core study Week 52 assessments, enter the PASI response on the eCRF and register the completion of Week 52 visit in the IRT system of core study. Based on the fulfillment of inclusion/exclusion criteria by the subject and IRT notification from the database of core studies at Week 52, the investigator must call the IRT set up of extension study (CAIN457A2302E1).

[16] PASI and other assessments must be completed, entered into the eCRFs before calling the IRT at each site visit from Week 56 to Week 256. For Week 52 refer to footnote 14.

[17]Patients who cannot self-administer medication at home may come to the site for administration of the medication.

[18] Informed consent for the extension amendment may be obtained any time prior to the first open label study exposure.

[19] The visits at the sites are scheduled every 12 weeks, except for the visits between Week 192 - Week 208 and between Week 244 – Week 260, which are scheduled every 16 weeks.

[20] Dosing only to be performed if the subject enters the open label treatment period. First treatment of the open label period will be administered at Week 156 once all assessments of Visit Week156 are performed, the call to IRT is done and the subject has signed the revised informed consent for amendment 1. Placebo subjects who enter the open label period will be given once weekly s.c. injections of secukinumab for 4 consecutive weeks and then s.c. injections every 4 weeks. Any subject starting on secukinumab 150 mg may continue on 150 mg every 4 weeks or switch to 300 mg at Week 156 or any other regular site visit if the investigator decides the subject would benefit from the higher dose.[21] 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 randomized withdrawal or treatment period will be considered screen failures. The IRT must be called within 2 days and the reason for not being randomized will be entered on the Screening Phase Disposition electronic Case Report Form (eCRF). The Screening visit date, the Demography eCRF, 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 randomized), 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 randomized. The Death eCRF should be completed in the case of a death.

6.2 Subject demographics/other baseline characteristics

6.2.1 Subject demographics

The investigator must consider the baseline data of the core study (e.g., CAIN457A2302 or CAIN457A2303) Demography eCRF at Week 52 randomization visit before a subject enters the extension study.

Subject demographic and baseline characteristics data to be collected on all subjects include: date of birth, age, sex, race, ethnicity, source of subject referral, prior and concomitant medications (relative to core studies), and relevant medical history/current medical condition present before signing informed consent. The demographic data of the extension study will be the same as the demographic data of the core study.

6.2.2 Other baseline characteristics

The investigator must consider the baseline data of the core study (e.g., CAIN457A2302 or CAIN457A2303) Smoking History eCRF, Cardiovascular History eCRF, Medical History eCRF, Psoriasis History eCRF, Psoriatic Arthritis History eCRF, and Prior Psoriasis Therapy eCRF at Week 52 randomization visit before a subject enters the extension study. The data on these eCRFs in the extension study will be same as the data entered for these eCRFs in the core 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 box counts and information provided by the investigator and/or site staff.

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 scale has been used in the core studies (e.g., CAIN457A2302 and CAIN457A2303), and in secukinumab phase II studies in collaboration with Health Authorities, in particular the FDA.

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 of core study 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 2 points on the IGA scale compared to baseline.

6.4.2 Assessment of 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:

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

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

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, the investigator or qualified designee should ensure that all the information required for the PASI calculation was entered into the PASI Score eCRF at Week 52 and that a PASI score is available prior to contacting IRT. The Investigator or qualified designee will enter the Week 52 PASI score into the IRT system at Week 52 before subject receives the study treatment.

Based on PASI at Week 52, a subject to be eligible must be either a PASI 75 responder or partial responder according to the definitions stated below:

- PASI 75 responders: subjects with PASI 75 response (subjects achieving ≥ 75% improvement [reduction] in PASI score compared to baseline of the core study) at Week 52
- Partial responders: subjects with PASI 50 response (subjects achieving ≥ 50% improvement [reduction] in PASI score compared to baseline of the core study, but not achieving a PASI 75 response) at Week 52

During the study, at each visit, the PASI score will be calculated and response will be classified according to the definitions from CHMP guidelines for psoriasis CHMP/EWP/2454/ 02 2004

- **PASI 75 response:** subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline of the core study are defined as PASI 75 responders
- **PASI 50 response:** subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline of the core study are defined as PASI 50 responders
- **PASI 90 response:** subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline of the core study 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 of core study is reduced by >50%

For subjects in PASI 75 responder group and entering the randomized withdrawal period, PASI response status at each visit (after Week 52 visit) will be calculated to determine if subject will enter the treatment period. PASI at the visit will be compared to the PASI baseline of the core study to assess if subject meets criteria for "**first full relapse**" (loss of >50% of maximum PASI gain compared to PASI baseline of the core study). Sites will have to enter relapse assessment into eCRFs and update the IRT at each visit in randomized withdrawal period. Subjects with first full relapse then stop randomized withdrawal period and enter treatment period.

6.4.3 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).

Definitions related to rebound

- **Rebound**: A Subject experiences a rebound, if PASI increases to > 125% of baseline (where baseline is the PASI at the randomization of the core study) 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 administered.

6.4.4 Appropriateness of efficacy assessments

The PASI score, 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 considered acceptable by Health Authorities (CHMP/EWP/2454/02 2004) to assess efficacy in conjunction with IGA mod 2011.

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 assessments
  - Hematology
  - Clinical chemistry
  - Urinalysis
  - Immunogenicity (IG; assessment of anti-secukinumab antibody development)
  - ECG
  - Pregnancy and assessments of fertility

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 AE must be recorded on the Adverse Event screen of the subject's eCRF (see 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).

Whether action needs to be taken to address notable vital signs 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.

6.5.3 Height and weight

Height and body weight will be measured as listed in Table 6-1. Height and 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. The body weight recorded at Week 52 will be used to stratify the subject population for randomization at Week 52.

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.

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.

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, uric acid, amylase and lipase. Serum chemistries will be measured at all scheduled study visits within the visit window specified in Table 6-1.

Local 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.

Immunogenecity (IG)

Blood samples for IG (anti-secukinumab antibodies) will be taken pre-dose at the scheduled timepoints as indicated in Table 6-1 and Appendix 2, Table 13-2. 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 Clinical Trial Head (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 3, Section 13.3.2.

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

Before entering the extension study, the investigator must consider the results of serum β-hCG test already performed on all women of child-bearing potential at the time of entering the core studies (e.g., CAIN457A2302 and CAIN457A2303).

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 randomization 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 (see 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 includes (as indicated in Table 6-1)

- Waist circumference and hip circumference
- Fasting laboratory evaluations,
- HRQoL assessments such as

1. DLQI©
2. EQ-5D©
3. HAQ©-DI (subjects with PsA at baseline of the core study)

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

Note: EQ-5D assessments will not be performed during the open label period.

6.6.1 Waist circumference and hip circumference

Waist and hip circumference (cm or inches) will be measured twice and recorded in the source documentation by the investigator (or designee) at scheduled visits as indicated in Table 6-1. The average of the two measurements will be recorded in the eCRF. Waist/hip circumference ratio will be calculated from the waist and hip circumference measurements. Waist and hip circumference will be measured as follows (WHO Document, 1988, Lohman TG, 1988).

The subject should stand with weight evenly balanced on both feet 25-30 cm apart. Mark the level of the lowest rib margin with a marker pen, palpate the iliac crest in the mid-axillary line and mark this level on the skin as well. Apply an elastic tape (e.g., a narrow string of silk covered elastic rubber band) horizontally midway between the lowest rib margin and the iliac crest (this is to assist in defining the levels of the waist circumference). The tape should be tied firmly enough to stay in position around the abdomen about the level of the umbilicus.

The subject should be asked to breathe normally and at the time of making the measurements, the subject should be asked to breathe out gently to prevent from contracting their muscles or holding their breath. Measure the circumference of the tape using a plastic tape measure (not elastic or metal).

Repeat the above with the elastic tape around the point yielding the maximum circumference over the buttocks.

It is recommended that the observer sits in front of the subject and that the same study site staff member carries out the assessment throughout the study wherever possible

Note: waist and hip circumference will not be performed during the open label period.

6.6.2 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.

6.6.2.1 Plasma glucose

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

6.6.2.2 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.

6.6.3 Resource utilization

Not applicable.

6.6.4 Health-related Quality of Life (HRQoL)

The impact of psoriasis on various aspects of subject's HRQoL 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 at baseline of core study)

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 initial and date the white box (and not the shaded area of the form) at the bottom left hand portion of the last page of the questionnaire. In those countries not permitting subjects to initial documents, the date and 3-letter initials of the country in which the subject participates is to be used. By ensuring that the initials are placed in the white box, the subject's initials will not be copied when the digital pen activates its camera to record a digitized copy of the completed questionnaires. The digitized pen writes in green ink. Only this pen may be used for making corrections and only the subject may make corrections. Corrections must be "single-lined" through, and should be dated and where permitted, initialed by the subject.

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.

6.6.4.1 Dermatology Life Quality Index© (DLQI©)

The DLQI© is a 10-item general dermatology disability index designed to assess HRQoL 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 HRQoL 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.

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

The 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.

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

The HAQ© was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. 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©-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 assess the functional ability of subjects with PsA at baseline of the core study.

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 core study.

6.6.5 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 2, Table 13-1.

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. 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 Clinical Trial Head (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 PK samples can be found in Appendix 3, Section 13.3.1.

PK sample stability

Secukinumab is stable in serum samples for at least 20 months at -20°C or at -80°C.

PK analytical methods

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

6.6.7 Other biomarkers

Not applicable.

6.6.8 Prospective suicidality assessment

Not applicable.

7 Safety monitoring

7.1 Adverse events

An 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 study treatment. Medical conditions/diseases present before starting study treatment are only considered AEs if they worsen after starting study treatment. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

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

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

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

- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subject with underlying disease.

The investigator must consider the AEs still ongoing at Week 52 of the core study (e.g., CAIN457A2302 or CAIN457A2303) at the time a subject enters the extension study. The ongoing AEs from the core study will be followed to final outcome in the extension study clinical trial database. New AEs with onset while subject is in the extension study will be entered in the Adverse Event eCRF of the extension study.

Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for labs and other test abnormalities are included in Appendix 1.

AEs should be recorded in the Adverse Events eCRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- The severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the study treatment (suspected: Yes or No)
- its duration (start and end dates) or if continuing at final examination)
- whether it constitutes a SAE
- action taken with study treatment
- concomitant medications taken
- outcome and
- whether the AE led to study discontinuation

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the subject's general condition

- is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

All AEs should be treated appropriately. The action taken to treat the AE should be recorded on the Adverse Event eCRF.

AEs that occur after informed consent has been obtained must be captured on the Adverse event eCRF. Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment the interventions required to treat it, and the outcome.

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

The investigator should also instruct each subject to report any new AE (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information 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 events

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 on the paper Serious Adverse Event Report Form (SAE report form) or where available the Serious Adverse Event Form within the remote data capturing (RDC) system. The investigator must assess the relationship to each specific study treatment and complete the paper or electronic SAE report form in its entirety in English.

When SAEs are recorded on the paper SAE form, these should be faxed **within 24 hours of awareness of the SAE** to the local Novartis Drug Safety and Epidemiology (DS&E) Department. The telephone and fax number of the contact persons in the local department of DS&E, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

When SAEs are recorded electronically in the Oracle Clinical/ Remote Data Capture (OC/RDC) system, these should be entered, saved and e-signed **within 24 hours of awareness of the SAE**. These data will automatically be submitted to Novartis DS&E immediately after investigator signature or 24 hours after entry, whichever occurs first.

The Investigator must assess the relationship to the study treatment.

Note that any follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not and whether the subject continued or withdrew from study participation. 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 IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a DS&E 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 Pregnancy reporting

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

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis DS&E 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.

7.4 Data Monitoring Committee

A data monitoring committee (DMC) will review the safety data of this trial at selected time intervals at least until the Week 68 PEA. Details regarding the DMC process will be available in relevant secukinumab DMC charter.

8 Data review and database management

8.1 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF 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 and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

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

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

8.3 Database management and quality control

Novartis staff [or CRO working on behalf of Novartis] review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make

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

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

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

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

Subjects will use electronic pens to enter data on HRQoL tools. This data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study treatment dispensed to the subject and all IVR recorded dosage changes will be tracked using an 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.

9 Data analysis

Treatment groups for analysis will include:

- **Subjects who were PASI 75 responders at Week 52**
  - Secukinumab 150 mg
  - Secukinumab 300 mg
  - Placebo (secukinumab 150 mg in core studies)
  - Placebo (secukinumab 300 mg in core studies)
- **Subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg**
  - Secukinumab 150 mg
  - Secukinumab 300 mg

- Subjects who were partial responders at Week 52
  - Secukinumab 150 mg
  - Secukinumab 300 mg

For open-label period analyses subjects being switched from 150 mg to 300 mg will be summarized as well.

NOTE: Week 52 assessments refer to Baseline extension assessments

9.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set: The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set. Mis-randomized subjects will be defined as those subjects where IRT contact is made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and double-blind study treatment was not administered to the subject.

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

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

9.2 Subject demographics and other baseline characteristics

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, ≥ 1 week, ≥ 2 weeks, ≥ 3 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 variable

9.4.1 Variable

The primary variable is the cumulative rate of subjects who lost PASI 75 response up to Week 68 (time=0 being defined as Week 52).

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypotheses are that the cumulative rate for subjects who lost PASI 75 response up to Week 68 are not different between secukinumab 150 mg and corresponding placebo as well as between secukinumab 300 mg and corresponding placebo.

Let $p_j(t)$ denote the proportion of PASI 75 responders at time t for treatment group j, and let $p_{0,j}(t)$ denote the proportion of PASI 75 responders at time t for placebo group j, j=1, 2, where

- 0,j corresponds to placebo (secukinumab 150 mg in core studies) for j=1 and to placebo (secukinumab 300 mg in core studies) for j=2,
- 1 corresponds to secukinumab 150 mg,
- 2 corresponds to secukinumab 300 mg.

The following hypotheses will be tested for 52 weeks$\leq$ t $\leq$68 weeks

- H_1: $p_1(t) - p_{0,1}(t) = 0$ versus H_{A1}: $p_1(t) - p_{0,1}(t) \geq 0$,
- H_2: $p_2(t) - p_{0,2}(t) = 0$ versus H_{A2}: $p_2(t) - p_{0,2}(t) \geq 0$,

In other words

- H_1: Secukinumab 150 mg is not different from placebo with respect to the cumulative rate for subjects who lost PASI 75 response up to Week 68
- H_2: Secukinumab 300 mg is not different from placebo with respect to the cumulative rate for subjects who lost PASI 75 response up to Week 68

Number and percentage of subjects with loss of PASI 75 response based on the number of subjects in the full analysis set at risk as denominator will be provided by treatment group.

For loss of PASI 75 response, between-treatment differences will be evaluated using a log-rank test, stratified by geographical region and body weight stratum, to compare the survival functions between secukinumab treatment groups versus placebo. The hazard ratios for these comparisons for loss of PASI 75 response and their corresponding 95% confidence intervals will be computed using a stratified Cox proportional hazards regression model with treatment group, core study and baseline PASI of core study and baseline PASI of extension study as explanatory variable and stratified by geographical region and body weight stratum. The primary analysis will be the log-rank test. Subjects who have not lost PASI 75 response up to Week 68 will be considered as censored observations.

The Kaplan-Meier estimates of the (1 minus cumulative rate loss of PASI 75 response) for each treatment will be plotted. The plot will include the number of subjects at risk for each treatment group at pre-specified time points (e.g., visits).

The number of subjects with loss of PASI 75 response, number of subjects in the analysis set, estimate of cumulative rate up to Week 68, median event time, and its estimated standard error, as estimable will be provided for each treatment group. In addition, for pre-specified time intervals (e.g., 4-week intervals) the following will be presented:

- for each treatment group and time interval: subjects at risk, subjects with loss of PASI 75 response, subjects with loss of PASI 75 response divided by subjects at risk, cumulative subjects with event and cumulative event probability including 95% confidence interval.

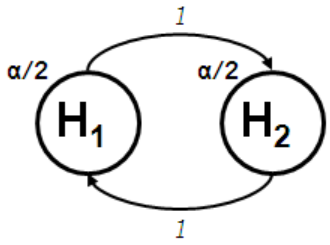
- for treatment comparisons the hazard ratio derived via Cox regression as well as log-rank test and Wilcoxon test.

Separate analyses will be performed for comparison of 150 mg secukinumab with placebo and 300 mg secukinumab with placebo. The two placebo groups will not be pooled for this analysis.

Testing strategy

The familywise error will be set to α=2.5% (one-sided). The two hypotheses H_1 (referring to 150 mg) and H_2 (referring to 300 mg) will be tested at α/2=1.25% one-sided. In case, a null hypothesis has been rejected for one dose, but not for the other dose, the alpha can be shifted to the other dose and the null hypotheses can be retested at level α=2.5% (one-sided). The graphical approach of [Bretz et al (2009)] for sequentially rejective testing procedures is used to illustrate the testing strategy (Figure 9-1):

Figure 9-1 Testing strategy



Other secondary endpoints will not be included in the testing strategy.

9.4.3 Handling of missing values/censoring/discontinuations

For the primary analysis subjects who did not lose PASI 75 response before Week 68 but with missing values at Week 68 will be considered as censored. Other time-to-event analyses will be handled analogously.

For other analyses (not time to event) missing values with respect to response variables based on PASI score and IGA mod 2011 score will be imputed with non-response regardless of 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 (e.g., if a subject discontinues treatment at Week 56, but has follow-up visit F4, the PASI score observed at Visit F4 might be used for Week 60 assessments).

The last observation carried forward method will be applied to PASI score and IGA mod 2011 score. Note, that responses based on PASI score or IGA mode will be imputed differently as described above.

If all post Randomization Visit efficacy values are missing for one efficacy parameter then these missing values will not be imputed and this subject will be removed from the analysis of the corresponding variable, *i.e.*, it might be that the number of subjects providing data to an analysis

is smaller than the number of subjects in the FAS. In addition, missing baseline values will not be imputed.

9.4.4 Supportive analyses

Sensitivity analyses will be performed as follows:

- Subjects fulfilling at least one of the following criteria will be classified as non-responders with respect to PASI 75 and IGA 0 or 1 response at Week 68 and the Cox proportional hazards regression analysis of the primary analysis will be repeated:
  - subjects with missing injection (s) up to Week 68,
  - dropouts due to AEs, unsatisfactory therapeutic effect up to Week 68, and
  - subjects with missing data at Week 68.
- PASI 75 will be evaluated using Cox proportional hazards regression as described above with multiple imputations instead of non-responder imputation for missing values. Within this analysis the PASI score will be imputed and response variables will be derived based on the imputed scores. For each treatment group values will be imputed separately. Further details will be given in the analysis plan.

In addition, the secukinumab treatment groups will also be compared, i.e. a Cox proportional hazards regression will be fitted as described above including all four treatment groups. Placebo (secukinumab 150 mg in core studies) and Placebo (secukinumab 300 mg in core studies) will be compared as well as secukinumab 150 mg and secukinumab 300 mg.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

Subjects who were PASI 75 responders at Week 52

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).

For PASI 50, PASI 75, PASI 90, PASI 100 and IGA 0 or 1 response at each visit, each secukinumab dose regimen will be compared to placebo (up to last visit with more than 5% of subjects in placebo group) by means of the stratified Cochran-Mantel-Haenszel-test as well as by means of a logistic regression model with treatment group, geographical region, body weight stratum, and baseline PASI as effects.

For PASI 50, PASI 75, PASI 90 and IGA 0 or 1 response the placebo-adjusted response rates including 95% confidence interval (based on normal approximation) will be derived by visit. Figures will be provided as well displaying estimates for responder rates by treatment including confidence intervals.

Subjects that were re-randomized at Week 52, hence who PASI 75 responder will be split into two subgroups based on the IGA 0 or 1 response at Week 52. For each of these subgroups 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.

Loss of PASI 75 response over time

The loss of PASI 75 response will be repeated, but not truncated at Week 68 and subjects who did not lose PASI 75 response up to Week 68 will not be considered as censored. In addition, the secukinumab treatment groups will also be compared, i.e. a Cox proportional hazards regression will be fitted as described above including all four treatment groups. Placebo (secukinumab 150 mg in core studies) and Placebo (secukinumab 300 mg in core studies) will be compared as well as secukinumab 150 mg and secukinumab 300 mg.

Loss of IGA 0 or 1 response over time

Loss of IGA 0 or 1 response over time will be analyzed analogously to the loss of PASI 75 response, but it will be restricted to the subset of subjects who have been IGA 0 or 1 responder at Week 52.

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

Relapse will be analyzed analogously to loss of PASI 75 response. Additional analyses will be performed for relapses observed in the follow-up period.

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.

Subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg

Time to PASI 75 response

Kaplan-Meier estimates including 95% confidence intervals for cumulative rate of subjects gaining PASI 75 response after relapse will be calculated (time point of re-initiation of secukinumab therapy will be defined as time zero).

Time to IGA 0 or 1 response

Time to IGA 0 or 1 response will be analyzed analogously to time to PASI 75 response but limited to the subset of subjects who were not IGA 0 or 1 responder at time of relapse.

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 after relapse 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

This analysis will be the same as for “subjects who were PASI 75 responders at Week 52”

Rebound

This analysis will be the same as for the “subjects who were PASI 75 responders at Week 52”

Subjects who were partial responders at Week 52

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

This analysis will be the same as for the “subjects who were PASI 75 responders at Week 52”

Rebound

This analysis will be the same as for the “subjects who were PASI 75 responders at Week 52”

9.5.2 Safety variables

All safety evaluations will be performed on the Safety set. For adverse events an analysis based on pooled treatment groups “any secukinumab 150 mg” and “any secukinumab 300 mg” will also be done. In the analysis of the subjects who were re-treated after relapse with secukinumab 150 mg or 300 mg only safety data after re-treatment after relapse will be reported. With the exception of adverse events that qualify as "treatment emergent" (see definition below), 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.

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.

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 events with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse events 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. Shifts will be presented for most extreme values 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 Health-related Quality of Life (HRQoL)

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.

For the "subjects who were PASI 75 responders at Week 52" the following analysis will be performed as well:

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

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

In addition, summary statistics will be provided for number of subjects achieving DLQI 0 or 1. For the "subjects who were PASI 75 responders at Week 52" the secukinumab treatment groups will be compared to placebo by means of Fisher's exact test.

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.

9.5.4 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]

9.5.6 Biomarkers

Not applicable.

[redacted]

9.6 Interim analyses

One interim analysis is planned for this study. At time of marketing authorization submission of the AIN457A project blinded safety data of this study will be reported.

A PEA is planned to be performed when all subjects have completed the visit at which the primary endpoint is assessed (Week 68). At this time point, the Sponsor will be unblinded, whereas investigators and study participants will remain blinded.

All data collected up to Week 68 will be analyzed.

Additional interim analyses may be conducted at various time points for publications or health authority requests. The study procedures will not be modified as a result of these interim analyses

9.7 Sample size calculation

Assumptions for the number of subjects eligible for randomized withdrawal (i.e for the analysis of primary endpoint):

- Drop-out rate on secukinumab at Week 12 in core studies: 5% (estimate from CAIN457A2211)
- Drop-out rate on placebo at Week 12 in core studies: 15% (from CAIN457A2211)
- Placebo PASI 75 response rate at Week 12: 5% (conservative assumption)
- Drop-out rate on secukinumab up to Week 52 in core studies: 15% (common for secukinumab induction and placebo induction regimens, as in Leonardi et al, 2008)
- PASI 75 response rate at Week 52 on secukinumab 150 mg in core studies: 65% (from dosing rationale in protocols of core studies) (power would be larger for 300 mg if we would assume similar loss of PASI75 rates)
- Type-I-error rate is defined to one-sided 2.5%

With these assumptions it is estimated to have 414 subjects eligible per dose to enter the randomized withdrawal, with a randomization ratio of 2:1 this would be 276 subjects on 150 mg and 138 subjects on placebo. With about 400 subjects the study would have more than 90% power to detect differences in the cumulative rates if 10% of subjects on secukinumab lost PASI 75 response versus 23% on placebo, PASS 2008 software (Log Rank Survival Power Analysis - Simple). [redacted]

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent

document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

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

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

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted IRB/IEC before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

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

If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis

and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

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

12 References

References are available upon request

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13 Appendices

13.1 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of keylaboratory 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 specific action 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

13.2 Appendix 2: Blood collection log for pharmacokinetics (PK) and immunogenicity (IG)

Table 13-1 Blood collection log for PK

Visit Name	Time point	Volume (approx.)	Analyte	Sample number	PK collection number**
Week 52[1]	Pre-dose	(2 mL)	AIN457 for PK	(5)	(5)
Week 56	Pre-dose	2 mL	AIN457 for PK	6	5
Week 60	Pre-dose	2 mL	AIN457 for PK	7	5
Week 64[2]	Pre-dose	2 mL	AIN457 for PK	8	5
Week 68	Pre-dose	2 mL	AIN457 for PK	9	5
Week 72	Pre-dose	2 mL	AIN457 for PK	10	5
Week 76[2]	Pre-dose	2 mL	AIN457 for PK	11	5
Week 80	Pre-dose	2 mL	AIN457 for PK	12	5
Week 84	Pre-dose	2 mL	AIN457 for PK	13	5
Week 88[2]	Pre-dose	2 mL	AIN457 for PK	14	5
Week 92	Pre-dose	2 mL	AIN457 for PK	15	5
Week 96	Pre-dose	2 mL	AIN457 for PK	16	5
Week 100	Pre-dose	2 mL	AIN457 for PK	17	5
Week 104[2]	Pre-dose	2 mL	AIN457 for PK	18	5
Week 108	Pre-dose	2 mL	AIN457 for PK	19	5
Week112	Pre-dose	2 mL	AIN457 for PK	20	5
Week 116[2]	Pre-dose	2 mL	AIN457 for PK	21	5
Week 120	Pre-dose	2 mL	AIN457 for PK	22	5
Week 124	Pre-dose	2 mL	AIN457 for PK	23	5
Week 128[2]	Pre-dose	2 mL	AIN457 for PK	24	5
Week 132	Pre-dose	2 mL	AIN457 for PK	25	5
Week 136	Pre-dose	2 mL	AIN457 for PK	26	5
Week 140[2]	Pre-dose	2 mL	AIN457 for PK	27	5
Week 144	Pre-dose	2 mL	AIN457 for PK	28	5
Week 148	Pre-dose	2 mL	AIN457 for PK	29	5
Week 152	Pre-dose	2 mL	AIN457 for PK	30	5
Week 156[2]	Pre-dose	2 mL	AIN457 for PK	31	5
Week 260[2]	672 hours*	2 mL	AIN457 for PK	32	5
Week 268[2](F8)	2016 hours*	2 mL	AIN457 for PK	33	5

[1]The data and sample numbering for Week 52 visit (randomization) will have been collected as part of the end of maintenance visit (Week 52) from core study (e.g., CAIN457A2302 or CAIN457A2303)

[2]The PK blood sampling at these time point must be collected for all subjects. PK blood collections at the other time points are “event driven” i.e., PK blood samples will only be collected in case of relapse.

*Scheduled post-dose time points for sample numbers 32 and 33 (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 13-2 Blood collection log for IG

Visit Name	Time point	Volume (approx.)	Analyte	IG collection number**
Week 52[1]	Pre-dose	(2 mL)	anti-AIN457 for IG	(503a)
Week 76	Pre-dose	2 mL	anti-AIN457 for IG	504
Week 104	Pre-dose	2 mL	anti-AIN457 for IG	505
Week 128	Pre-dose	2 mL	anti-AIN457 for IG	506
Week 140	Pre-dose	2 mL	anti-AIN457 for IG	507
Week 156	Pre-dose	2 mL	anti-AIN457 for IG	508
Week 260	672 hours*	2 mL	anti-AIN457 for IG	509
Week 268 (F8)	2016 hours*	2 mL	anti-AIN457 for IG	510

[1]The data and sample numbering for Week 52 visit (randomization) will have been collected as part of the end of maintenance visit (Week 52) from core study (e.g., CAIN457A2302 or CAIN457A2303)

* Scheduled post-dose time points for sample numbers 509 and 510 (672 hours and 2016 hours post-dose, respectively) refer to the last dose given at Week 256 as time 0.

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

13.3 Appendix 3: Pharmacokinetics (PK) and immunogenicity (IG) sample labeling information

13.3.1 PK sample handling

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

Study code: CAIN457A2302E1

Site: cccc (4 digits for the current site number)

Subject: Ccccrrr (4 digits for the site number where the subject was randomized 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 13-1

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.

13.3.2 IG sample handling

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

Study code: CAIN457A2302E1

Site: cccc (4 digits for the current site number)

Subject: Ccccrrr

(4 digits for the site number where the subject was randomized 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 13-2

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.