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Clinical Development

Secukinumab (AIN457)

Clinical Trial Protocol CAIN457AIT01 / NCT02394561

A 24-week, multicenter, proSpective stUdy to evaluate the PASI 90 clinical response rate and the safety PRofile of sEcukinuMab 300 mg in Cw6-negativE and Cw6-positive patients with moderate to severe chronic plaque-type psoriasis (SUPREME) – amended with an extension treatment period of up to 48 weeks

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CRF	Case Report Form
DAR	Dose Administration Record
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FAS	Full Analysis Set
GGT	Gamma Glutamyl Transpeptidase
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
hs-CRP	High Sensitivity C Reactive Protein
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-treat

LDH	Lactate Dehydrogenase
LFT	Liver Function test
LOCF	Last Observation Carried Forward
PASI	Psoriasis Area Severity Index
PP	Per-Protocol
PPD	Purified Protein Derivative
PUVA	Psoralen combined with Ultraviolet A
SAE	Serious Adverse Event
SD	Standard Deviation
SNP	Single Nucleotide Polymorphism
SUSAR	Suspected Unexpected Adverse Reaction
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal

Glossary of terms

Biological agents	A substance that is made from a living organism or its products and is used in the prevention, diagnosis, or treatment of cancer and other diseases. Biological drugs include antibodies, interleukins, and vaccines.
Cohort	A group having one or more similar characteristics (such as habit of smoking or a particular disease) closely monitored over time.
Human Leukocyte Antigen	A collection of human genes on chromosome 6 that encode proteins that function in cells to transport antigens from within the cell to the cell surface. These proteins are sometimes referred to as the MHC, or major histocompatibility complex.
Interleukin	Any of a class of glycoproteins produced by leukocytes for regulating immune responses.
Investigational treatment	All investigational drugs whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Monoclonal Antibody	An antibody produced by a single clone of cells. A monoclonal antibody is therefore a single pure type of antibody. Monoclonal antibodies can be made in large quantities in the laboratory and are a cornerstone of immunology. Monoclonal antibodies are increasingly coming into use as therapeutic agents.
Phase IIIb study	Clinical trials conducted after regulatory submission of a dossier, but prior to the medicine's approval and launch. These trials may supplement earlier trials, complete earlier trials, or may be directed toward new types of trials (e.g., quality of life, marketing) or Phase IV evaluations. This is the period between submission and approval of a regulatory dossier for marketing authorization.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up).
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Protocol synopsis

Protocol number	CAIN457AIT01
Title	A 24-week, multicenter, proSpective stUdy to evaluate the PASI 90 clinical response rate and the safety PRofile of sEcukinuMab 300 mg in Cw6-negativE and Cw6-positive patients with moderate to severe chronic plaque-type psoriasis (SUPREME) – amended with an extension treatment period of up to 48 weeks
Brief title	A study to evaluate the differences in the efficacy and safety of secukinumab between Cw6-negative and Cw6-positive patients with moderate to severe plaque-type psoriasis
Sponsor and Clinical Phase	Novartis IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Biological agents represent the most advanced type of treatment for psoriasis. Secukinumab is a human monoclonal anti IL-17A antibody that binds to human IL-17A and neutralizes its bioactivity by inhibiting IL17A produced by both Th17 cells and those of the innate immune system, thus providing complete anti IL17A blockage. Targeting IL-17A has the potential to reduce autoimmune inflammation while leaving other immune functions undisturbed. While targeting of Th1-promoting or Th17-promoting cytokines affects critical mediators such as IFN-γ, IL-22 and IL-21, selective targeting of IL-17A leaves these Th1/17 activities, as well as certain protective functions of innate cells intact. Furthermore, as a fully human monoclonal antibody, secukinumab should reduce immunogenic risks compared to current or emerging antibody therapies that are not fully human. Many recent studies have shown that highly selective biologic drugs are not effective in every patient and that variations in the genome can be associated with different clinical responses or side effects to a given drug. The PSORS1 locus on chromosome 6p is generally understood to confer the most risk for psoriasis. A specific allele for this locus, HLA C*06, is present in about 60% of psoriatic patient cases. Data linking secukinumab efficacy to a particular genetic marker are lacking. Recent research has revealed a marked difference in the proportion of PASI 90 achievers at 12 weeks between Cw6-positive and Cw6-negative patients (85.7% vs 56.5%) treated with ustekinumab (Talamonti M et al. 2013) and a greater efficacy of anti-TNFα drugs in CW6 negative patients (Galli et al. 2013).Unlike anti-IL-12/23 agents, secukinumab inhibits IL-17 produced by both Th17 cells after presentation by antigen presenting cells (in this case Cw6) and cells of the innate immune system whose activation does not require antigen presentation. Providing a drug that is equally effective on both Cw6-negative and Cw6-positive patients would be an important clinical accomplishment and would eliminate the need for costly HLA-Cw6 tests. The choice of a cohort study would therefore seem appropriate for this clinical context. The purpose of this study is to explore the different efficacy and safety

	profiles of secukinumab 300 mg in patients with moderate to severe chronic plaque-type psoriasis, stratified for the presence of HLA-C*06, whose determination will be blinded for patients and investigators. The study will be conducted both on anti-TNFα-naïve and anti-TNFα failure patients and will also stratify for TNFα - 308 polymorphism, BMI, smoking and metabolic syndrome, among others. In addition, through amendment 2 of this protocol, a treatment extension of up to 48 weeks will be offered to willing patients reaching at least a PASI 75 response after 24 weeks of treatment during the core study. The purpose of the treatment extension is threefold; to explore response sustainability to secukinumab after 72 weeks of continuous treatment, to understand if HLA-CW6 can influence the kinetics of the response to secukinumab in the long term, and to generate long-term safety and tolerability data. Furthermore, as a consequence of the European Medicines Agency's (EMA) approval of secukinumab in February 2015 "for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy," inclusion criteria have been updated in order to guarantee treatment to systemically naïve patients, as per label. The study extension, for those patients who will enter, can be terminated for any reason by Novartis after a period of at least 12 weeks. Termination may occur only in selected regions where the drug is commercially available; this decision will be made on a region-by-region basis, as for some regions the study will continue as planned even though secukinumab may have become commercially available.
Primary Objective(s) and Key Secondary Objective	To evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks, and thereafter for up to 72 weeks.
Secondary Objectives	- To compare the proportion of responders to PASI 50/75/90/100 between cohorts at each time point. - To compare the mean changes vs baseline in IGA mod 2011 between cohorts at each time point. - To compare time to reach PASI 90 between cohorts. - To compare time to reach PASI 75 between cohorts. - To evaluate the Quality of Life by means of the Dermatology Life Quality Index (DLQI) in all patients at each time point. - To evaluate anxiety and depression in all patients at each time point. - To evaluate the correlation between the Hospital Anxiety and Depression Scale (HADS) and PASI in all patients. - To evaluate changes from baseline in weight, BMI and waist in all patients at each time point. - To compare safety and tolerability between cohorts for 24 weeks, and thereafter for up to 72 weeks. - To evaluate the amount of resources used during the study in comparison with the 6 months prior to the beginning of the study.
Study design	This is a multicenter, prospective study involving Cw6-negative and Cw6-positive patients affected by moderate to severe chronic plaque

	psoriasis. Patients will be centrally tested and stratified into two cohorts (Cw6-negative and Cw6-positive patients). Both patients and investigators will be blinded to the results with respect to Cw6. After a full screening visit, each eligible patient will be treated according to an induction regimen of two injections of secukinumab 150 mg a week for five weeks starting at baseline (week 0), followed by a maintenance period of one treatment (two injections) per month. At week 16, patients achieving a PASI 50 response will be eligible to continue on secukinumab for an additional 8 weeks. After a total of 24 weeks, willing patients reaching at least a PASI 75 response will enter an extension treatment period of up to 48 weeks. The total duration of the study, including the extension period, is therefore of 72 weeks.
Population	The study plans to enroll about 406 adult men or women, of which 365 are evaluable patients, diagnosed with moderate to severe chronic plaque psoriasis for at least 6 months. The patients must be candidates for systemic therapy and may be treatment naïve or have failed to respond to other systemic therapy (including cyclosporine, methotrexate, psoralen combined with ultraviolet A (PUVA) or to an anti-TNFα (or is intolerant and/or has a contraindication to these).The study plans to involve approximately 50 centers. The extension phase will include approximately 306 of the patients initially enrolled in the core study.
Inclusion criteria	1. Subject must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study related activity is performed. 2. Men or women at least 18 years of age at time of screening. 3. Diagnosis of moderate to severe chronic plaque-type psoriasis for at least 6 months (including concomitant psoriatic arthritis as per the Classification Criteria for Psoriatic Arthritis criteria [CASPAR]). 4. Moderate to severe psoriasis as defined at enrollment by: • PASI score ≥ 10 or • PASI score > 5 but < 10 and DLQI ≥10 5. Patients that are candidates for systemic therapy, whether treatment naïve or after failed response to other systemic therapy (i.e. cyclosporine, methotrexate and PUVA) or to an anti-TNFα (or is intolerant and/or has a contraindication to these).
Key Exclusion criteria	1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis). 2. Cyclosporine or methotrexate therapy within 4 weeks prior to Day 1. 3. Anti-TNFα therapy within timelines depending on drug half-life. 4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor. 5. Previous exposure to ustekinumab or any other biologic drug for the treatment of psoriasis that is not anti-TNFα therapy. 6. Intravenous or intramuscular steroids within 2 weeks prior to screening and during screening. 7. Ongoing use of corticosteroid topical treatments unless a washout period, as described in table 5-1, will be performed or UV

	therapy.
Inclusion criteria for extension treatment period	1. Patients who have completed the CAIN457AIT01 core study. 2. Written informed consent for protocol amendment 2 must be obtained before patients proceed to the extension treatment period. 3. Patients must be deemed to be benefiting from the study drug based on at least a PASI 75 response rate after 24 weeks of treatment.
Investigational therapy	Secukinumab 300 mg (two s.c. injections of secukinumab 150 mg).
Efficacy assessments	– The Psoriasis Area and Severity Index (PASI) – The Investigator's Global Assessment Scale (IGA mod 2011)
Safety assessments	– Physical examination, vital signs – Height, weight, waist – Laboratory assessments (hematology, blood chemistry, urinalysis) – hs-CRP – Electrocardiogram – Chest X-ray – Serum pregnancy test – Adverse event monitoring
Other assessments	– Health related quality of life • The Dermatology Life Quality Index • The Hospital Anxiety and Depression Scale – [redacted]
Data analysis	The primary efficacy variable is the PASI 90 response after 16 weeks of treatment, defined as the achievement of ≥ 90% improvement (reduction) in PASI score after 16 weeks of treatment compared to baseline. The proportion of patients who reach PASI 90 at 16 weeks will be presented with the one-tailed 97.5% confidence interval of the Cw6 positive – Cw6 negative difference. The primary objective as well as the secondary ones will be based on the ITT population. A supportive analysis will be done on the PP population. Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 response by visit will be presented with absolute, relative frequencies and confidence intervals. Summary statistics will be provided for absolute PASI scores and for percent changes from baseline by visit and cohort. Differences between cohorts in time to reach PASI 90, as well as PASI 75, will be evaluated also by means of time to event analysis. Summary statistics for the IGA mod 2011 score over time will be presented by visit and cohort. Summary statistics for IGA 0 or 1 response by visit and cohort will be presented with absolute and relative frequencies. Summary statistics will be provided for all the safety parameters: AEs, SAEs, laboratory data, height, weight, waist, BMI, vital signs and physical examination. **Sample size calculation** Phase III data on secukinumab show a PASI 90 response at 16 weeks of 71%. Under the assumption that 60% of all the enrolled patient population is represented by Cw6-positive patients, we can reasonably assume to observe a proportion of patients with PASI 90 of 80% in the Cw6-positive cohort.

	Under these assumptions, considering a one-side alpha level of 0.025 and a power of 80%, 365 patients (219 Cw6-positive and 146 Cw6-negative) are sufficient to evaluate if the response in terms of PASI 90 in the Cw6 negative cohort is not less than 12% respect to the Cw6 positive cohort. Considering a dropout rate at 16 weeks of 10% equally divided in the two studied cohorts, a total of 406 patients should be enrolled. Although the sample size was calculated considering only Cw6 haplotype, it will also be adequate for a regression model assessing differences from baseline of clinically relevant variables such as BMI, metabolic syndrome, smoking and TNFα-308 polymorphism, which, among the six existing polymorphisms, is the one most greatly affecting response to treatment with anti-TNFα drugs.
Key words	Chronic plaque psoriasis, PASI, HLA determination, IL-17A, Cw6, secukinumab.

Amendment 3

The purpose of this amendment is to correct some minor inconsistencies found in the inclusion and exclusion criteria detailed in the study protocol. The paragraph 6.4.2 has also been corrected. The informed consent form has been updated in order to correct minor discrepancies with the study protocol.

Furthermore, we took advantage of this amendment in order to correct some typos present in the study protocol.

Amendment 2

The purpose of this amendment is to provide continued treatment of patients on secukinumab

for an additional 48 weeks (overall up to 72 weeks), and thus allow for safety, tolerability, and efficacy data to be collected from the participating patients over a longer period of time. The extension period will allow meeting the following needs:

1) Investigate response sustainability to secukinumab after 72 weeks of continuous treatment.
2) Explore if HLA-CW6 can influence the kinetics of the response to secukinumab in the long term (ustekinumab data showed a faster response in CW6 positive patients compared with CW6 negative patients).

Furthermore, as a consequence of the European Medicines Agency's (EMA) approval in February 2015 of secukinumab "for the treatment of moderate severe plaque psoriasis in adults who are candidates for systemic therapy," inclusion criterion number 5 has been changed in order to guarantee treatment to the population of systemically naïve patients, as per label. The study extension can be terminated by Novartis for any reason after a period of at least 12 weeks. Termination may occur only in selected regions where the drug is commercially available; this decision will be made on a region-by-region basis, as for some regions the study will continue as planned even though secukinumab may have become commercially available.

Changes to the protocol (the protocol synopsis has also been modified accordingly)

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 font for insertions.

The major changes in this version of the protocol are as follows:

- Title: "A 24-week, multicenter, proSpective stUdy to evaluate the PASI 90 clinical response rate and the safety PRofile of sEcukinuMab 300 mg in Cw6-negativE and Cw6-positive patients with moderate to severe chronic plaque-type psoriasis (SUPREME) – amended with an extension treatment period of up to 48 weeks"
- Section 1 – Introduction – has been updated to introduce the purpose of this amendment:

  Amendment 2 of the protocol has a threefold purpose; to explore response sustainability to secukinumab after 72 weeks of continuous treatment, to understand if HLA-CW6 can influence the kinetics of the response to secukinumab in the long term, and to generate long-term safety and tolerability data.

  Furthermore, as a consequence of the European Medicines Agency's (EMA) approval of secukinumab in February 2015 "for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy," inclusion criteria have been updated in order to guarantee treatment to systemically naïve patients, as per label.
- Section 2.1 – Primary objective – now reads: "To evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with

respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks, and thereafter for up to 72 weeks."

- Section 2.2: A secondary objective has been modified: "To compare safety and tolerability between cohorts during the 24 weeks, and thereafter for up to 72 weeks."
- Section 3.1 – Study design – has been changed to reflect the addition of the extension period:

  The study has four periods: a screening period consisting of two visits (pre-screening and screening), an induction period of 4 weeks, a maintenance period of 20 weeks and an extension period of 48 weeks. Timelines of the study design are presented in Figure 3-1 and Figure 3-2. Detailed visit schedules can be found in Table 6-1 and Table 6.2.

  After the full screening visit (day -14 to -7), eligible patients will begin treatment at baseline (week 0) and will be followed for 24 weeks (core study), plus an additional 48 weeks if participating in the extension treatment period.

  After a total of 24 weeks, willing patients reaching at least a PASI 75 response will enter an extension treatment period of an additional 48 weeks. The PASI score will be evaluated during the 72-week period.
- Figure 3.2 has been added to illustrate the extension treatment period.
- Section 3.6 – Risks and benefits – has been updated with recent efficacy and safety data.
- Section 4 – Population – has been modified to guarantee treatment to systemically naïve patients and to indicate the number of patients to be enrolled in the extension period:

  The patients must be candidates for systemic therapy and may be treatment naïve or have failed to respond to other systemic therapy, including cyclosporine, methotrexate, psoralen combined with ultraviolet A (PUVA), or to an anti-TNFα (or is intolerant and/or has a contraindication to these). The study plans to involve about 50 centers.

  The extension phase will include 306 of the patients taking part in the core study.
- Section 4.1 – Inclusion criteria – Criterion no. 5 has been modified:

  5. Patients that are candidates for systemic therapy, whether treatment naïve or after failed response to other systemic therapy (i.e. cyclosporine, methotrexate and PUVA) or to an anti-TNFα (or is intolerant and/or has a contraindication to these).
- Section 4.3 – Eligibility criteria for entering the extension treatment period – has been added:

  1. Patients who have completed the CAIN457AIT01 core study.
  2. Written informed consent for protocol amendment 2 must be obtained before patients proceed to the extension treatment period.
  3. Patients must be deemed to be benefiting from the study drug based on at least a PASI 75 response rate after 24 weeks of treatment.

- Section 5.1.1 – Investigational treatment – has been modified to include instructions for the extension period:

  The study treatment will be administered by the site staff during the visit. Patients enrolled in the extension period will self-administer secukinumab and will be asked to keep a self-administration log during this period.

- Section 5.5.4 – Instructions for prescribing and taking study treatment – has been modified to include instructions for the extension period:

  Patients proceeding to the extension period will self-administer treatment (two 150 mg injections) once every 4 weeks for an additional 48 weeks.

  Willing patients reaching at least a PASI 75 response at the end of the 24-week core study will enter an extension treatment period of an additional 48 weeks.

- Section 5.5.11 – Study completion and post-study treatment – has been modified to include information regarding the extension period:

  Willing patients reaching at least a PASI 75 response during the core study will be eligible to enter an extension treatment period of an additional 48 weeks.

- Section 5.5.12 – Early study termination – now contains the following paragraph:

  The study extension can be terminated by Novartis for any reason after a period of at least 12 weeks. Termination may occur only in selected regions where the drug is commercially available; this decision will be made on a region-by-region basis, as for some regions the study will continue as planned even though secukinumab may have become commercially available.

- Table 6-2 – Assessment schedule of extension treatment period – has been added.

  Table 6-2 lists all of the assessments of the extension phase and indicates with an "x" when the visits are performed.

  Patients should be seen for all visits on the designated day but a time window of ± 7 days is allowed.

- Section 6.4, Section 6.5 and Section 6.6 have been modified to include assessments in the extension-phase visits:

  6.4.1: The PASI will be assessed at each visit from V2 to V12 of the core study and at all four visits of the extension period.

  6.4.2: The IGA mod 2011 will be evaluated at each visit from V2 to V12 of the core study and at all four visits of the extension period.

  6.5.3: Body weight (to the nearest 0.1 kilogram in indoor clothing, but without shoes) and waist will be measured at visits 2, 3 and 12 of the core study and at all four visits of the extension period.

  6.5.4.1: Hemoglobin, hematocrit, red blood cells count, white blood cells count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes), and platelets count will be measured at visits 2 and 3 and then at each visit starting from

visit 7 (including extension period). Appendix 1 shows the extended laboratory ranges that are considered clinically notable.

6.5.4.2: Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, creatine kinase (CK), gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/blood urea nitrogen (BUN) and uric acid will be measured at visits 2 and 3 and then at each visit of the core study starting from visit 7.

The following clinical chemistry assessments will be run at all four visits of the extension period: albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, creatinine, CK, GGT, glucose, LDH, potassium, total protein, AST, ALT, sodium, triglycerides, uric acid.

6.5.4.3: Dipstick measurements for specific gravity, protein, glucose and blood will be performed. WBC and RBC sediments will also be analyzed at visits 2, 10 and 12 of the core study and at all four visits of the extension period.

6.5.4.4: hsCRP will be assessed at visits 3, 10, and 12 of the core study and at all four visits of the extension period.

6.6.2: Patients will be asked to complete the questionnaire at visits 3, 10 and 12 of the core study and at visits 2 and 4 of the extension period.

6.6.3: Patients will be asked to complete the questionnaire at visits 3, 10 and 12 of the core study and at visits 2 and 4 of the extension period.

- Section 7.2 – Serious adverse event reporting – has been modified:

  The investigator will complete the SAE Report Form in English, assess the relationship to the study treatment and send the completed and signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department Novartis (DS&E). The original and the duplicate copies of the SAE Form, and the fax confirmation sheet will be kept with the case report forms at the study site.

- Section 9.4 – Analysis of the primary variable – now reads:

  The primary objective of this study is to evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks, and thereafter for up to 72 weeks

Additional minor changes have been made to the protocol to improve clarity and correct typographic errors.

IRB/IEC

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 must be approved by the IRB/IEC prior to implementation. The same applies to a revised Informed Consent that will take into account the changes described in this amended protocol.

Amendment 1

The aim of this amendment was to address concerns raised by the Italian Regulatory Authority (Agenzia Italiana del Farmaco – AIFA) following its evaluation of the original study protocol.

1. The Agency pointed out a limit in the study's methodological approach in that it adopts a measure of "non-inferiority," a design used for randomized studies whose primary objective is to verify that one treatment is not less effective than another. Furthermore, the Agency questioned the study's main objective; demonstrating a similar therapeutic response to secukinumab in a population stratified into Cw6 positive and Cw6 negative cohorts. This without having data available from trials comparing secukinumab and ustekinumab, a drug which has shown to be less effective in Cw6 negative patients.

   The robust efficacy of secukinumab has been demonstrated in various comparative studies. Two phase III, double-blind, 52-week trials, ERASURE and FIXTURE, randomly assigned 738 patients and 1306 patients, respectively, to subcutaneous secukinumab, placebo, or (in the FIXTURE study only) etanercept. The proportion of patients who met the criterion for PASI 75 at week 12 was significantly higher with secukinumab than with placebo or etanercept. The PASI 75 rate for secukinumab 300 mg was 81.6% in the ERASURE study and 76% in the FIXTURE study (Lang RG et al. 2014).

   The amount of efficacy and safety data related to secukinumab prompted, on 20 November 2014, the Committee for Medicinal Products for Human Use (CHMP) to adopt a positive opinion, recommending the granting of marketing authorization for secukinumab intended for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

   Concerning data related to PASI 90 rates at week 12 for secukinumab and ustekinumab, they are substantially similar (59% vs. 51% respectively) (Langley RG et al. 2014, Leonardi CL et al. 2008, Papp KA et al. 2008) and a study comparing the two biologic drugs was to have data available by the end of 2014.

   In the last few years, a lot of attention has been given to associations of genome variations with different clinical responses to these highly selective biologic drugs (Costanzo et al. 2011).

   Studies have demonstrated the influence of TNF-α-308 promoter polymorphism on the responsiveness to anti-TNF-α drugs in patients with psoriasis, rheumatoid arthritis and spondyloarthritis (Gallo E et al 2013, Cuchacovich M et al. 2006, Cuchacovich M et al. 2004, Seitz M et al. 2007, O'Rielly DD et al. 2009).

   A recently published paper demonstrated an increased and faster response to ustekinumab in Cw6-positive compared to Cw6-negative patients (PASI 75 at week 12: 96.4% in Cw6-positive vs. 65.2% in Cw6-negative patients; P = 0.008; PASI 50 at 4 weeks 89.3% in Cw6- positive vs 60.9% in Cw6-negative) (Talamonti M et al. 2013).

   Unlike anti-IL-12/23 agents, secukinumab inhibits IL-17 produced by both Th17 cells after presentation by antigen presenting cells (in this case Cw6) and cells of the innate immune system whose activation does not require antigen presentation. If secukinumab were equally effective on both Cw6 negative and Cw6 positive patients, as its mechanism

of action suggests, this would be a significant clinical accomplishment and would eliminate the need for costly HLA-Cw6 tests. The choice of a cohort study could therefore be appropriate for this clinical context.

To better convey the purpose of the study, the title was changed to "A 24-week, multicenter, proSpective stUdy to evaluate the PASI 90 clinical response rate and the safety PRofile of sEcukinuMab 300 mg in Cw6-negativE and Cw6-positive patients with moderate to severe chronic plaque-type psoriasis (SUPREME)."

The primary objective of the study was reworded: "To evaluate the clinical response in Cw6-negative patients compared to Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks."

Other parts of the protocol, as well as the description of the study rational, were also modified to suit the aim of the study.

2. The Agency indicated the need to analyze a population stratified for different variables that could condition therapeutic response, and appropriately identified TNF-α polymorphism, smoking, BMI and metabolic syndrome as factors not considered in the original protocol.

   Although the sample size was calculated considering only Cw6 haplotype, it is also adequate for regression models assessing differences from baseline for clinically relevant variables. In fact, the expected number of patients who reach PASI 90 at week sixteen is at least 250 (roughly 71% of 365). Therefore, using a conservative criterion of a minimum of 10 "events" for each predictor in the model, we can add up to 25 variables without loss of power (Vittinghoff E et al. 2007). As suggested, this model will take into account variables including BMI, smoking, metabolic syndrome and TNFα-308 polymorphism, which, among the six existing polymorphisms, is the one most greatly affecting response to treatment with anti-TNFα drugs.

   Section 9.7 of the protocol was updated to add these concepts.

This amendment was also an opportunity to correct or clarify other items of the protocol:

- Better define the inclusion criteria concerning the psoriasis diagnosis.

  Given the positive opinion of the CHMP previously mentioned, inclusion criteria were changed to include patients failing not two, but at least only one prior systemic therapy (even if CHMP opinion is related to first line systemic therapy, the decision was to be more conservative).

  Patients with a diagnosis of moderate to severe chronic plaque-type psoriasis for at least 6 months will be included in the study; localization of the disease on scalp and hands, and psoriatic arthritis are allowed disease manifestations and are not to be considered as mandatory for study inclusion (as previously stated by indicating them as a separate criterion).

- Differentiate the wash-out periods to be used for biological immunomodulating agents before starting treatment with secukinumab, and add golimumab to the list of treatments requiring a wash-out period.

- Specify the hepatitis B surface antigens and antibodies used for required hepatitis B testing.
- Remove fasting plasma glucose (FPG) and lipid panel from the "fasting lab assessments" as they are already present among the "clinical chemistry" assessments.
- Clarify the number of injections of secukinumab to be administered during the treatment period.
- Clarify the period of Adverse Event reporting.
- Update the introduction with current study results.
- Clarify data collection procedures.

Changes to the protocol (the protocol synopsis was also modified where applicable)

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 font for insertions:

The major changes in this version of the protocol were as follows:

- Title: "A 24-week, multicenter, proSpective stUdy to evaluate the PASI 90 clinical response rate and the safety PRofile of sEcukinuMab 300 mg in Cw6-negativE and Cw6-positive patients with moderate to severe chronic plaque-type psoriasis (SUPREME).
- Section 1.1 was updated with current study results.
- Section 2.1: The primary objective was changed: "To evaluate the clinical response in Cw6-negative andCw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks."
- Section 2.3: [redacted]
- Section 3.1 – Study design, was revised by specifying that two injections of secukinumab 150 mg would be administered each week for five weeks during the induction phase, followed by a maintenance period of two injections per month. The section now also indicates that both Cw6 and 308-TNFα polymorphism will be centrally determined from samples taken during the pre-screening visit.
- Section 3.2 – Rationale of study design, was revised to better convey the purpose of the study.
- Section 4 – Population: "The patients must have failed to respond to at least one systemic therapy, including cyclosporine, methotrexate, psoralen combined with ultraviolet A (PUVA), or to an anti-TNFα (or is intolerant and/or has a contraindication to these)."
- Section 4.1: Inclusion criteria No. 4 was deleted.
- Section 4.1: Inclusion criteria No. 3 now reads: "Diagnosis of moderate to severe chronic plaque-type psoriasis for at least 6 months (including concomitant psoriatic arthritis as per the Classification Criteria for Psoriatic Arthritis criteria [CASPAR])."

- Section 4.1: Inclusion criteria No. 5 was changed: "Failed response to at least one systemic therapy (i.e. cyclosporine, methotrexate and PUVA) or to an anti-TNFα (or is intolerant and/or has a contraindication to these)."
- Section 4.2: Exclusion criteria No. 12 now reads: "Subject tested positive for hepatitis B virus surface antigen (HBV) or virus B latent infection, hepatitis C virus antibody (HCV), or human immunodeficiency virus (HIV) at screening (an exam performed within the 6 months prior to inclusion and documented will be considered as valid)."
- Table 5-1 Prohibited treatment, was revised by adding golimumab and specifying the washout periods for etarnecept, adalimumab and infliximab.
- Section 5.5.4 – Instructions for prescribing and taking study treatment.

  Paragraph 1 was changed: All patients will receive Secukinumab 300 mg subcutaneously using the Phase III regimen: 300 mg (two 150 mg injections) a week for the first five weeks (visits 3-7), and once every 4 weeks thereafter (visits 8-12).
- Table 6-1 Assessment schedule, was revised by substituting "fasting lab assessments" with "hsCRP", by indicating the surface antigens and antibodies used for hepatitis B testing in the footnotes (HBsAg, HBsAb, HBcAb), by adding metabolic syndrome and testing for TNFα - 308 polymorphism and by extending the AE recording period to include screening.
- Section 6.1 – Information to be collected on screening was revised and now reads "HLA-Cw6 determination will be performed at screening for patients who have provided written informed consent. A central laboratory will be used to determine Cw6. Patients will thereafter be stratified into the two cohorts. TNFα-308 polymorphism will be centrally determined at the same time."
- Section 6.2 – Patient demographics/other baseline characteristics, was revised as follows:
  - A chest X-ray, an ECG and HCV, HBV (HBsAg, HBsAb, HBcAb), HIV tests will be required unless performed within the previous 6 months. Adequate documentation (assessment reports, tracking and imagines as applicable) must be available for previous evaluations to be considered valid at baseline.
  - High sensitivity C-reactive protein (hsCRP).
  - History (medical, smoking, psoriasis).
- Section 6.5.1 – Physical examination: The following paragraph was added "Metabolic syndrome will require any 3 of the following 5 criteria: increased waist circumference (≥102 cm for men, ≥ 88 cm for women), elevated triglycerides (≥150 mg/dl), reduced high-density lipoprotein (HDL) cholesterol (≤ 40 mg/dl in men and ≤ 50 mg/dl in women), elevated blood pressure (≥ 130 mmHg systolic and ≥ 85 mmHg diastolic or ongoing treatment for hypertension) or elevated glucose (≥100 mg/dl or ongoing treatment for elevated glucose) (Expert Panel JAMA 2001)."
- Section 6.5.3 – Height, waist and weight, was changed:

  Height in centimeters (cm) will be measured at visit 2 or 3 only.

Body weight (to the nearest 0.1 kilogram in indoor clothing, but without shoes) and waist will be measured at visits 2, 3 and 12. Body Mass Index (BMI) will be derived from weight and height results.

- Section 6.5.4.4 – Fasting laboratory assessments, was modified by substituting "fasting laboratory assessments" with "hsCRP."
- Section 8.2 – Data collection, presents the following change: "On-line validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected by the CRO working on behalf of Novartis."
- Section 9.2, paragraph 2, was changed and now reads:

  In order to interpret results adequately, the homogeneity of patients' distribution between cohorts will be tested on selected baseline demographics and anamnestic variables (e.g. for gender, age, race, ethnicity, BMI, baseline PASI, baseline IGA, TNFα - 308 polymorphism, metabolic syndrome, smoking). Categorical variables will be analyzed by Cochran-Mantel-Haenszel test stratified by geographical region (i.e. north vs south/central) and BMI (< 25 vs ≥ 25).

  Paragraph 3 now reads: "Continuous variables will be analyzed by means of ANOVA model corrected by geographical region and BMI classes, as appropriate. Statistically significant variables will be included as covariates in the explanatory analysis model. Whenever necessary, normality will be assessed by means of Shapiro-Wilk test and with graphical methods. In case of non-normality, a non-parametric test will be used."
- Section 9.4 – Analysis of the primary variable was modified: "The primary objective of this study is to evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks."
- Section 9.4.2 - Statistical model, hypothesis, and method of analysis

  Paragraph 1: "The proportion of patients who reach PASI 90 at 16 weeks will be presented with the one-tailed 97.5% confidence interval of the Cw6 positive (POS) – Cw6 negative (NEG) difference."

  Paragraph 4: "A logistic regression analysis model will be also fitted, considering the geographical region, BMI, smoking, metabolic syndrome and TNFα-308 polymorphism as well as the clinically relevant baseline variables as strata factors."
- Section 9.5.1 – Efficacy Variables

  PASI

  "The differences between cohorts in time to reach PASI 90, as well as PASI 75, will be evaluated by means of a log-rank test. The hazard ratios and their corresponding 95% confidence intervals will be also computed using a stratified Cox proportional hazards regression model with Cw6 group and baseline PASI as explanatory variable and stratified by geographical region and BMI, as well as the clinically relevant baseline variables. The Kaplan-Meier estimates of the cumulative rate for each cohort will be plotted."

- Section 9.7 – Sample size calculation was expanded to further justify the appropriateness of the calculation.

  Paragraph 1 was changed to: The primary objective of this study is to evaluate the clinical response in PASI 90 at week 16 of Cw6-negative and Cw6-positive psoriatic patients.

  Paragraph 3 was changed to: From a previous study with ustekinumab (Talamonti et al. 2013) we can observe a difference in response to PASI 90 between Cw6-positive vs Cw6-negative patients of around 30%, in favor of Cw6-POS. Therefore, it is sensible to expect a response in the Cw6 negative cohort not less than 12 % respect to the Cw6 positive group.

  The following paragraph was added at the end of the section: "Although the sample size was calculated considering only Cw6 haplotype, it is also adequate for regression models assessing differences from baseline for clinically relevant variables. In fact, the expected number of patients who reach PASI 90 at week sixteen is at least 250 (roughly 71% of 365). Therefore, using a conservative criterion of a minimum of 10 "events" for each predictor in the model, we can add up to 25 variables in the model without loss of power (Vittinghoff E et al. 2007). This model will take into account variables such as BMI, smoking metabolic syndrome and TNFα-308 polymorphism, which, among the six existing polymorphisms, is the one most greatly affecting response to treatment with anti-TNFα drugs."

IRB/IEC

A copy of this amended protocol was sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol were approved by the IRB/IEC prior to implementation. The same applies to a revised Informed Consent that took into account the changes described in this amended protocol.

1 Introduction

1.1 Background

Psoriasis is a chronic, immune-mediated skin disease with a prevalence in Europe ranging between 0.73% (in Scotland) and 2.9% (in Italy) when considering individuals of all ages (Parisi R et al. 2012, Saraceno R et al. 2008, Simpson CR et al. 2002).

Plaque-type psoriasis is characterized by increased proliferation of keratinocytes, and hyperplasia and marked dilation of vessels in the papillary dermal region, leading to the formation of red, scaly, raised plaques. Other histological features include the presence of neutrophils within small foci in the epidermis and prominent aggregates of mononuclear leukocytes in the dermis. These regions might function as organized lymphoid tissue that perpetuates immune inflammatory infiltrates (Lew W et al. 2004). Even normal skin contains abundant stores of T lymphocytes (Clark RA et al. 2006) and resident dendritic cells (Boyman O et al. 2005), suggesting that skin might be a potential site for the direct triggering of recall immune responses. It is also likely that keratinocytes are active participants in the recruitment and activation of leukocytes in psoriatic lesions. Thus in the skin of plaque-type psoriasis, there is the concomitant activation of innate and acquired immune cell types (Lowe MA et al. 2007).

The chronic colonization of T lymphocytes in the dermis and epidermis is thought to depend on environmental and genetic factors responsible for a dysregulation of the immune responses in the skin. Innate immune cells produce key cytokines (tumor necrosis factor α [TNF-α], interferon-α, interferon-γ, interleukin-1β, and interleukin-6) that activate myeloid dendritic cells. Activated dendritic cells present antigens and secrete mediators such as interleukin-12 (IL12) and interleukin-23, leading to the differentiation of type 17 and type 1 helper T cells (Th17 and Th1). T cells, in turn, secrete mediators (e.g., interleukin-17A, interleukin-17F, and interleukin-22) that activate keratinocytes and induce the production of antimicrobial peptides (e.g., LL-37 cathelicidin and β-defensins), proinflammatory cytokines (TNF-α, interleukin-1β, and interleukin-6), chemokines (CXCL8 through CXCL11 and CCL20), and S100 proteins. These mediators feed back into the proinflammatory disease cycle and shape the inflammatory infiltrate (Nestle FO et al. 2009).

Family and twin studies have clearly demonstrated that psoriasis has a strong genetic basis (Elder JT et al. 1994). Recent genome-wide association studies have expanded the group of genomic loci that are associated with the susceptibility to psoriasis (Chandran V et al. 2010, Liu H et al. 2008, Nair RP et al. 2009). In particular, the PSORS1 locus on chromosome 6p is generally understood to confer the most risk. A specific allele for this locus, human leukocyte antigen (HLA) C*06, is also the only genetic variance repeatedly observed to associate with the phenotypic features of psoriasis and is present in about 60% of psoriatic patient cases (Strange A et al. 2010, Stuart PE et al. 2010, Rahman P et al. 2005, Queiro R et al. 2013).

The advent of biological drugs during the last decade has brought about radical changes in the management of various diseases, including psoriasis. Today, these agents represent the most advanced type of treatment for psoriasis.

Etanercept, adalimumab, infliximab and golimumab are drugs that block tumor necrosis factor alpha (TNFα), a cytokine responsible for joint and skin inflammation and damage both in psoriasis and psoriatic arthritis.

Ustekinumab is a human monoclonal antibody against interleukins 12 and 23 that has shown therapeutic potential for psoriasis. In a phase III, parallel, double-blind, placebo-controlled study, 766 patients with moderate-to-severe psoriasis were randomly assigned to receive ustekinumab 45 mg (n=255) or 90 mg (n=256) at weeks 0 and 4 and then every 12 weeks; or placebo (n=255) at weeks 0 and 4, with subsequent crossover to ustekinumab at week 12. 171 (67.1%) patients receiving ustekinumab 45 mg, 170 (66.4%) receiving ustekinumab 90 mg, and eight (3.1%) receiving placebo achieved PASI 75 at week 12 (difference in response rate vs placebo 63.9%, 95% CI 57.8-70.1, p<0.0001 for 45 mg and 63.3%, 57.1-69.4, p<0.0001 for 90 mg). At week 40, long-term response was achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group (Leonardi CL et al 2008).

Two phase III, double-blind, 52-week trials, ERASURE and FIXTURE, randomly assigned 738 patients and 1306 patients, respectively, to subcutaneous secukinumab at a dose of 300 mg or 150 mg, placebo, or (in the FIXTURE study only) etanercept at a dose of 50 mg. The objective of each study was to show the superiority of secukinumab over placebo at week 12 with respect to the proportion of patients that had a reduction of 75% or more from baseline in the psoriasis area-and-severity index score (PASI 75) and a score of 0 (clear) or 1 (almost clear) on a 5-point modified investigator's global assessment (co-primary endpoints). The proportion of patients who met the criterion for PASI 75 at week 12 was higher with each secukinumab dose than with placebo or etanercept: in the ERASURE study, the rates were 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo; in the FIXTURE study, the rates were 77.1% with 300 mg of secukinumab, 67.0% with 150 mg of secukinumab, 44.0% with etanercept, and 4.9% with placebo (P<0.001 for each secukinumab dose vs. comparators). The proportion of patients with a response of 0 or 1 on the modified investigator's global assessment at week 12 was higher with each secukinumab dose than with placebo or etanercept (Langley RG et al 2014).

Many recent papers have shown that these highly selective drugs are not effective in every patient and that variations in the genome can be associated with different clinical response or side effects to a given drug (Costanzo A et al. 2011).

The presence of the Single Nucleotide Polymorphisms (SNPs) in the TNF-α promoter and IL12B/IL23R genes seem to be associated with susceptibility to psoriasis and the response to anti-TNF-α drugs. In one study, SNPs for the TNF-α promoter and IL12B/IL23R genes, and the presence of the HLA-Cw6 haplotype were genotyped for 109 patients. The study identified a relationship between TNF-α and IL12B/IL23R polymorphisms and the short-term response to anti-TNF-α drugs in terms of Psoriasis Area and Severity Index (PASI) and involved body surface area (BSA)] (Gallo E et al 2013). Other studies demonstrated the influence of TNF-α-308 promoter polymorphism on the responsiveness to anti-TNF-α drugs in patients with rheumatoid arthritis and spondyloarthritis (Cuchacovich M et al. 2006, Cuchacovich M et al. 2004, Seitz M et al. 2007, O'Rielly DD et al. 2009).

A recently published paper demonstrated an association between the presence of the HLA-C*06 allele and the response to ustekinumab. The study showed an increased response to ustekinumab in Cw6-positive (Cw6POS) patients [PASI 75 at week 12: 96.4% in Cw6POS vs. 65·2% in Cw6-negative (Cw6NEG) patients; P = 0.008] and that HLA-Cw6POS patients

also responded faster to ustekinumab, 89.3% of them reaching PASI 50 at week 4, after a single injection (vs. 60.9% of HLA-Cw6NEG patients). The superior response of HLA-Cw6POS patients was maintained throughout the study period and reached the highest statistical significance for PASI 75 at week 28 (96.35% Cw6POS vs. 72.7% Cw6NEG; odds ratio 9.8). Analysis of TNFAIP3 rs610604 polymorphism and LCE3B/3C gene deletions did not show any significant association with response to ustekinumab (Talamonti M et al. 2013).

Secukinumab is a high-affinity human monoclonal anti-human IL-17A antibody of the IgG1/κ isotype that demonstrated a favorable safety and tolerability profile with robust clinical activity in a series of Phase II studies, and is undergoing an extensive Phase III program (Gisondi P et al 2014). Secukinumab binds to human IL-17A and neutralizes its bioactivity by inhibiting IL17A produced by both Th17 cells and cells of the innate immune system, thus providing complete anti IL17A blockage. Targeting IL-17A has the potential to reduce autoimmune inflammation while leaving other immune functions undisturbed. While targeting of Th1-promoting or Th17-promoting cytokines affects critical mediators such as IFN-γ, IL-22 and IL-21, selective targeting of IL-17A leaves these Th1/17 activities, as well as certain protective functions of innate cells intact (Patel DD et al. 2013). Furthermore, as a fully human monoclonal antibody, secukinumab has low immunogenicity (i.e., antidrug antibodies) compared to current or emerging biologic therapies that are not fully human. Data linking secukinumab efficacy to a particular genetic biomarker are lacking. However, due to its mechanism of action, the efficacy of secukinumab should not be HLA restricted, and when considering the main haplotype associated with psoriasis, no difference between Cw6-negative and positive patients is expected.

The purpose of this study is to explore the different efficacy and safety profiles of secukinumab 300 mg in patients with moderate to severe chronic plaque-type psoriasis, stratified for the presence of HLA-C*06, whose determination will be blinded for patients and investigators. The study will be conducted both on anti-TNFα-naïve and anti-TNFα failure patients and will also stratify for various variables such as TNFα - 308 polymorphism, BMI, smoking and metabolic syndrome.

Amendment 2 of the protocol has a threefold purpose; to explore response sustainability to secukinumab after 72 weeks of continuous treatment, to understand if HLA-CW6 can influence the kinetics of the response to secukinumab in the long term, to generate long-term safety and tolerability data.

Furthermore, as a consequence of the European Medicines Agency's (EMA) approval of secukinumab in February 2015 "for the treatment of moderate to severe plaque psoriasis in adults who are candidate for systemic therapy", inclusion criteria have been updated in order to guarantee treatment to systemically naïve patients, as per label.

2 Study objectives

2.1 Primary objective

To evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks, and thereafter for up to 72 weeks.

2.2 Secondary objectives

- To compare the proportion of responders to PASI 50/75/90/100 between cohorts at each time point.
- To compare the mean changes vs baseline in the Investigator's Global assessment (IGA) mod 2011 between cohorts at each time point.
- To compare time to reach PASI 90 between cohorts.
- To compare time to reach PASI 75 between cohorts.
- To evaluate the quality of life by means of the Dermatology Life Quality Index (DLQI) in all patients at each time point.
- To evaluate anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) in all patients at each time point.
- To evaluate the correlation between HADS and PASI in all patients.
- To evaluate changes from baseline in weight, BMI and waist in all patients at each time point.
- To compare safety and tolerability between cohorts during the 24 weeks, and thereafter for up to 72 weeks.
- To evaluate the amount of resources used during the study in comparison with the 6 months prior to the beginning of the study.

3 Investigational plan

3.1 Study design

This is a multicenter, prospective study involving Cw6-negative and Cw6-positive patients affected by moderate to severe chronic plaque psoriasis.

The study has four periods: a screening period consisting of two visits (pre-screening and screening), an induction period of 4 weeks, a maintenance period of 20 weeks and an extension period of 48 weeks. Timelines of the study design are presented in Figure 3-1 and Figure 3-2. Detailed visit schedules can be found in Table 6-1 and Table 6.2.

At pre-screening (day -28), patients will be centrally assessed for Cw6 positivity or negativity and stratified into two cohorts. Both patients and investigators will be blinded to the results. 308-TNFα polymorphism will be centrally determined at the same time.

After the full screening visit (day -14 to -7), eligible patients will begin treatment at baseline (week 0) and will be followed for 24 weeks (core study), plus an additional 48 weeks if participating in the extension treatment period.

The enrollment of patients into the two cohorts will be monitored during the study to prevent exceeding the number required by the sample size calculation (see Section 9.7 for details).

All patients will be treated with Secukinumab 300 mg according to an induction regimen of two injections of secukinumab 150 mg a week for five weeks starting at baseline (week 0), followed by a maintenance period of two injections per month. Following the evaluation of psoriasis severity at week 16, patients achieving PASI 50 response will be eligible to continue on the study treatment for an additional 8 weeks. After a total of 24 weeks, willing patients reaching at least a PASI 75 response will enter an extension treatment period of an additional 48 weeks. The PASI score will be evaluated during the 72-week period. Safety and tolerability data will be collected at every scheduled visit.

Figure 3-1: Study design

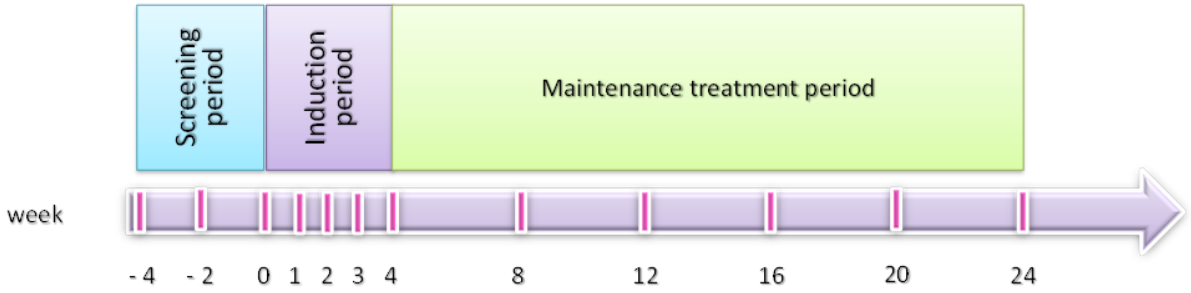
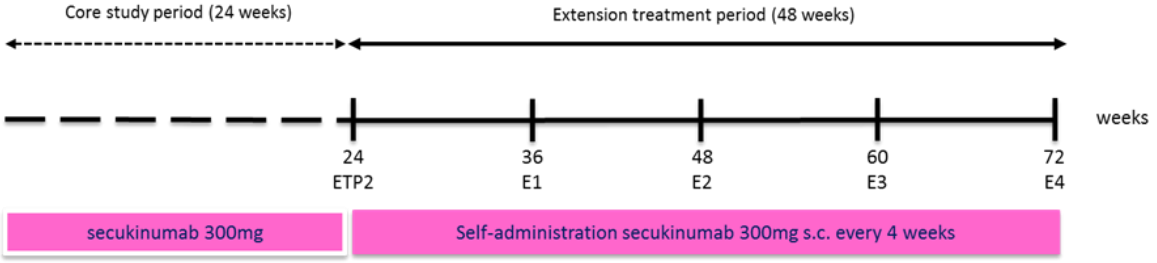


Figure 3-2: Extension Study design



3.2 Rationale of study design

The efficacy of secukinumab, as well as the proposed dose/regimen, has already been clinically substantiated through extensive Phase II and III programs. Therefore, all patients will be treated with active drug using the same therapeutic regimen.

Recent research has revealed a marked difference in the proportion of PASI 90 achievers between Cw6-positive and Cw6-negative patients (85.7% vs 56.5%) treated with ustekinumab (Talamonti M et al. 2013) and a greater efficacy of anti-TNFα drugs in CW6 negative patients (Galli E et al. 2013). Unlike anti-IL-12/23 agents, secukinumab inhibits IL-17 produced by both Th17 cells after presentation by antigen presenting cells (in this case Cw6) and cells of the innate immune system whose activation does not require antigen presentation. If secukinumab were equally effective on both Cw6 negative and Cw6 positive patients, as its

mechanism of action suggests, this would be an important clinical accomplishment and would eliminate the need for costly HLA-Cw6 tests. The choice of a cohort study would therefore seem appropriate for this clinical context.

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

Extensive Phase II and Phase III programs have shown secukinumab to be very effective in treating plaque psoriasis. The protocol regimen and 300 mg dose delivered the most clinically meaningful benefit at 16 weeks to patients with respect to achievement of almost clear - clear skin, improved quality of life, speed of onset of action, and sustainability of symptoms relief.

3.4 Rationale for choice of comparator.

Not applicable.

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

As of 12 July 2014, over 10,900 subjects were enrolled in studies with secukinumab, with over 8,600 having received active drug at doses ranging from single and/or multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c.

In total, 4,546 patients with moderate to severe plaque psoriasis were included in studies in the registration program. These included 3,430 patients treated with secukinumab in 10 phase II/III studies, 2,727 of whom were treated for at least 6 months and 2,029 for at least 48 weeks. The Phase III program demonstrated secukinumab to be very effective in treating plaque psoriasis, with 300 mg being the dose that delivered the most clinically meaningful benefit to patients. The majority of patients treated with this dose achieved clear to almost clear skin, as shown by PASI 90 response and Investigator Global Assessment modified (IGA mod) 2011 0 or 1 response.

The 3,430 psoriasis patients treated with secukinumab covered 2725 patient-years of exposure during the 10 Phase II/III clinical trials. The overall exposure-adjusted incidence of AEs per 100 patient-years over the entire treatment period was lower in the 300 mg and 150 mg secukinumab groups (236.1 and 239.9, respectively) compared with the placebo and etanercept groups (351.8 and 243.4, respectively). Most AEs in all treatment groups were mild or moderate in severity.

Secukinumab obtained EMA approval in February 2015 for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The Investigator’s Brochure (IB) provides a more detailed review of the pre-clinical and clinical information on secukinumab.

4 Population

The study plans to enroll 406 adult men or women, of which 365 are evaluable patients, diagnosed with moderate to severe chronic plaque psoriasis for at least 6 months. The patients must be candidates for systemic therapy and may be treatment naïve or have failed to respond to other systemic therapy, including cyclosporine, methotrexate, psoralen combined with ultraviolet A (PUVA), or to an anti-TNFα (or is intolerant and/or has a contraindication to these). The study plans to involve about 50 centers.

The extension phase will include 306 of the patients taking part in the core study.

4.1 Inclusion criteria

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

1. Subject must be able to understand and communicate with the investigator and comply with the requirements of the study and must give written, signed and dated informed consent before any study related activity is performed.
2. Men or women at least 18 years of age at time of screening.
3. Diagnosis of moderate to severe chronic plaque-type psoriasis for at least 6 months (including concomitant psoriatic arthritis as per the Classification Criteria for Psoriatic Arthritis criteria [CASPAR]).
4. Moderate to severe psoriasis as defined at enrollment by:
   - PASI score ≥ 10

   or
   - PASI score > 5 but < 10 and DLQI ≥10
5. Patients that are candidates for systemic therapy, whether treatment naïve or after failed response to other systemic therapy (i.e. cyclosporine, methotrexate and PUVA) or to an anti-TNFα (or is intolerant and/or has a contraindication to these).

4.2 Exclusion criteria

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

1. Forms of psoriasis other than chronic plaque-type (e.g., pustular, erythrodermic and guttate psoriasis).
2. Cyclosporine or methotrexate administration within 4 weeks prior to Day 1.
3. Anti-TNFα therapy within timelines depending on drug half-life.
4. Previous exposure to secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor.
5. Previous exposure to ustekinumab or any other biologic drug for the treatment of psoriasis that is not anti-TNFα therapy.

6. Intravenous or intramuscular steroids within 2 weeks prior to screening and during screening.
7. Ongoing use of corticosteroid topical treatments unless a washout period, as described in table 5-1, will be performed or UV therapy.
8. Previous allogeneic bone marrow transplant or history of cell-based transplantation (e.g. islet cell transplantation or autologous stem cell transplantation).
9. Treatment for infection with IV or oral antibiotics or antivirals within 14 days of Day 1.
10. Subjects with known history of active TB. Accepted TB tests include:
    a. Negative purified protein derivative (PPD); < 5 mm of induration at 48 to 72 hours after test is placed).
    b. Negative Quantiferon –TB test (an exam performed within the 3 months prior to inclusion and documented will be considered as valid).
11. Subject received any type of live attenuated vaccine < 6 weeks prior to Day 1 or is planning to receive any such vaccine over the course of the study.
12. Subject tested positive for hepatitis B virus surface antigen (HBV) or virus B latent infection, hepatitis C virus antibody (HCV), or human immunodeficiency virus (HIV) at screening (an exam performed within the 6 months prior to inclusion and documented will be considered as valid).
13. Subject has any underlying condition that predisposes to infections (history of splenectomy).
14. History of cancer in the past three years.
15. Underlying condition (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiovascular, infectious or gastrointestinal) that, in the opinion of the Investigator, would pose a risk to subject safety or interfere with study evaluation, procedures and completion.
16. Abnormal laboratory results at screening: Liver tests: either aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) > 2.0 × upper limit of normal (ULN) or total bilirubin > 1.5 × ULN (except for subjects with Gilbert Syndrome).
17. White blood cell count < 3,000 cells/mm3 (< 3×10^9/L in SI [international system] units).
18. Hemoglobin < 10 g/dL.
19. Subject is currently enrolled in another investigational study unless a washout period, as described in table 5-1, will be performed.
20. Donation or transfusion of blood, plasma, or platelets within 90 days prior to inclusion.
21. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of female after conception until the termination of gestation, confirmed by a positive HCG laboratory test (> 10 mIU/mL).

22. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use effective contraception during the study and for 16 weeks after stopping treatment. Highly effective contraception methods include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Combination of any two of the following (a+b or a+c, or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
        c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

In case of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

23. Known history of allergy to the investigational product formulation or to any other biologic therapy.

4.3 Eligibility criteria for entering the extension treatment period

1. Patients who have completed the CAIN457AIT01 core study.
2. Written informed consent for protocol amendment 2 must be obtained before patients proceed to the extension treatment period.
3. Patients must be deemed to be benefiting from the study drug based on at least a PASI 75 response rate after 24 weeks of treatment.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Secukinumab 300 mg (two s.c. injections of secukinumab 150 mg).

Secukinumab will be administered as solution for injection in a pre-filled syringe: clear to opalescent, colorless to slightly yellowish liquid (150 mg/1.0 mL) in a in a 1 mL long, single-use, prefilled glass syringe with fluortec-coated bromobutyl rubber plunger stopper staked 27G ½ inch needle and rigid needle sheet and needle safety device. The pre-filled syringe is incorporated into a triangular auto-injector/pen.

The study treatment will be administered by the site staff during the visit. Patients enrolled in the extension period will self-administer secukinumab and will be asked to keep a self-administration log during this period.

5.1.2 Additional study treatment

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

5.2 Treatment arms

Not applicable, all patients will receive secukinumab 300 mg.

5.3 Treatment assignment

All patients will receive secukinumab 300 mg subcutaneously.

5.4 Treatment blinding

Not applicable, this is an open label study. All patients will receive secukinumab 300 mg.

5.5 Treating the patient

5.5.1 Patient numbering

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

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank Case Report Form (CRF) book available from the Electronic Data Capture (EDC) system.

If an enrolled patient fails to be treated for any reason, the reason will be entered on the Screening Study Disposition CRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance. This is an open label study.

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

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

Medication labels will be in the local language and comply with the legal requirements of each country.

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

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

Handling of other study treatment: not applicable.

5.5.4 Instructions for prescribing and taking study treatment

All patients will receive Secukinumab 300 mg subcutaneously using the Phase III regimen: 300 mg (two 150 mg injections) a week for the first five weeks (visits 3-7), and once every 4 weeks thereafter (visits 8-12). Patients proceeding to the extension period will self-administer treatment (two 150 mg injections) once every 4 weeks for an additional 48 weeks.

The study treatment solution must be injected subcutaneously in non-affected areas of the skin.

Following the evaluation of psoriasis severity at 16 weeks, patients achieving a PASI 50 response will be eligible to continue on the study treatment for another 8 weeks. Their PASI score will be evaluated at 24 weeks. Willing patients reaching at least a PASI 75 response at the end of the 24-week core study will enter an extension treatment period of an additional 48 weeks.

All dates of injections given to the subject during the study must be recorded on the Dosage Administration Record e-CRF.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Investigational treatment dose adjustments and/or interruptions are not permitted.

5.5.6 Rescue medication

The investigator may prescribe any medications and/or supportive care during the study based on clinical needs. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies/Dose Administration Record in the Electronic Case Report Form (eCRF).

5.5.7 Concomitant treatment

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

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 is NOT allowed after screening.

If a prohibited treatment listed in Table 5-1 is used during the study, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study. At the discretion of the investigator, if the patient's use of a prohibited treatment presents undue safety risk for the patient, he/she should be discontinued from study treatment as per Section 5.5.9. If the patient receives a live virus vaccination during the study, he/she must discontinue study treatment and enter the post-treatment follow up period.

Table 5-1: Prohibited treatment

Prohibited treatments	Washout period (before day 1)
Secukinumab or any other biologic drug directly targeting IL-17 or the IL-17 receptor	No prior use allowed
Ustekinumab	No prior use allowed
Alefacept, briakinumab, efalizumab	6 months
Biological immunomodulating agents other than the above:	
Etarnecept	3 weeks
Adalimumab	6 weeks
Infliximab	12 weeks
Golimumab	8 weeks
Other systemic immunomodulating treatments [e.g., MTX, cyclosporine A, corticosteroids (oral, i.v., intramuscular, s.c., intra-articular, transdermal), cyclophosphamide]	4 weeks
Other systemic psoriasis treatments (e.g. retinoid, fumarates)	4 weeks
Photo chemotherapy (e.g. PUVA)	4 weeks
Phototherapy (e.g., UVA, UVB)	2 weeks
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g. vitamin D analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea alpha-hydroxy or fruit acids)	2 weeks

Live virus vaccinations	6 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)
Prohibited regimen of Topical Corticosteroids (TCS):	
TCS higher than moderate potency on any body location	2 weeks
TCS mild to moderate potency on any body location other than the face, scalp and or genitoanal area	2 weeks
TCS mild to moderate potency on the face, scalp and or genitoanal area	1 day

5.5.9 Discontinuation of study treatment and premature patient withdrawal

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

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information.

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

The investigational treatment must be discontinued under the following circumstances:

- Withdrawal of informed consent
- Severe adverse events that, in the opinion of the Investigator, warrant discontinuation
- Pregnancy
- Use of prohibited treatment as per Table 5-1
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients that do not achieve PASI 50 at week 16 will terminate treatment. For patients who are lost to follow-up (i.e. those patients 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 the steps taken to contact the patient, e.g. dates of telephone calls, registered letters in the source, etc.

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

5.5.10 Emergency breaking of treatment assignment

Not applicable.

5.5.11 Study completion and post-study treatment

The core study will have a duration of 24 weeks. Following the evaluation of psoriasis severity at week 16, patients achieving PASI 50 response will be eligible to continue on the study treatment for an additional 8 weeks. Willing patients reaching at least a PASI 75 response during the core study will be eligible to enter an extension treatment period of an additional 48 weeks.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.12 Early study termination

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

The study extension can be terminated by Novartis for any reason after a period of at least 12 weeks. Termination may occur only in selected regions where the drug is commercially available; this decision will be made on a region-by-region basis, as for some regions the study will continue as planned even though secukinumab may have become commercially available.

6 Visit schedule and assessments

Table 6-1 lists all of the assessments and indicates with an "x" when the visits are performed. All data obtained from these assessments must be supported in the patient's source documentation.

Patients should be seen for all visits on the designated day. A time window of ± 2 days for weekly visits and ± 7 days for the monthly visits is allowed.

Patients who discontinue the investigational treatment should also return for the assessments in Table 6-1. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone, reporting it in the source documents.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit, including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

Table 6-1: Assessment schedule (core study)

Visit	1	2	3	4	5	6	7	8	9	10	11	12/EoS
Week (relative to baseline)	-4	-2	0 (± 2 days)	1 (± 2 days)	2 (± 2 days)	3 (± 2 days)	4 (± 2 days)	8 (± 7 days)	12 (± 7 days)	16 (± 7 days)	20 (± 7 days)	24 (± 7 days)
Day	-28	-14 to -7	1	7	14	21	28	56	84	112	140	168
Informed consent	X											
Demographic data		X										
Inclusion/Exclusion criteria		X	X									
Smoking history		X										
Medical History		X										
TNFα - 308 polymorphism	X											
Psoriasis: medical history		X										
Previous Psoriasis therapies		X										
Quantiferon TB-Gold (within 3 months)		X										
Physical Examination		X	X	X	X	X	X	X	X	X	X	X
Height, weight, BMI and waist		X	X							X		X
Vital signs		X	X				X	X	X	X	X	X
PASI		X	X	X	X	X	X	X	X	X	X	X
IGA mod 2011		X	X	X	X	X	X	X	X	X	X	X
Lab assessments: hematology and chemistry[]		X	X				X	X	X	X	X	X
hsCRP			X							X		X
HCV, HBV* and HIV tests (within 6 months)		X										
Serum pregnancy test		X										
Urinalysis		X								X		X
Secukinumab administration			X	X	X	X	X	X	X	X	X	X
DLQI			X							X		X
HADS			X							X		X
Cw6 centralized determination	X											
[redacted]												
ECG (within 6 months)		X										
Chest X-ray (within 6 months)		X										
Study completion												X^
Concomitant medication			As needed									
Adverse events	As needed											
Liver events			As needed									

[]Hematology: Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count; Chemistry: Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, CK, GGT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid.

¥ Height will be assessed only at screening or at baseline

* HBsAg, HBsAb, HBcAb

^ End of Study visit for patients not proceeding to the extension treatment period.

Table 6-2 lists all the assessments of the extension phase and indicates with an "x" when the visits are performed.

Patients should be seen for all visits on the designated day but a time window of ± 7 days is allowed.

Table 6-2: Assessment schedule of extension treatment period

Visit	E0*	E1	E2	E3	E4/ End of Extension or PPD
Week (relative to baseline)	24	36	48	60	72
Recommended visit window (days)	±7	±7	± 7	±7	±7
Informed consent	X				
Inclusion/Exclusion criteria	X				
Physical Examination		X	X	X	X
Weight and waist		X	X	X	X
Vital signs		X	X	X	X
PASI		X	X	X	X
IGA mod 2011		X	X	X	X
Lab assessments: hematology and chemistry[ʃ]		X	X	X	X
Urinalysis		X	X	X	X
Secukinumab administration	AS NEEDED				
DLQI			X		X
HADS			X		X
Check self-administration log		X	X	X	X
Dispensing Secukinumab for self-administration at home	X	X	X	X	
Study extension completion					X
Concomitant medication	AS NEEDED				
Adverse events	AS NEEDED				
Liver events	AS NEEDED				

* E0 corresponds to visit at week 24 of the core study (end of study) for patients proceeding to the extension treatment period. The assessments indicated here are in addition to those already scheduled for EOS visit (see table 6-1)

ʃ Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count. Chemistry: albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, creatinine, CK, GGT, glucose, LDH, potassium, total protein, AST, ALT, sodium, triglycerides, uric acid, hsCRP.

6.1 Information to be collected at screening

HLA-Cw6 determination will be performed at screening for patients who have provided written informed consent. A central laboratory will be used to determine Cw6. Patients will thereafter be stratified into the two cohorts. TNFα-308 polymorphism will be centrally determined at the same time.

6.2 Patient demographics/other baseline characteristics

The following data will be gathered/documented at visit 2 (day -14 to -7):

- Demographic data [age, sex, race, ethnicity, and childbearing potential (for females only)].
- Verification of inclusion/exclusion criteria.
- History (medical, smoking, psoriasis).
- Previous psoriasis therapies in the 6 months prior to study entry.
- A chest X-ray, an ECG and HCV, HBV (HBsAg, HBsAb, HBcAb), HIV tests will be required unless performed within the previous 6 months. Adequate documentation (assessment reports, tracking and imagines as applicable) must be available for previous evaluations to be considered valid at baseline.

- A Quantiferon TB-Gold test or PPD test will be required unless performed within the previous 3 months. Adequate documentation (assessment report) must be available for previous evaluations to be considered valid at baseline.
- Height, weight and waist.
- Physical examination (only as source document).
- Vital signs (heart rate, blood pressure).
- PASI, IGA mod 2011.
- Hematology, blood chemistry, urinalysis.
- Serum pregnancy test.
- [redacted]

Treatment with secukinumab will begin at visit 3 (day 1), during which the following data will be collected/documented:

- Verification of inclusion/exclusion criteria.
- Physical examination.
- Vital signs.
- Height (if not obtained at visit 2), weight and waist.
- Hematology, blood chemistry.
- High sensitivity C-reactive protein (hsCRP).
- PASI, IGA mod 2011.
- DLQI, HADS.

6.3 Treatment exposure and compliance

Data on investigational drug will be reported on the Dosage Administration Record (DAR) of the eCRF in order to provide information about drug exposure.

6.4 Efficacy

6.4.1 Psoriasis Area and Severity Index (PASI)

The primary efficacy variable is the measurement of the severity of psoriasis using the Psoriasis Area and Severity Index (**PASI**) (Richard GB et al. 2013), the most widely used tool for this purpose. PASI combines the assessment of the severity of lesions and the area affected into a single score with a range of 0 (no disease) to 72 (maximal disease). The PASI will be assessed at each visit from V2 to V12 of the core study and at all four visits of the extension period.

A PASI score (Weisman et al. 2003) will be calculated as indicated in Appendix 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. In particular:

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.

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

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

Usually, a PASI 75 improvement is used as a minimum threshold to evaluate the clinical efficacy of new psoriasis treatments (Callen JP et al. 2003). A PASI 90 improvement will be used as primary endpoint in this study.

The following definitions of PASI will be used in this study:

- PASI 50 response: subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders.
- PASI 75 response: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders.
- PASI 90 response: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders.
- PASI 100 response / remission: complete clearing of psoriasis (PASI=0).

6.4.2 Investigator's Global Assessment Scale (IGA)

The IGA mod 2011 rating scale for overall psoriatic disease is shown in Appendix 4. The IGA mod 2011 scale has been developed based on a previous version of the scale used in secukinumab Phase II studies in collaboration with health authorities, in particular the FDA. The explanations/descriptions of the points on the scale have been improved to ensure their differentiation. The IGA mod 2011 will be evaluated at each visit from V2 to V12 of the core study and at all four visits of the extension period. It measures the severity of the disease on a five-point scale ranging from 0 (no disease, 'clear') to 4 ('very severe') (Richard GB et al 2013).

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.

6.4.3 Appropriateness of efficacy assessments

The PASI is widely considered the gold standard for assessing psoriasis severity in a clinical trial setting (Richard GB et al. 2013). 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 Investigator's Global Assessment mod 2011 (IGA mod 2011).

6.5 Safety

6.5.1 Physical examination

An overall physical examination will be performed by the investigational staff at visit 2 and include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. A short physical exam will include the examination of general appearance and vital signs (blood pressure and pulse) and will be performed at all visits starting from visit 3.

Detailed information on each evaluated apparatus from all physical examinations must be included in the source documentation at the study site.

Metabolic syndrome will require any 3 of the following 5 criteria: increased waist circumference (≥102 cm for men, ≥ 88 cm for women), elevated triglycerides (≥150 mg/dl), reduced high-density lipoprotein (HDL) cholesterol (≤ 40 mg/dl in men and ≤ 50 mg/dl in women), elevated blood pressure (≥ 130 mmHg systolic and ≥ 85 mmHg diastolic or ongoing treatment for hypertension) or elevated glucose (≥100 mg/dl or ongoing treatment for elevated glucose) (Expert Panel JAMA 2001).

6.5.2 Vital signs

Sitting blood pressure and heart rate will be measured at visits 2 and 3 and then at each visit starting from visit 7. Clinically notable vital signs are defined in Appendix 1.

6.5.3 Height, weight and waist

Height in centimeters (cm) will be measured at visit 2 or 3 only.

Body weight (to the nearest 0.1 kilogram in indoor clothing, but without shoes) and waist will be measured at visits 2, 3 and 12 of the core study and at all four visits of the extension period. BMI will be derived from weight and height results.

6.5.4 Laboratory evaluations

6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes), and platelet count will be measured at visits 2 and 3 and then at each visit starting from visit 7 (including extension period). Appendix 1 shows the extended laboratory ranges that are considered clinically notable.

6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, creatine kinase (CK), gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH), inorganic phosphorus, lipase, amylase, magnesium, potassium,

total protein, AST, ALT, sodium, triglycerides, urea/blood urea nitrogen (BUN) and uric acid will be measured at visits 2 and 3 and then at each visit of the core study starting from visit 7.

The following clinical chemistry assessments will be run at all four visits of the extension period: albumin, alkaline phosphatase, total bilirubin, calcium, cholesterol, creatinine, CK, GGT, glucose, LDH, potassium, total protein, AST, ALT, sodium, triglycerides, uric acid.

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

6.5.4.3 Urinalysis

Dipstick measurements for specific gravity, protein, glucose and blood will be performed. WBC and RBC sediments will also be analyzed at visits 2, 10 and 12 of the core study and at all four visits of the extension period.

6.5.4.4 hsCRP

hsCRP will be assessed at visits 3, 10, and 12 of the core study and at all four visits of the extension period.

6.5.5 Electrocardiogram (ECG), chest X-ray

An ECG and chest X-ray will be required at visit 2 unless performed within the previous 6 months. Adequate documentation (assessment reports, tracking and imagines as applicable) must be available for previous evaluations to be considered as baseline.

6.5.6 Pregnancy and assessments of fertility

A serum pregnancy test will be performed at visit 2 in all fertile women.

6.5.7 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/patient population.

6.6 Other assessments

6.6.1 Resource utilization

The amount of resources used during the study will be evaluated in comparison with the 6 months prior to the beginning of the study.
Resource utilization will be extrapolated from data collected from single items in the flow chart such as “medical history, psoriasis medical history, concomitant medications and adverse events.”

6.6.2 Health-related Quality of Life

Quality of life will be assessed by means of the Dermatology Life Quality Index (DLQI), a validated, 10-item general dermatology disability index designed to assess health-related quality of life in adult subjects with skin diseases such as eczema, psoriasis, acne, and viral warts (Finlay AY et al. 1994). The measure is self-administered and includes domains of daily activities, leisure, personal relationships, symptoms and feelings, treatment, and work/school activities. The DLQI has well-established reliability and validity as determined in several studies (Shikiar et al 2003, Badia X et al. 1999, Lewis V et al. 2004, Shikiar et al. 2006).

Moreover, it is frequently used in clinical psoriasis trials, has been tested across 32 different skin conditions and is available in 55 languages. The recall period is the previous week, and the instrument requires 1 to 2 minutes to complete. Each item has four response categories ranging from 0 (not at all) to 3 (very much). "Not relevant" is also a valid response and is scored as 0. The DLQI© total score is a sum of the 10 questions. Scores range from 0 to 30 and higher scores indicate greater health-related quality of life impairment. Each subscale of the DLQI© may be analyzed separately.

Patients will be asked to complete the questionnaire at visits 3, 10 and 12 of the core study and at visits 2 and 4 of the extension period.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.2 of the protocol.

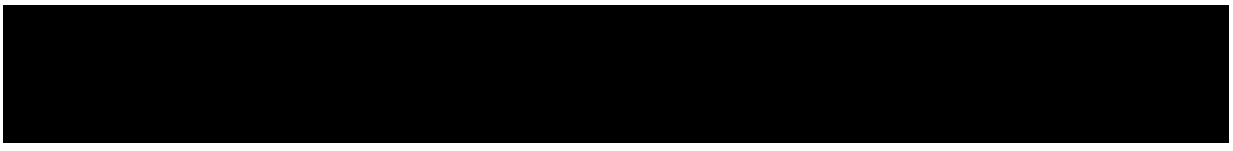
6.6.3 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) is a fourteen-item scale that generates ordinal data. Seven of the items relate to anxiety and seven relate to depression. This outcome measure was specifically developed to avoid reliance on aspects of these conditions that are also common somatic symptoms of illness, for example fatigue and insomnia or hypersomnia. Calculations of scores: each of the 14 items is rated on a 4-point scale ('Yes, definitely', 'Yes, sometimes', 'No, not much' and 'No, not at all'). All items except 7 and 10 are scored as 'Yes, definitely' = 3 to 'No, not at all' = 0. Items 7 and 10 are scored as 'Yes, definitely' = 0 to 'No, not at all' = 3. The HADS consists of two sub-scores: the HAD‑A for anxiety and HAD‑D for depression; each sub-score ranges from 0 to 21 points; scores ≥11 indicate the presence of anxious or depressive disorders; scores between 8-10 points are borderline abnormal, and scores of ≤7 indicate that the disorder is not present.

Patients will be asked to complete the questionnaire at visits 3, 10 and 12 of the core study and at visits 2 and 4 of the extension period.

Completed questionnaires will be reviewed and examined by the investigator before the clinical examination for responses that may indicate potential AEs or SAEs. The investigator should review not only the responses to the questions in the questionnaires but also any unsolicited comments written by the patient.

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7.2 of the protocol.



7 Safety monitoring

7.1 Adverse events

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

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

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

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

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

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

- the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
- its relationship to the investigational treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding the investigational treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

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

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is:
  - for a routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - for an 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
  - for treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
  - for social reasons and respite care in the absence of any deterioration in the patient's general condition
  - medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

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

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

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

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

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

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

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit must be reported to

Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30-day period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

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

The investigator will complete the SAE Report Form in English, assess the relationship to the study treatment and send the completed and signed form by fax within 24 hours to the local Novartis Drug Safety and Epidemiology Department Novartis (DS&E). The original and the duplicate copies of the SAE Form, and the fax confirmation sheet will be kept with the case report forms at the study site.

Follow-up information will be sent to the same person to whom the original SAE Form was sent, re-stating the date of the original report. A new SAE Form will be used (stating that this is a "follow-up"). The follow-up report should describe whether the event is resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet will be retained at the study site.

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

7.3 Liver safety monitoring

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

Liver events are divided into two categories:

- Liver events of special interest, which consist of liver function test (LFT) elevations.
- Medically significant liver events that are considered as serious adverse events and consist of marked elevations of LFTs and / or pre-specified adverse events.

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

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

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

- Repeat the LFT to confirm elevation as appropriate.
- Discontinue the investigational drug if appropriate.
- Hospitalize the patient if appropriate.
- Assess the causality of the liver event via exclusion of alternative causes (e.g., disease, co-medications).
- An investigation of the liver event needs to be followed until resolution.

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

7.4 Pregnancy reporting

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

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

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

8 Data review and database management

8.1 Site monitoring

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

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification of the presence of informed consent, adherence to the inclusion/exclusion criteria,

documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Web based software will be used: no installation procedure will be needed. Each site will be authorized by the Administrator to access the eCRF. Each investigator site qualified personnel will be allowed to access the eCRF by means of a 'login mask' requiring User ID and Password and will be able to read, modify and update only the information he/she has previously reported. Each page should report site code and patient code. On-line validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected by the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data or a CD-ROM for archiving at the investigational site.

8.3 Database management and quality control

CRO working on behalf of Novartis will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. The Data Manager of the CRO working on behalf of Novartis will perform the cleaning session reviewing the warning messages raised by on-line checks and running post-entry checks by means of validation programs. During this process, if clarifications are needed, the Data Manager will raise queries by means of data query forms through the WEB application. Designated investigator site staff is required to respond to the query and the Data Manager will make the correction to the database based on the query response. The data collection and the Queries flow as well as the on-line and off-line control checks will be detailed in the Data Management Plan and Data Validation documents.

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

A central laboratory will analyze samples for Cw6 determination and enter the results in a dedicated section of the eCRF. Cohort status will be monitored to maintain the Cw6+/Cw6- ratio foreseen in the protocol.

Data about study drug will be tracked using the eCRF. The system will be supplied by a CRO, who will also manage the database.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared completed and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made

after written agreement between the Clinical Trial Leader, the Trial Statistician and the Data Manager.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

All the data collected in this study will be listed and summarized as appropriate as described below. The data from all centers will be pooled and summarized. Continuous data will be summarized by mean, standard deviation (SD), median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %).

Unless stated otherwise, two-sided p-values will be presented.

All statistical tables, listings and analyses will be produced using SAS® release 9.2 or later (SAS Institute Inc. Cary, NC, USA).

More details about data analysis will be provided in the Statistical Analysis Plan.

The data will be analyzed by the CRO working on behalf of Novartis.

9.1 Analysis sets

The following analysis populations will be defined for statistical analysis.

- Full Analysis Set (FAS): all enrolled patients.
- Safety: all enrolled patients who were given at least one dose of study drug.
- Intent-to-treat (ITT): all patients included in the safety population with at least one post-baseline efficacy assessment.
- Per-Protocol (PP): all patients included in the ITT population who completed the study without any major protocol violation.

The primary and secondary objectives will be evaluated on the ITT population. A supportive analysis will be done on the PP population.

All safety evaluations will be based on the safety population.

9.2 Patient demographics and other baseline characteristics

All data about patient demographics and baseline characteristics, including derived variables, will be summarized overall and by cohort with summary descriptive statistics. Continuous data will be summarized by mean, standard deviation, median, first and third quartiles, minimum and maximum. Categorical data will be presented by absolute and relative frequencies (n and %).

In order to interpret results adequately, the homogeneity of patient distribution between cohorts will be tested on selected baseline demographics and anamnestic variables (e.g. for gender, age, race, ethnicity, BMI, baseline PASI, baseline IGA, TNFα - 308 polymorphism, metabolic syndrome, smoking). Categorical variables will be analyzed by Cochran-Mantel-Haenszel test stratified by geographical region (i.e. north vs south/central) and BMI (< 25 vs ≥ 25).

Continuous variables will be analyzed by means of ANOVA model corrected by geographical region and BMI classes, as appropriate. Statistically significant variables will be included as covariates in the explanatory analysis model. Whenever necessary, normality will be assessed by means of Shapiro-Wilk test and with graphical methods. In case of non-normality, a non-parametric test will be used.

The number of the analysis populations will be described and the reasons for excluding a patient from any particular population will be provided with the number of protocol violators for each criterion. The difference between cohorts with respect to protocol deviations and reasons for dropout will be examined.

Any condition entered as medical history or current medical conditions at baseline will be coded using the MedDRA dictionary. They will be summarized by system organ class and preferred term of the MedDRA dictionary.

Summaries of psoriasis-specific medical history will be provided as well.

9.3 Treatments

Study treatment administration details will be summarized overall and by cohort for the Safety population. The exposure to investigational drug (number of doses) and duration of exposure (days) will be summarized by means of usual descriptive statistics. Total actual dose will be compared with the total dose patients should take as per protocol and derived compliance will be summarized. The number of patients with permanent study drug interruptions will be described and the reasons that led to the interruption will be examined.

The use of rescue medication, concomitant medications and significant non-drug therapies will be summarized by Anatomic Therapeutic Chemical (ATC) class, overall and by cohort for the Safety population.

9.4 Analysis of the primary variable

The primary objective of this study is to evaluate the clinical response in Cw6-negative and Cw6-positive patients treated with secukinumab 300 mg with respect to the Psoriasis Area Severity Index (PASI) 90 response rate after 16 weeks, and thereafter for up to 72 weeks.

9.4.1 Variable

The primary efficacy variable is the PASI 90 response after 16 weeks of treatment, defined as the achievement of $\geq 90\%$ improvement (reduction) in PASI score after 16 weeks of treatment compared to baseline.

The primary analysis will be based on the ITT population. A supportive analysis will be performed on the PP population.

9.4.2 Statistical model, hypothesis, and method of analysis

The proportion of patients who reach PASI 90 at 16 weeks will be presented with the one-tailed 97.5% confidence interval of the Cw6 positive (POS) – Cw6 negative (NEG) difference.

The null hypothesis:

H0: Cw6 POS – Cw6 NEG ≥ 0.12: The difference in proportion of subjects achieving PASI 90 response between the Cw6-positive cohort (Cw6 POS) and the Cw6-negative cohort (Cw6 NEG) is at least 12%.

The alternative hypothesis:

HA: Cw6 POS – Cw6 NEG < 0.12: The difference in the proportion of subjects achieving PASI 90 response between the Cw6-positive cohort (Cw6 POS) and the Cw6-negative cohort (Cw6 NEG) is less than 12%.

A logistic regression analysis model will be also fitted, considering geographical region, BMI, smoking, metabolic syndrome, TNFα-308 polymorphism, as well as the clinically relevant baseline variables as strata factors.

9.4.3 Handling of missing values/censoring/discontinuations

All attempts will be made to ensure that the database contains full information for all data. For subjects who prematurely discontinue the study for any reason or subjects with missing visits (after baseline), PASI will be imputed using the Last Observation Carried Forward (LOCF) approach. If all PASI post-baseline efficacy values are missing, then these missing values will not be imputed and this subject will be removed from the analysis.

9.4.4 Supportive analyses

A sensitivity analysis on the primary efficacy variable will be performed considering the subjects who prematurely discontinued the study without a 16-week PASI assessment as non-responders.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The primary analysis and the analyses of all secondary variables will be based on the ITT population.

PASI

Summary statistics for PASI 50, PASI 75, PASI 90, PASI 100 response by visit will be presented with absolute and relative frequencies.

The following definitions of PASI response will be used:

- PASI 50 response: subjects achieving ≥ 50% improvement (reduction) in PASI score compared to baseline are defined as PASI 50 responders.
- PASI 75 response: subjects achieving ≥ 75% improvement (reduction) in PASI score compared to baseline are defined as PASI 75 responders.

- PASI 90 response: subjects achieving ≥ 90% improvement (reduction) in PASI score compared to baseline are defined as PASI 90 responders.
- PASI 100 response / remission: complete clearing of psoriasis (PASI=0).

Confidence intervals for response rates will be derived as well, based on the score method including continuity correction (Newcombe 1998).

Summary statistics will be provided for absolute PASI scores and for percent changes from baseline by visit and cohort. A graphical representation will also be provided.

The proportion of patients who reach PASI 75 after 16 weeks will be compared between cohorts with the same method presented for the primary endpoint.

The differences between cohorts in time to reach PASI 90, as well as PASI 75, will be evaluated by means of a log-rank test. The hazard ratios and their corresponding 95% confidence intervals will be also computed using a stratified Cox proportional hazards regression model with Cw6 group and baseline PASI as explanatory variable and stratified by geographical region and BMI, as well as the clinically relevant baseline variables. The Kaplan-Meier estimates of the cumulative rate for each cohort will be plotted.

IGA mod 2011

Summary statistics for the IGA mod 2011 score over time, as well as percent changes from baseline, will be presented by visit and cohort. Summary statistics for IGA 0 or 1 response by visit and cohort will be presented with absolute and relative frequencies. Subjects achieving IGA score 0 or 1 are defined as IGA 0 or 1 responders.

[redacted]

9.5.2 Safety variables

Vital signs

Summary statistics of vital signs and changes from baseline will be provided by visit and cohort. Clinically notable vital signs will be listed and absolute and relative frequencies will be presented by visit and cohort.

Height, weight and waist

Summary statistics will be provided for height, weight, waist and derived BMI (calculated from body weight and height) by visit and cohort including changes from baseline.

Hematology, clinical chemistry, urinalysis, hsCRP

Summary statistics of raw data and absolute and changes from baseline will be provided for laboratory data by visit and cohort.

Patients with values above (H) or below (L) notable criteria (see Appendix 1) will be listed and absolute and relative frequencies will be presented by visit and cohort. Laboratory values will be presented for each subject in a data listing with an indication of whether the value is above (H) or below (L) the normal reference range.

Laboratory data will also be summarized by presenting shift tables for each laboratory parameter showing the number and percentage of subjects in each cohort with the most extreme post-baseline value that falls outside normal ranges by the classification of value at baseline (H/N/L).

Adverse Events

A summary table of AEs will be produced by cohort specifying the number of total events and the absolute and relative frequency of patients with AEs. The absolute and relative frequency of patients with study drug related AEs, severe AEs, SAEs, AEs with an outcome of death, AEs leading to discontinuation of treatment will be also reported.

AEs will be tabulated also by System Organ Class, Preferred Term.

SAEs will be summarized as well.

All study drug related AEs, AEs with an outcome of death, AEs leading to discontinuation of treatment will be listed.

The above reported analysis will focus on treatment emergent adverse events. A treatment-emergent adverse event is defined as any adverse event that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment. Non-treatment emergent adverse events will be listed separately.

9.5.3 Resource utilization

Data relating to health resources use will be used for the purpose of economic evaluation, particularly, to compare the amount of health resources used in the 6 months prior to the beginning of the study and during the study. Health resources use will refer to all items of assistance provided to the patients in the 6 months prior to the beginning of the study and during the study.

The analysis of health resources use will be conducted considering the patients' demographic characteristics, anthropometric parameters (such as weight, BMI and waist circumference), co-morbidities (such as anxiety and depression), and scores provided by the Study (such as PASI, DLQI, HADS).

The cost for all items of assistance provided to the patient and included into the economic evaluation will be calculated according to price (such as for drugs) or tariffs (such as for tests).

Given the skewed distribution of costs, median value will also be presented (in addition to mean value).

9.5.4 Health-related Quality of Life

Dermatology Life Quality Index

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.

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

Change from baseline will be analyzed by means of a pairwise test for categorical data.

In addition, summary statistics will be provided for the number of subjects achieving DLQI 0 or 1 at each time point.

Hospital Anxiety and Depression Scale

Descriptive statistics of HAD-A and HAD-D score at each time point with changes vs baseline will be provided.

The sub-scores, HAD-A and HAD-D, will be displayed per class (i.e. scores ≥11 indicate the presence of anxious or depressive disorders; scores between 8-10 points are borderline abnormal, and scores of ≤7 indicate that the disorder is not present) at each time point by means of a shift table.

In addition, the prevalence of anxiety and depression will be presented on the basis of the following three criteria: as per the score on the corresponding sub-scores of the HAD questionnaire, in terms of the treatment they are receiving for anxiety/depression, and according to both criteria.

A correlation between HADS and PASI will be explored by means of a Spearman coefficient (or Pearson, according to the data distribution). A cross-table for PASI90 or PASI75 and HAD score ≥11 at baseline and at 16 weeks will also be provided.

9.5.5 Pharmacokinetics

Not applicable.

9.5.6 Pharmacogenetics/pharmacogenomics

Not applicable.

9.5.8 PK/PD

Not applicable.

9.6 Interim analyses

Not applicable.

9.7 Sample size calculation

The primary objective of this study is to evaluate the clinical response in PASI 90 at week 16 of Cw6-negative and Cw6-positive psoriatic patients.

According to literature data, Cw6-positive patients will be about 60% of the entire psoriatic patient population.

From a previous study with ustekinumab (Talamonti et al. 2013) we can observe a difference in response to PASI 90 between Cw6-positive vs Cw6-negative patients of around 30%, in favor of Cw6-POS. Therefore, it is sensible to expect a response in the Cw6-negative cohort not less than 12 % respect to the Cw6-positive group. Further considerations are stated in the paragraph below.

Phase III data on secukinumab show a PASI 90 response at 16 weeks of 71%. Under the assumption that 60% of all the enrolled patient population is represented by Cw6-POS patients, we can reasonably assume to observe a proportion of patients with PASI 90 of 80% in the Cw6-POS cohort.

Under these assumptions, considering a one-side alpha level of 0.025 and a power of 80%, 365 patients (219 Cw6-POS and 146 Cw6-NEG) are sufficient to evaluate if the response in terms of PASI 90 in the Cw6-negative cohort is not less than 12% respect to the Cw6-positive cohort.

Considering a dropout rate at 16 weeks of 10% equally divided in the two studied cohorts, a total of 406 patients should be enrolled.

All calculations were done with NQuery 7.0.

A power analysis based on a different Cw6 patient distribution was made in order to facilitate patient enrollment without power-loss in the primary endpoint evaluation. Table 9-1 shows how the enrollment rate should be set free until the ratio between Cw6-POS and Cw6-NEG reaches the 1:1 rate-distribution, with a power of at least 80%.

In particular, the number of Cw6-POS evaluable patients will range from 219 to 182, whereas those in the Cw6-NEG cohort will range from 146 to 182.

Based on the table below, the enrollment in one of the two cohorts will be stopped when the target number is achieved (a maximum of 244 Cw6-POS patients will be allowed).

Table 9-1: Power analysis

Power	Ratio	Cw6 POS %	Cw6 NEG %	Cw6 POS N	Cw6 NEG N	Overall N	Drop out 10% Cw6 POS N	Drop out 10% Cw6 NEG N
80%	0,66	60%	40%	219	146	365	244	163
80%	0,70	59%	41%	215	150	365	239	167
80%	0,72	58%	42%	212	153	365	236	170
80%	0,75	57%	43%	209	156	365	233	174
81%	0,79	56%	44%	204	161	365	227	179
81%	0,82	55%	45%	200	165	365	223	184

81%	0,85	54%	46%	197	168	365	219	187
81%	0,89	53%	47%	193	172	365	215	192
81%	0,92	52%	48%	190	175	365	212	195
81%	0,96	51%	49%	186	179	365	207	199
81%	1,00	50%	50%	182	182	364	203	203

The choice of clinically relevant differences is based on the following considerations:

- As the efficacy of secukinumab has already been clinically substantiated through extensive Phase II and III programs, all patients will be treated with active drug using the same therapeutic regimen (no placebo comparison will be done).
- The primary variable is the proportion of patients who reach PASI 90 after 16 weeks. This endpoint is quite challenging and much more restrictive compared to PASI 75. Only the investigator is responsible for collecting the components or scoring signs and total regional areas in the PASI assessment. Therefore, it has great internal variability, which should be taken into account.
- The paper on HLA-Cw6 ustekinumab data (Talamonti M et al. 20134) revealed a striking difference between Cw6-positive and Cw6-negative patients in the proportion of PASI 90 achievements, 85.7% vs 56.5%. This difference in PASI 90 is very relevant in the daily clinical management of patients.

Considering the above statements, it seems reasonable to claim that more than halving the difference observed with ustekinumab between Cw6-positive and Cw6-negative patients, secukinumab would be an advantage in terms of efficacy for Cw6-negative patients who do not respond properly to ustekinumab and other approved biologic drugs.

Although the sample size was calculated considering only Cw6 haplotype, it is also adequate for regression models assessing differences from baseline for clinically relevant variables. In fact, the expected number of patients who reach PASI 90 at week sixteen is at least 250 (roughly 71% of 365). Therefore, using a conservative criterion of a minimum of 10 “events” for each predictor in the model, we can add up to 25 variables in the model without loss of power (Vittinghoff E et al. 2007). This model will take into account variables such as BMI, smoking, metabolic syndrome and TNFα-308 polymorphism, which, among the six existing polymorphisms, is the one most greatly affecting response to treatment with anti-TNFα drugs.

10 Ethical considerations

10.1 Regulatory and ethical compliance

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

10.2 Informed consent procedures

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

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

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

It is Novartis' policy for multi-center clinical trials that the first publication is based on consolidated data from all centers, analyzed as stipulated in the protocol and agreed upon by investigators before trial initiation.

11 Protocol adherence

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

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

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

11.1 Protocol Amendments

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

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13 Appendix 1: Clinically notable laboratory values and vital signs

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. No specific action is pre-defined within this protocol to respond to specific abnormal laboratory values, as it will be decided by the investigator/qualified site staff whether and which specific action needs to be taken to respond to any abnormal values, taking into account the overall status of the subject.

Liver Function and Related Variables

ALT (SGPT):	> 3 x Upper Limit of Normal (ULN)
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)

Blood Pressure and Heart Rate

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. Notable blood pressure will be hypertension (systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg) or hypotension (systolic blood pressure of <90 mmHg and/or a diastolic blood pressure of <60 mmHg). A blood pressure indicative of prehypertension (systolic blood pressure of 120 to

<140 mmHg and/or diastolic blood pressure of 80 to <90 mmHg) will not be regarded as notable.

A normal pulse rate will be defined as a rate of 60 to 100 beats per minute (bpm). 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 patient. No specific action is foreseen as part of the study protocol.

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

Table 14-1: Liver Event Definitions

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

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

Table 14-2: Liver Event Follow Up Requirements

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

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

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

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

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

15 Appendix 3: 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.

16 Appendix 4: 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	Very 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.