NOVARTIS

Clinical Development

Secukinumab, AIN457

Clinical Trial Protocol CAIN457AFR01 / NCT02595970

A 52-week (plus extension until commercialization), single-arm study to evaluate psoriasis severity and its psychosocial impact using the Simplified Psoriasis Index at 16 weeks, as well as long-term safety, tolerability and efficacy of secukinumab administered subcutaneously in patients suffering from moderate to severe psoriasis.

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List of abbreviations

AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST (SGOT)	Aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
BISF-m/w	Brief Index of Sexual Functioning (man or woman)
BL	Baseline
BSA	Body Surface Area
CI	Confidence Interval
CRO	Contract Research Organization
CS	CorticoSteroids
CsA	Cyclosporine A
CT	Computed Tomography
DLQI	Dermatology Life Quality Index
DS&E	Drug Safety and Epidemiology
ECG	ElectroCardioGram
eCRF	electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
EOE	End of Extension
EOT	End of Treatment
FAS	Full Analysis Set
FU	Follow-Up
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transpeptidase
hCG	Human Chorionic Gonadotropin
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
i	Intervention
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IL	Interleukin
i.m.	Intramuscular
IN	Investigator Notification

IRB	Institutional Review Board
IS	Included Set
IUD	IntraUterine Device
IUS	IntraUterine System
i.v.	Intravenous
LDL	Low Density Lipoprotein
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
p	Psychosocial
PASI	Psoriasis Area and Severity Index
PFS	Pre-Filled Syringes
PPS	Per Protocol Set
Pro	Professional
PRO	Patient-Reported Outcome
PsA	Psoriatic Arthritis
PT	Preferred Term
PUVA	Psoralen + UVA therapy
QFT	QuantiFERON TB-Gold test
RBC	Red Blood Cell
REB	Research Ethics Board
s	Severity
s.c.	Subcutaneous
sa	Self-assessed
SA	Self-Administered
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SD	Standard Deviation
SGA	Subject's Global Assessment
SOC	System Organ Class
SPI	Simplified Psoriasis Index
TB	Tuberculosis
TCS	Topical CorticoSteroids
TEAE	Treatment-Emergent Adverse Event
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal

UV	UltraViolet
VAS	Visual Analog Scale
W	Week
WBC	White Blood Cell
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Baseline	Time point before attribution of study treatment (Visit 1) All Baseline assessments should be performed at the latest immediately prior to the first study treatment administration *i.e.* at Visit 0 and Visit 1
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product."
Patient number	A number assigned to each patient who enrolls into the study
Period	The planned stage of the patients' participation in the study. Each period serves a purpose in the study as a whole. Typical periods are: determination of patient eligibility, wash-out of previous treatments, exposure of patient to treatment or to follow-up of patients after treatment has ended.
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study drug administration and all assessments (including follow-up)
Investigational drug discontinuation	Point/time when patient permanently stops taking investigational drug for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 1

Amendment rationale :

The purpose of this amendment is to modify the inclusion criteria N°3 :

" Patients eligible for treatment with a biotherapy i.e. not adequately controlled with at least two conventional systemic therapies (including methotrexate, cyclosporine, phototherapy). "

To
" Patients candidates for systemic therapy. "

This modification is in line with the positive opinion published on November 2014 by the Committee for Medicinal Products for Human Use (CHMP) opinion. Cosentyx (secukinumab) was recommended by the CHMP as new treatment option for psoriasis with the following indication :

"Cosentyx® (Secukinumab, INN) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy."

Changes to the protocol are related to the following sections:

- Section 1 Introduction
- Section 3.6 Risks and benefits
- Section 4 Population
- Section 4.1 Inclusion criteria

Amendment 2

Amendment rationale :

The purpose of this amendment is to modify the inclusion criterion N° 14 and add one exclusion criterion and one precaution for use :

N° 14 : "Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for **16** weeks after stopping treatment."

To

N° 14 : "Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for **20** weeks after stopping treatment."

N° 20 : Patients with a history of hypersensitivity to latex.

The following precaution for use is added after the list of exclusion criteria :
"Caution should be exercised when prescribing Cosentyx® to patients with Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both Cosentyx® and placebo groups. Patients who are treated with Cosentyx® and have Crohn's disease should be followed closely."

The changes are in line with the Summary of Product Characteristics and the Health Authority (ANSM) requests.

Changes to the protocol are related to the following section:

- Section 4.2 Exclusion criteria

Amendment 3

Amendment rationale :

The purpose of this amendment is to use the Cosentyx Summary of Product Characteristics as reference document to assess whether reported adverse events are of expected or unexpected nature.

Amendment 4

Amendment rationale :

The purpose of this amendment is to bring clarifications to the study population, to define baseline, to update instructions for administration of questionnaires, to correct inconsistencies about X-ray assessment as well as other minor inconsistencies, and to add details on PASI, BSA and IGAmod2011 assessments. The reason for these changes is feedback from the first initiated study sites.

List of changes and reasons are given below:

- to clarify the inclusion criteria 2: 'Patient with a history of chronic M/S psoriasis …' Protocol requests that patient have moderate to severe psoriasis for at least 6 months. It is not requested that patients have documented PASI and IGA scores 6 months before inclusion. These scores are assessed at inclusion.
- to add exclusion criteria 21: 'Form of psoriasis other than plaque … ' As the SPI contains question on erythrodemic and pustular psoriasis (this questionnaire is intended for all forms of psoriasis), it might be understood that such patients could be included. In line with non inclusion criterion n° 5 'Patient with skin condition other than M/S plaque psoriasis that may confound psoriasis evolution … ', a specific non inclusion criterion is added.
- to define the Baseline visit in The Glossary of terms table. No formal definition was given in previous version of the protocol.
- to clarify assessments described in Table 6-1 and Section 6.2 at screening visit:
  - to delete reference to the Educational prospect at Baseline (there was a confusion between the question on education level at V0 and the optional Education prospect questionnaire)
  - to correct the delay for X-ray (from 6 months to 12 weeks) in accordance with exclusion criteria n° 17 (now § 6.2.1.3).
  - to add a formal description of IGAmod2011 and BSA (now § 6.2.1.4&5).
  - In Table 6.1:
    - to add assessment of PASI score at V0, in line with amended inclusion criterion # 1.
    - to correct 'Optional Education level' to 'Education level'(same confusion as cited above).
    - to add foot note on home administration of study drug (to be consistent to § 5.5.4.1).
- to add Baseline definition and time of completion of scores in § 6.3.
- to add instructions for the order of psoriasis questionnaires and scores (now § 6.5.1).

- PASI scores section was updated to provide the full table of detailed measurements for the PASI score (now § 6.5.1.2).
- to clarify the PRO questionnaire completion in § 8.3 (Questionnaires will not be completed at home).
- to update the PASI and SAPasi scores detailed in Appendix.

Changes in the Informed consent form

- to correct the table of evaluations in the Informed consent form:
    - deletion of the questionnaire on the impact of psoriasis on education prospects and work limitations at V0 (same confusion as cited above);
    - addition of PASI evaluation at V0 (to be consistent with amended inclusion criterion 1).

Amendment 5

Amendment description and rationale :

The purposes of this amendment and reasons for changes are:

- to add an extension treatment period until 3 January 2017 or until commercialization of Cosentyx in France, whichever occurs first. The aim of this extension is to prevent any interruption of Cosentyx treatment for patients who are deemed to be benefiting from the study drug and to collect further safety data.

  Because current LPLV is planned on 3 January 2017, this extension treatment period will not increase the overall treatment period of this study.
- to delete the optional assessment related to the education prospects and work limitations questionnaire (DANIELE) [redacted]
- to specify the optional nature of band neutrophils (an intermediary step prior to the complete maturation of segmented neutrophils) in hematology evaluations, to do this assessment in optional. This is related to the feedback from the first patients' data showing that this tests was unfrequently performed;
- to correct inconsistencies about the record of AEs occurring after signature of informed consent form and before starting investigational treatment on Case Report Form, due to the feedback of such initiated study sites;
- to update the method of analysis of primary objectives and secondary variables because the more appropriate statistical analysis for an one armed trial is a paired t-test;
- to specify the sample size calculation based on an analysis of paired differences;
- and other minor inconsistencies for clarify (1) the amendment 4 rational, (2) the use of regimen of topical corticosteroids and the record of procedures, (3) significant non-drug therapies recorded on CRFs due to the feedback of such initiated study sites.

These changes to the protocol are related to the following sections:

- About the extension treatment period
  - Section 2.2 Secondary objectives
  - Section 3.1 Study design
  - Section 3.2 Rationale of study design
  - Section 4.1 Inclusion criteria

- Section 5.5.5 Extension period
- Section 6 Visit schedule and assessments
- Section 9 Data analysis

- About the Daniele questionnaire:
  - Section 2.3 Exploratory objectives
  - Section 6.5.1 Psoriasis questionnaires and scores
  - Section 6.7.2 Education prospects and work limitations
  - Section 8.3 Database management and quality control
  - Section 9.7 Exploratory analyses
  - Appendix 8 Education prospects and work limitation
  - Section 12 References
- About the optional nature of band neutrophils:
  - Table 6-1 Assessment schedule
  - Section 6.6.4 Laboratory evaluations
- About the record of AEs on CRFs:
  - Section 7.1 Adverse events
- About the methods of statistical analysis:
  - Section 9.1 Analysis sets
  - Section 9.4 Treatments
  - Section 9.5 Analysis of the primary and key secondary variable(s)
  - Section 9.6 Efficacy variables
- About the Sample size calculation:
  - Section 9.9 Sample size calculation
- About the other minor inconsistencies:
  - Section 5.5.7 Prior and concomitant treatment
  - Section 5.5.8 Prohibited Treatment (Table 5-1 Prohibited Treatment)
  - Section 12 References

Protocol synopsis

Protocol number	CAIN457AFR01
Title	A 52-week (plus extension until commercialization) single-arm study to evaluate psoriasis severity and its psychosocial impact using the Simplified Psoriasis Index at 16 weeks, as well as long-term safety, tolerability and efficacy of secukinumab administered subcutaneously in patients suffering from moderate to severe psoriasis
Brief title	Study of the severity and psychosocial impact on patients suffering from moderate to severe psoriasis treated by secukinumab
Sponsor and Clinical Phase	Novartis, Phase IIIb
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Chronic plaque psoriasis is a common inflammatory dermatosis that can have a profound impact on a patient's life as it can cause major distress since it impacts on physical and psychological functioning. A new tool has been developed (Simplified Psoriasis Index: SPI), to provide a concise but holistic summary of psoriasis assessment. It has several advantages over current tools: 1) it evaluates specifically several critical localizations (scalp, face, hands, feet, anogenital skin); 2) it is assessed by both the physician (proSPI component) and the patient (saSPI); and 3) it assesses psychological impact and includes historical features. This single-arm study is designed to evaluate the psoriasis severity and its psychosocial impact using the SPI at 16 weeks in patients suffering from moderate to severe psoriasis and treated by secukinumab. This index comprises 3 components: severity (s), psychosocial (p) and intervention, (i) evaluated by both the physician (proSPI) and the patient (self-assessed: saSPI). This study will assess the changes from Baseline of the severity (s) component of SPI evaluated by both the physician (proSPI (s)) and the patient (saSPI (s)). In order to collect efficacy and safety data related to the long-term administration of secukinumab, patients will be followed up to 56 weeks.
Primary Objective(s) and Key Secondary Objective	**Primary objective:** To evaluate the benefit of secukinumab on the severity of psoriasis

	based on the SPI (Simplified Psoriasis Index). This index comprises 3 components: severity (s), psychosocial (p) and intervention (i) evaluated by both the physician (proSPI) and the patient (self-assessed: saSPI). Only the severity (s) component will be evaluated for the primary objective (both proSPI (s) and saSPI (s)). Changes at Week 16 compared to Baseline in patients suffering from moderate to severe plaque psoriasis will be analyzed. **Key secondary objectives:** • To assess PASI (weekly from week 0 to 4 then every 4 to 8 weeks until Week 56). • To evaluate correlation between PASI and proSPI (s).
Secondary Objectives	• To assess each component of proSPI (s, p and i) over time (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56). • To assess each component of saSPI (s, p and i) over time (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56). • To assess DLQI over time (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56). • To assess self-administered PASI (SA-PASI) (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56). • To assess pain, itching and scaling using the Psoriasis Symptom Diary questionnaire over time (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56). • To evaluate correlation between proSPI (for each component: s, p and i) and DLQI. • To evaluate correlation between proSPI (for components p and i) and PASI. • To evaluate safety during the treatment period (until the W52) and during the extension period (after the W52)
Exploratory Objectives	• To evaluate correlation between saSPI (for each component: s, p and i) and DLQI. • To evaluate correlation between proSPI and saSPI for component s and p. • To evaluate correlation between saSPI (s) and PASI. • To evaluate the ability of SPI to discriminate between responders and non-responders based on PASI response. • To explore sexual dysfunction using the Brief Index of Sexual Functioning (BISF-m or BISF-w) questionnaire (in a subset of subjects willing to complete sexual function questionnaire).

Study design	This is an open-label multicenter, single arm study in approximately 120 patients with moderate to severe psoriasis in approximately 20 centers in France. The study consists of three periods (Screening, Treatment and Follow-up) with a total of 15 visits and 16 injections with investigational drug. Eligible patients who have received their injection of study drug at W48 before Cosentyx® is marketed in France will enter the extension period to receive secukinumab until commercialization of Cosentyx® in France. Patients who have received their last injection (W48) after secukinumab is marketed in France will complete the study as initially planned (EOT visit at W52 and Follow-up visit at W56). An initial one-month (maximum) screening period after screening visit allows wash-out of prohibited medications prior to starting the study. Eligible patients are scheduled to receive weekly injections of investigational drug during the first month (induction period), followed by monthly injections thereafter to Week 16. The primary objective will be assessed at 16 weeks prior to injection of investigational drug at this visit. If the investigational drug is judged by the investigator and patient to be beneficial to the patient, the response to treatment will be considered to be favorable and monthly injections will continue to Week 48. In the absence of a favorable response at Week 16, the investigational drug will be discontinued and the patient should attend End of Treatment visit and will then enter the follow-up period (after EOT visit, the investigator will discuss with the patient the best treatment options). Treatment should last a maximum of 12 months, except for patients receiving their W48 injection of study drug before secukinumab is marketed in France. Patient receiving their W48 injection of study drug before secukinumab is marketed in France will enter an extension period until 3 January 2017 (LPLV) or until commercialization of secukinumab in France, whichever occurs first. Patients will be monitored over a further eight weeks after the last injection of investigational drug. LPLV will be no later than 3 January 2017, therefore the last possible administration of secukinumab during the study can be 3 November 2016 at the latest, whether Cosentyx® is commercialized or not.
Population	The study population will consist of adult male and female out-patients (≥ 18 years old) with a history of moderate to severe plaque psoriasis for at least 6 months before the screening visit and who are candidates for systemic therapy. Patient may either have received previous biotherapy or be biological naïve. At screening visit, patients need to have the following scores: PASI ≥ 12; Body Surface Area: BSA ≥ 10 and Investigator Global Assessment: IGA mod 2011 ≥ 3. At baseline visit, patients need to have a PASI score ≥ 12.

	It is planned to include a total of approximately 100 patients in around 20 centers. Anticipating a drop-out of 20 patients, approximately 120 patients will need to be screened.

Inclusion criteria	• Patients aged ≥ 18 years old at the Screening visit. Patients with a history of chronic moderate to severe plaque psoriasis for at least 6 months before the Screening visit. Furthermore, patients need to have the following scores:
	  • PASI ≥ 12, BSA ≥ 10 and IGA mod 2011 ≥ 3 at Screening visit and
	  • PASI ≥ 12 at Baseline visit
	• Patients candidates for systemic therapy
	• Patients able to understand and communicate with the investigator and comply with the requirements of the study (including administration of s.c. injections at home), capable of and willing to complete several questionnaires at visits, and must provide written, signed and dated informed consent before any study related activity is performed.
	• For the extension treatment period (Patient who receiving their injection of study drug at W48 before Cosentyx® is marketed in France): favorable clinical benefit of study treatment as judged by the investigator and patient. Patient willing to continue receiving secukinumab.

Exclusion criteria	1. Patients with a history of hypersensitivity to the study drug or to drugs of a similar chemical class. 2. Patients with recent (previous 6 weeks) or planned vaccination with live virus. 3. Patient participation in another clinical study during the 4 weeks prior to study drug initiation or 5 half-lives (whichever is the longest). 4. Patients taking other drugs for psoriasis (e.g. corticosteroids, vitamin D analogs, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids). 5. Patients suffering from a skin condition other than moderate to severe plaque psoriasis that may confound psoriasis evaluation, or other inflammatory disease. 6. Patients suffering from drug-induced psoriasis (e.g. new onset or current exacerbation by beta-blockers, calcium channel inhibitors, or lithium), as judged by investigator. 7. Patients with underlying condition(s) (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiovascular (eg: heart failure NYHA class III or IV, unstable angina….), infectious,

	gastrointestinal or psychiatric) which in the opinion of the investigator significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy). 8. Patients with previous treatment with any agent targeting Interleukin (IL)-17 directly or IL-17 receptor (e.g. secukinumab, ixekizumab, or brodalumab). 9. Patients refusing to limit sunlight or Ultraviolet (UV) light exposure. 10. Patients unwilling to be subjected to repeated s.c. injections and venipuncture. 11. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis (TB) infection as defined by a positive or indeterminate QuantiFERON TB-Gold test (QFT) at screening visit. Patients with a positive QFT test may participate in the study if a full tuberculosis work up (according to local practice/guidelines) completed at least 12 weeks prior to study drug initiation establishes conclusively that the patient has no evidence of active tuberculosis. If the presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to guidelines for at least 4 weeks prior to study drug initiation. 12. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed). 13. Pregnant or nursing (lactating) women (where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test). 14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 20 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 6 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 methods (a+b or a+c or b+c): a. Use of oral, injected or implanted hormonal methods of contraception or other forms or hormonal contraception that have complete efficacy (failure <1%), e.g. 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 use of oral contraception, women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment. NOTE: Women are considered post-menopausal and not of child-bearing potential if they have had: • 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms). • Surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential. 15. Active systemic infections during the 2 weeks prior to study drug initiation (exception: common cold) or any infection that reoccurs on a regular basis; investigator discretion should be used regarding patients who have traveled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for patients with underlying conditions that may predispose them to infection, such as advanced or inadequately controlled diabetes.

	16. Past medical history record of, or current infection at study drug initation with, human immunodeficiency virus (HIV), hepatitis B or hepatitis C. 17. Chest X-ray, computerized tomography (CT scan), or Magnetic Resonance Imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to investigational drug administration, and evaluated by a qualified physician. 18. Serum creatinine level exceeding 2.0 mg/dL (176.8 μmol/L) at screening visit. 19. Total white blood cell (WBC) count <2 500/μL, platelets <100 000/μL, neutrophils <1 500/μL or hemoglobin <8.5 g/dL at screening visit. 20. Patients with a history of hypersensitivity to latex. 21. Forms of psoriasis other than plaque psoriasis (e.g., pustular psoriasis, palmoplantar pustulosis, erythrodermic and guttate psoriasis). Caution should be exercised when prescribing Cosentyx® to patients with Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both Cosentyx® and placebo groups. Patients who are treated with Cosentyx® and have Crohn's disease should be followed closely.
Investigational and reference therapy	The investigational drug, secukinumab AIN 457, is to be injected subcutaneously and will be provided by Novartis in pre-filled syringes (PFS) of 150 mg. Two injections will therefore be necessary to obtain the required dosage of 300 mg. The patient will be trained by the investigator or qualified personnel and will be encouraged to self-administer the injections at the investigation site at each visit until Week 16. Thereafter, the patient will be asked to self-administer the injection at the investigation site when attending a site visit (Weeks 24, 32, 40 and 48) or at home between visits (Weeks 20, 28, 36 and 44). If patient is not comfortable with self-injections, injections at home can be performed by a caregiver.
Efficacy assessments	The following patient-reported outcomes will be used: • ProPSI and saSPI. • PASI. • SA-PASI. • DLQI. • PSD (pain, itching, scaling).

Safety assessments	• Adverse Events. • Physical examination. • Vital signs. • Hematology/Biochemistry.
Other assessments	• BISF-w/m (optional) •
Populations	The following analysis sets will be used in this study: • Included Set (IS): The included set will comprise all patients included in the study. • Full Analysis Set (FAS): The FAS will comprise all patients from the IS administered at least one dose of investigational drug during the treatment period with at least one Baseline and one post-Baseline SPI evaluation. • Safety Analysis Set (SAF): The SAF will comprise all patients administered at least one dose of investigational drug during the treatment period. • Per Protocol Set (PPS): The PPS will comprise all patients administered at least one dose of investigational drug during the treatment period without any major protocol deviation.
Data analysis	**Primary analysis** The primary variables for this study are the changes from Baseline of proSPI (s) and saSPI (s) at Week 16. The primary analysis of this study will be performed on the FAS population at Week 16 compared to Baseline and will be: • To evaluate the change from baseline of proSPI (s). • To evaluate the change from baseline of saSPI (s). The key secondary variable for this study is the PASI score. The key secondary analysis will be to assess PASI and to evaluate the correlation between PASI and proSPI (s) in the FAS. **Statistical model, hypothesis, and method of analysis** Summary statistics (mean, standard deviation, median, extreme values) will be presented for changes from Baseline to Week 16 (proSPI (s), saSPI (s) and PASI) for all patients in the FAS. To assess the primary objective, the proSPI (s) and saSPI (s) will be analyzed using a paired t-test (baseline vs Week 16). The null hypothesis tested in this model is that there is no difference between means at baseline and Week 16. As there are co-primary endpoints an adjustment for multiplicity

	will be performed using the Hochberg procedure and the family-wise type-I-error will be set to α=5% (2-sided). The Hochberg procedure was chosen as the most powerful adjustment due to the positive association between proSPI (s) and saSPI (s) (L Chularojanamontri et al., 2013). The Hochberg procedure will be applied as follows, if the maximum of the two p-values is rejected at the 5% level (2-sided) then both hypotheses are rejected and statistical significance is claimed for both endpoints. Otherwise if the maximum of the 2 p-values is not rejected, then the minimum p-value is tested at the 2.5% level (2-sided), if rejected then statistical significance is claimed just for this endpoint. In the event the data is non-normal the Wilcoxon signed rank test will be performed. Evolution of PASI score and PASI response during the study will be described and associated 95% CIs will be presented. Change from baseline to Week 16 of the PASI score will be analyzed as for the primary analysis. Spearman's correlation coefficient and the associated test will be used to evaluate the correlation between PASI and proSPI (s). The same analysis will be performed on the PPS population as supportive. **Secondary analysis** Absolute values and change from baseline (at all assessment periods) for each SPI component will be described and analyzed as for the primary efficacy analysis. ProSPI (s) and saSPI (s) will be analyzed using a paired t-test. For each of the seven scores of the DLQI the percentage change from baseline will be derived. Summary statistics will be provided for absolute values as well as for the percentage change by visit and treatment group. Summary statistics will be provided for number of subjects achieving DLQI 0 or 1. Absolute values and change from baseline of the sa-PASI (at all assessment periods) will be described. For PSD, descriptive summary statistics will be presented for absolute values and change from baseline by visit for intensity of pain, itching and scaling. Relationships between scores will be explored using Spearman's correlation coefficient and the associated test. Appropriate statistical tests performed on these secondary efficacy

	variables will be detailed in the SAP. **Exploratory analysis** Correlations between saSPI and DLQI, between saSPI (s) and PASI, and between proSPI and saSPI (component s and p) will be evaluated using the Spearman correlation coefficient and the associated p-value. To explore sexual dysfunction, descriptive summary statistics will be presented for absolute values and change from baseline of BISF-m and BISF-w scores. An analysis of the SPI responsiveness to change will be led in order to investigate if reductions in psoriasis severity resulting from treatment would be accompanied by corresponding reductions in proSPI–s and saSPI–s scores. This analysis will be performed by the calculation of receiver operating characteristic (ROC) area under the curve (AUC). Three criteria of response will be examined to evaluate each score: ≥75, ≥90, and 100% reduction in PASI score. **Safety analysis** All safety evaluations will be performed on the SAF. Treatment-emergent adverse events (TEAEs: events starting after the first dose of investigational drug or events present prior to the first injection of investigational drug but with increased severity) will be summarized by PT. AEs will be summarized by presenting the number and percentage of patients with: • An AE. • An AE by primary SOC. • An AE by PT. Summaries will also be presented for AEs by severity and for investigational drug related AEs. If a patient reports more than one AE with the same PT, only the greatest severity will be presented for this AE. If a patient reports more than one AE within the same primary SOC, the patient will be counted only once with the highest severity at the SOC level, where applicable. All other information collected will be tabulated and listed as appropriate. Separate summaries will be provided for any death, SAE, any other significant AE leading to investigational drug discontinuation. These summaries will be presented for the whole study period.

	Sample size calculation The sample size calculation is based upon the SPI variable which is the primary endpoint. A similar study by Chularojanamontri *et al.* J Inv dermatol 2013 showed that it is possible to detect responsiveness and a minimum clinically important difference (an absolute change of 5 and 7 for proSPI (s) and saSPI (s), respectively) derived from PASI changes with n=100 patients. The study showed a standard deviation at week 10 in change from baseline of 7.35 in proSPI (s) and 10.35 in saSPI (S) as the standard deviation at week 16 is expected to be higher, conservative standard deviation estimates of 14 and 19 will be assumed for change at week 16 for proSPI (s) and saSPI (s) respectively. Based on an analysis of paired differences, in order to have at least 90% power to detect a significant clinical difference for each index at the 2.5% level (2-sided), it can be estimated that a sample size of 100 evaluable patients would be sufficient. Taking into account an anticipated drop-out of 20 patients, 120 patients will need to be included in the study.
Key words	Chronic moderate or severe plaque psoriasis, secukinumab, biologic, IL-17, AIN457, SPI, PASI.

1 Introduction

Chronic plaque psoriasis is a common inflammatory dermatosis that can have a profound impact on a patient's life as it can cause major distress since it impacts on physical and psychological functioning. The skin lesions associated with plaque psoriasis are associated with significant symptoms, such as itching, pain and scaling, which can ultimately impact a patient's emotional, social, occupational, and physical functioning (Chularojanamontri *et al*., J Inv Dermatol 2013, Lebwohl *et* al. Int J Dermatol 2013). Most commonly tools used to assess the severity and impact of psoriasis are the PASI (Psoriasis Area and Severity Index) and the DLQI (Dermatology Life Quality Index). Limitations of the PASI are inter-rater variability (Lebwohl *et* al. Int J Dermatol 2013, Ramsey & Lawrence, BJD 1991), requirement for cumbersome arithmetic that discourages most clinicians from using it in routine and modest correlation with Patient Reported Outcomes (PRO) and patient satisfaction (Schäffer *et al.* Eur J Dermatol 2010). In addition, it does not take into account the importance of specific localizations (hands, feet, buttocks, genitals).

Secukinumab (AIN457) is a human monoclonal antibody that selectively inhibits interleukin-17A. [redacted] Outstanding response rates have been demonstrated in pivotal phase II and III studies (Rich *et al.*, BJD 2012); Langley *et al.*, NEJM 2014; Blauvelt *et al.*, BJD 2014). Phase III development has used PASI and DLQI.

In November 2014, the CHMP (Committee for Medical Products in Human Use) has granted a positive opinion including the following indication : "Cosentyx® is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy".

Secukinumab is administered subcutaneously at a dosage of 300 mg per week during the induction phase (first month) and thereafter at a dosage of 300 mg per month. Such a regimen and dosage have been demonstrated to be the most efficient in patients in the pivotal studies (data on file).

A new tool has been developed (Simplified Psoriasis Index: SPI), to provide a concise but holistic summary of psoriasis assessment. It has several advantages over current tools: 1) it evaluates specifically several critical localizations (scalp, face, hands, feet, anogenital skin); 2) it is assessed by both the physician (proSPI component) and the patient (saSPI); and 3) it assesses psychological impact and includes historical features. The responsiveness to clinical changes measured using this tool has already been studied recently in patients initiating a new treatment for plaque psoriasis (Chularojanamontri *et al*., J Inv Dermatol 2013).

This study will assess the changes from Baseline of SPI and its correlation with standard tests DLQI and PASI.

2 Study objectives

2.1 Primary and key secondary objectives

2.1.1 Primary objective

To evaluate the benefit of secukinumab on the severity of psoriasis based on the SPI (Simplified Psoriasis Index). This index comprises 3 components: severity (s), psychosocial (p) and intervention, (i) evaluated by both the physician (proSPI) and the patient (self-assessed: saSPI).

Only the severity (s) component will be evaluated for the primary objective (both proSPI (s) and saSPI (s)). Changes at Week 16 compared to Baseline in patients suffering from moderate to severe plaque psoriasis will be analyzed.

2.1.2 Key secondary objectives

- To assess PASI (weekly from week 0 to 4 then every 4 to 8 weeks until Week 56).
- To evaluate correlation between PASI and proSPI (s).

2.2 Secondary objectives

- To assess each component of proSPI (s, p and i) over time (weekly from Week 0 to 4 then every 4 to 8weeks until Week 56).
- To assess each component of saSPI (s, p and i) over time (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56).
- To assess DLQI over time (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56).
- To assess self-administered PASI (SA-PASI) (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56).
- To assess pain, itching and scaling using the Psoriasis Symptom Diary questionnaire over time (weekly from Week 0 to 4 then every 4 to 8 weeks until Week 56).
- To evaluate correlation between proSPI (for each component: s, p and i) and DLQI
- To evaluate correlation between proSPI (for components p and i) and PASI
- To evaluate safety during the treatment period (until the W52) and during the extension treatment period (after the W52)

2.3 Exploratory objectives

- To evaluate correlation between saSPI (for each component: s, p and i) and DLQI.
- To evaluate correlation between proSPI and saSPI for components s and p.
- To evaluate correlation between saSPI (s) and PASI.
- To evaluate the ability of SPI to discriminate between responders and non-responders based on PASI response.

- To explore sexual dysfunction using the Brief Index of Sexual Functioning (BISF-m or BISF-w) questionnaire (in a subset of subjects willing to complete sexual function questionnaire).

3 Investigational plan

3.1 Study design

This is an open-label multicenter, single arm study in approximately 120 patients with moderate to severe psoriasis in approximately 20 centers in France. The study consists of four periods (Screening, Treatment, Extension and Follow-up) with a total of 15 visits, plus a maximum of 4 visits during the extension period.

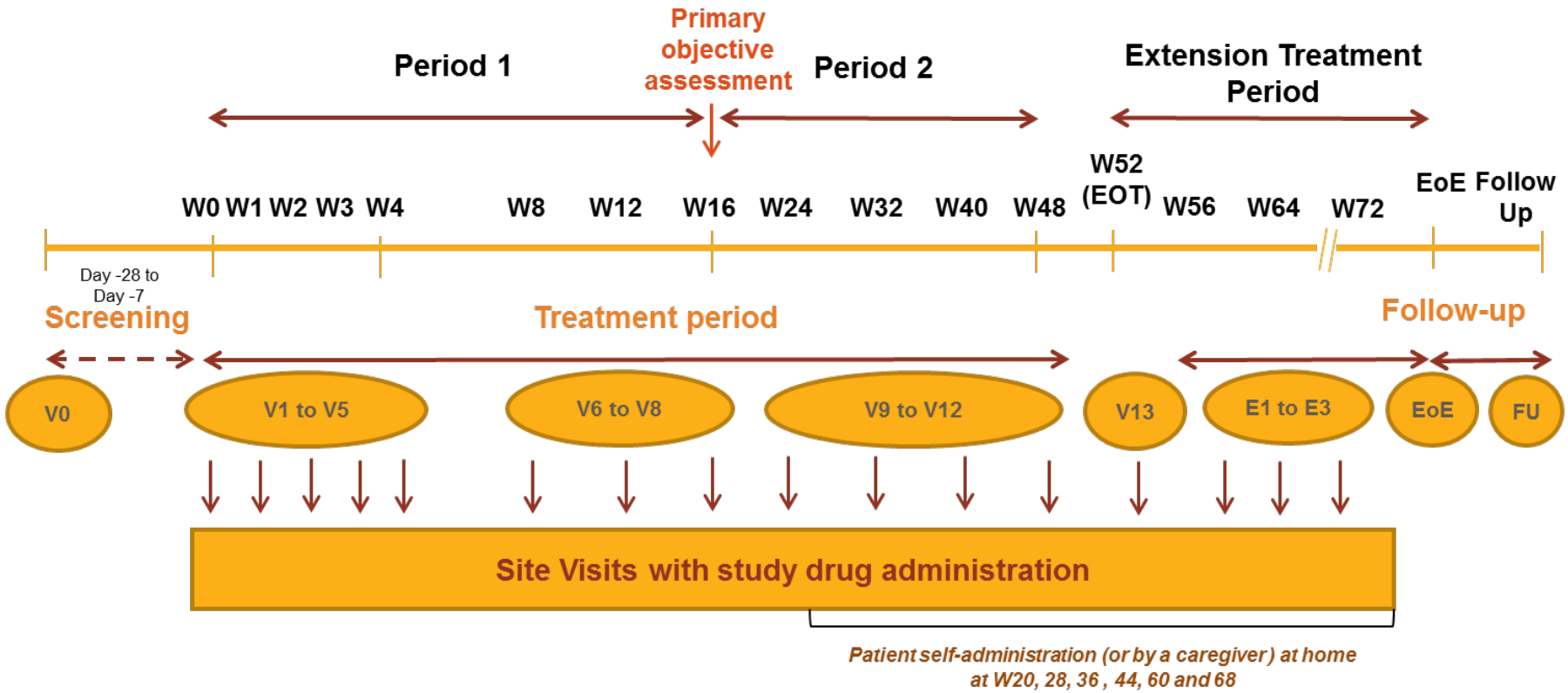
An initial one-month (maximum) screening period after screening visit allows wash-out of prohibited medications prior to starting the study. Eligible patients are scheduled to receive weekly injections of investigational drug during the first month (induction period), followed by monthly injections thereafter to Week 16. The primary objective will be assessed at 16 weeks prior to the administration of investigational drug at this visit. The patient will then continue with monthly injections until Week 48 in case of a favorable response to treatment at week 16 (cf §3.1.2). Treatment should last a maximum of 12 months. Patients will be monitored over a further eight weeks with an End of treatment visit at Week 52.

Patients eligible for the extension period, i.e. having received their injection of study drug at W48 before Cosentyx® is marketed in France, will enter an extension period until 3 January 2017 or until commercialization of Cosentyx® in France, whichever occurs first. LPLV will be no later than 3 January 2017, therefore the last possible administration of secukinumab during the study can be 3 November 2016 at the latest, whether Cosentyx® is commercialized or not.

Patients who have received their last injection (W48) after secukinumab is marketed in France will complete the study as initially planned (EOT visit at W52 and Follow-up visit at W56).

For patients who discontinue study treatment prematurely for any reason during the treatment or extension treatment periods, or for patients who finished the extension treatment period, End of Treatment (EoT) or End of Extension (EOE) visits should be performed 4 weeks after the last administration of study drug. In addition a Follow-up (FU) visit should be performed 8 weeks after the last administration of study drug. An outline of the study design is presented in Table 6.1.

Figure 3-1 Study design



3.1.1 Screening period

Between screening visit (assessment of patient eligibility) and first s.c. injection with secukinumab 300 mg, there is a screening period of 7 to 28 days for wash-out of prohibited medications (detailed in Section 5.5.9).

Baseline assessments should be performed prior to the first study treatment administration, *i.e.* at Week 0 and Visit 1.

3.1.2 Treatment period

During the treatment period, patients will initially attend five weekly visits (induction period), each with a s.c. injection of secukinumab 300 mg. Three subsequent monthly injections to Week 16 are planned. The primary and key secondary endpoints will be assessed at Week 16, prior to injection at this visit. If the investigational drug is judged by the investigator and patient to be beneficial to the patient, the response to treatment will be considered to be favorable and monthly injections will continue to Week 48. In the absence of a favorable response at Week 16, the investigational drug will be discontinued and the patient should attend End of Treatment visit and will then enter the follow-up period (after EOT visit, the investigator will discuss with the patient the best treatment options). The maximum duration of the treatment period is approximately 12 months (not including follow up) and the maximum number of sits visits is 12.
Patients who discontinue the investigational drug prematurely for any reason (other than withdrawal of informed consent) should performed the End of Treatment visit 4 weeks after last injection of investigational drug and enter the post-treatment follow-up period.

3.1.3 Extension period

Eligible patients who have received their injection of study drug at W48 before Cosentyx® is marketed in France will enter the extension period until 3 January 2017 or until commercialization of Cosentyx® in France, whichever occurs first.
During this extension they will continue to receive monthly injections until End of Extension visit. They will continue to attend the study site every 2 months and self-inject study drug at home between site visits. In case the commercialization is announced as imminent, subjects will be asked to return at study site on the date of the next scheduled injection where they will receive their last injection of study drug. They will then return to the site for the EOE and follow-up visits.
The maximum duration of the extension period is approximately 8 months (including follow up), assuming that the current date of First Patient Last Treatment (FPLT) is expected in May 2016 and the latest possible date for Last Patient Last Visit is 3 January 2017. The potential maximum number of site visits is 4: three visits every 2 months (with study drug administration) and the End of Extension visit planned 4 weeks after last study drug administration. LPLV will be no later than 3 January 2017, therefore the last possible administration of secukinumab during the study can be 3 November 2016 at the latest, whether Cosentyx® is commercialized or not.

For patients who discontinue study treatment prematurely for any reason (other than withdrawal of informed consent) during the extension treatment period or patients who finish the extension treatment period, End of Extension (EoE) visit should be performed 4 weeks after the last administration of study drug.

3.1.4 Follow-up period

All patients should attend an End of Extension visit, even if they do not complete the study for any reason (other than withdrawal of inform consent), in order to collect safety data.

For all patients, a Follow-up visit should be performed 8 weeks after the last administration of study drug.

3.2 Rationale of study design

The design of this study, including the extension treatment period, is based on previous Phase III trials and published data for the treatment of psoriasis with secukinumab. The primary endpoint will be assessed at Week 16 (Visit 8) and efficacy and safety will be monitored at each visit. However, patients should continue treatment with investigational drug for a further 32 weeks (8 more injections between Weeks 16 and 48: Visits 9 to 12). Patients who are deemed to be benefiting from the study drug after 48 weeks of treatment could be continuously treated until 3 November 2016 or until commercialization of Cosentyx® in France, whichever occurs first.

There will be an End of Treatment visit at Week 52, an End of Extension visit four weeks after last injection of study drug and a Follow-up visit in order to collect efficacy and safety data related to the long-term administration of secukinumab.

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

The dose of secukinumab chosen in this study (2 x 150 mg injection; 300 mg) is the dose which combines maximum efficacy with maximum safety. There will be an initial induction phase (weekly injections) before switching to monthly injections, with a follow-up period in order to monitor the long-term efficacy and safety of secukinumab 300 mg administration. These schedules are in keeping with previous studies (for psoriasis and other indications such as rheumatoid arthritis) and are not expected to give rise to any safety concerns. The s.c. route was chosen for injection in this study (to facilitate patient self-administration). Details are provided in the Cosentyx Summary of Product Characteristics.

3.4 Rationale for choice of comparator

Not applicable since this is a study with a single arm.

3.5 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned in this study.

3.6 Risks and benefits

[redacted] Full safety results including all reported AEs are currently available for several completed studies across different indications. In general, these show comparable numbers of AEs in patients treated with secukinumab compared to placebo without indication of any specific organ toxicity. The Cosentyx Summary of Product Characteristics provides a more detailed review of the pre-clinical and clinical information related to secukinumab.

At the time of finalization of this protocol, safety data including AE data, laboratory parameters, available immunogenicity data from the completed studies and SAE data from the ongoing larger studies have not highlighted any individual safety risk or particular pattern of event clustering. Any future changes to benefit/risk ratio resulting from data that becomes available from the Phase III studies will be communicated as needed and appropriate (e.g. via the Cosentyx Summary of Product Characteristics).

In common with other biologic immune modulators, secukinumab has the potential to interfere with the immune response to infections. Thus, continuing vigilance will be applied with respect to capturing all information concerning treatment-emergent infections or infestations. A number of different infections have been reported for patients receiving secukinumab and these are summarized in the Cosentyx Summary of Product Characteristics. [redacted] Taking into account all AE data from the completed studies and SAE data from ongoing studies, no specific pattern of infection, or a specific pathogen involved, has been identified as clearly prevalent.

The effect of secukinumab on vaccination has been evaluated in a study in adult healthy volunteers exposed to a single 300 mg s.c. dose of secukinumab in addition to vaccination with the influenza and meningococcus vaccines [redacted] administration of a single 300 mg dose of secukinumab in adult healthy volunteers vaccinated with influenza and meningitis C vaccines does not impair the efficacy of the immune response to these vaccines. [redacted] Live vaccines should not be administered in patients exposed to secukinumab.

Patients with pre-existing malignancies within the past 5 years are generally excluded from studies with secukinumab, although there is no scientific evidence to suggest that secukinumab would increase the risk for malignancies.

Based upon the results of toxicology studies which demonstrated a lack of effect of secukinumab on fertility and embryo-fetal development, women of child-bearing potential can be included in studies with secukinumab, however, pregnancy must be prevented by proven effective measures. No contraceptive measures are required for males participating in studies with secukinumab.

In summary, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar to or improved compared to approved cytokine-targeting therapies. [redacted]

The risk to patients in this trial will be minimized by compliance with the eligibility criteria and close clinical monitoring.

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

On 21 November 2014, Novartis received Cosentyx® positive CHMP (Committee for Medical Products in Human Use) opinion for the first-line treatment of moderate to severe psoriasis patients. This opinion states that PASI 90, PASI 100 and IGA 0/1 response rates were statistically significantly better with Cosentyx® compared to placebo. Moreover, Cosentyx® was statistically significantly superior to Etanercept in systemic treatment naive, biologic-naive, biologic/anti-tumour necrosis factor (TNF)-exposed and biologic/anti-TNF-failure patients. Finally, most of the reactions were mild or moderate in severity. The proposed indication is: “Cosentyx® is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy”.

4 Population

The study population will consist of adult male and female out-patients (≥ 18 years old) with a history of moderate to severe plaque psoriasis for at least 6 months before the screening visit and who are candidates for systemic therapy. Patient may either have received previous biotherapy or be biological naïve. At screening visit, patients need to have the following scores: PASI ≥ 12; Body Surface Area: BSA ≥ 10 and Investigator Global Assessment: IGA mod 2011 ≥ 3. At baseline visit, patients need to have a PASI score ≥ 12.

It is planned to include a total of approximately 100 patients in around 20 centers. Anticipating a drop-out of 20 patients, approximately 120 patients will need to be screened.

4.1 Inclusion criteria

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

1. Patients aged ≥ 18 years old at the Screening visit.
2. Patients with a history of chronic moderate to severe plaque psoriasis for at least 6 months before the Screening visit.

   Furthermore, patients need to have the following scores:

- PASI ≥ 12, BSA ≥ 10 and IGA mod 2011 ≥ 3 at Screening visit and
- PASI ≥ 12 at Baseline visit

3. Patients candidates for systemic therapy.
4. Patients able to understand and communicate with the investigator and comply with the requirements of the study (including administration of s.c. injections at home), capable of and willing to complete several questionnaires at visits, and must provide written, signed and dated informed consent before any study related activity is performed.
5. For the extension period (patients who received their injection of study drug at W48 before Cosentyx® is marketed in France): favorable clinical benefit of study treatment as judged by the investigator and patient. Patient willing to continue receiving secukinumab.

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. Patients with a history of hypersensitivity to the study drug or to drugs of a similar chemical class.
2. Patients with recent (previous 6 weeks) or planned vaccination with live virus.
3. Patient participation in another clinical study during the 4 weeks prior to study drug initiation or 5 half-lives (whichever is the longest).
4. Patients taking other drugs for psoriasis (e.g. corticosteroids, vitamin D analogs, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids).
5. Patients suffering from a skin condition other than moderate to severe plaque psoriasis that may confound psoriasis evaluation, or other inflammatory disease.
6. Patients suffering from drug-induced psoriasis (e.g. new onset or current exacerbation by beta-blockers, calcium channel inhibitors, or lithium), as judged by investigator.
7. Patients with underlying condition(s) (including, but not limited to metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiovascular (eg: heart failure NYHA class III or IV, unstable angina….), infectious, gastrointestinal or psychiatric) which in the opinion of the investigator significantly immunocompromises the patient and/or places the patient at unacceptable risk for receiving an immunomodulatory therapy).
8. Patients with previous treatment with any agent targeting Interleukin (IL)-17 directly or IL-17 receptor (e.g. secukinumab, ixekizumab, or brodalumab).
9. Patients refusing to limit sunlight or Ultraviolet (UV) light exposure.
10. Patients unwilling to be subjected to repeated s.c. injections and venipuncture.
11. History of an ongoing, chronic or recurrent infectious disease, or evidence of tuberculosis (TB) infection as defined by a positive or indeterminate QuantiFERON TB-Gold test (QFT) at screening visit. Patients with a positive QFT test may participate in the study if a full tuberculosis work up (according to local practice/guidelines) completed at least 12 weeks prior to study drug initiation

establishes conclusively that the patient has no evidence of active tuberculosis. If the presence of latent tuberculosis is established, then treatment must have been initiated and maintained according to guidelines for at least 4 weeks prior to study drug initiation.

12. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for skin Bowen's disease, or basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 12 weeks; carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
13. Pregnant or nursing (lactating) women (where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test).
14. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing of study treatment and for 20 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 6 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 methods (a+b or a+c or b+c):

      a. Use of oral, injected or implanted hormonal methods of contraception or other forms or hormonal contraception that have complete efficacy (failure <1%), e.g. 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 use of oral contraception, women should have been stable on the same pill for a minimum of 12 weeks before taking study treatment.

      NOTE: Women are considered post-menopausal and not of child-bearing potential if they have had:
    - 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms).
    - Surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 weeks ago. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child-bearing potential.

15. Active systemic infections during the 2 weeks prior to study drug initiation (exception: common cold) or any infection that reoccurs on a regular basis; investigator discretion should be used regarding patients who have traveled or resided in areas of endemic mycoses, such as histoplasmosis, coccidioidomycosis or blastomycosis and for patients with underlying conditions that may predispose them to infection, such as advanced or inadequately controlled diabetes.
16. Past medical history record of, or current infection at study drug initation with, human immunodeficiency virus (HIV), hepatitis B or hepatitis C.
17. Chest X-ray, computerized tomography (CT scan), or Magnetic Resonance Imaging (MRI) with evidence of ongoing infectious or malignant process, obtained within 12 weeks prior to investigational drug administration, and evaluated by a qualified physician.
18. Serum creatinine level exceeding 2.0 mg/dL (176.8 µmol/L) at screening visit.
19. Total white blood cell (WBC) count <2 500/µL, platelets <100 000/µL, neutrophils <1 500/µL or hemoglobin <8.5 g/dL at screening visit.
20. Patients with a history of hypersensitivity to latex.
21. Forms of psoriasis other than plaque psoriasis (e.g., pustular psoriasis, palmoplantar pustulosis, erythrodermic and guttate psoriasis).

Caution should be exercised when prescribing Cosentyx® to patients with Crohn's disease as exacerbations of Crohn's disease, in some cases serious, were observed in clinical studies in both Cosentyx® and placebo groups. Patients who are treated with Cosentyx® and have Crohn's disease should be followed closely.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational drug

The investigational drug, secukinumab AIN 457, is to be injected subcutaneously and will be provided by Novartis in pre-filled syringes (PFS) of 150 mg. Two injections will therefore be necessary to obtain the required dosage of 300 mg.

5.1.2 Additional study treatment

No additional treatment.

5.2 Treatment arms

The study is a single arm study.

5.3 Treatment assignment, randomization

Since this is an open label single-arm study, there will be no randomization for this study.

5.4 Treatment blinding

Since this is an open label single-arm study, treatment blinding will not be necessary.

5.5 Treating the patient

5.5.1 Patient numbering

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

Upon signing the Informed Consent Form (ICF), the patient is assigned the next sequential number as given by the investigator using the next blank CRF book available from the EDC system.

5.5.2 Dispensing the investigational treatment

Novartis will supply each study site with investigational drug: Secukinumab 300 mg, provided in two PFS of 1 mL each, labeled with the study number.

5.5.3 Handling of study drug

5.5.3.1 Handling of investigational drug

Investigational drug 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, investigational drug should be stored according to the instructions specified on the label. Clinical supplies are to be dispensed only in accordance with the protocol.

The PFS (150 mg secukinumab) sealed in their outer box must be stored in a locked refrigerator between 2°C and 8°C (36°F and 46°F, DO NOT FREEZE) and must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

Medication labels will be in French in compliance with legal requirements. They will include storage conditions for the investigational drug but no information about the patients.

The investigator must maintain an accurate record of the shipment and dispensing of investigational drug 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. Patients will be asked to return all unused investigational drug and packaging at the end of the study or at the time of discontinuation of investigational drug.

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

5.5.3.2 Handling of other study treatment

Not applicable.

5.5.4 Instructions for prescribing and taking investigational drug

5.5.4.1 Treatment administration

Two PFS of 150 mg secukinumab will be necessary for each injection (total dose: 300 mg).

Investigational drug administration will be either weekly or monthly as described in Section 5.5.4.2.

Secukinumab must be injected subcutaneously in non-affected areas of the skin preferably to one of the following body regions: front of thighs, lower abdomen (but not the area 2 inches around the navel (belly button)) or outer upper arms. A different site should be used for each injection. Secukinumab should not be injected into areas where the skin is tender, bruised, red, scaly or hard, and areas with scars or stretch marks should be avoided. As far as possible, the injection site should be changed from administration to administration, throughout the study.

The patient will be trained by the investigator or qualified personnel and will be encouraged to self-administer the injections at the investigation site at each visit until Week 16. Thereafter, the patient will be asked to self-administer the injection at the investigation site when attending a site visit (Weeks 24, 32, 40 and 48) or at home between visits (Weeks 20, 28, 36 and 44 during the treatment period and Weeks 60 and 68 during the extension period). If patient is not comfortable with self-injections, injections at home can be performed by a caregiver.

All injections must be documented in self-administration log.

All dosages prescribed and dispensed to the patient and any dose or schedule modification during the study must be recorded on the Dosage Administration Record CRF.

5.5.4.2 Treatment periods

There are 3 treatment periods:

- A 4-week induction phase with weekly injections at the investigational site.
- A 12-week treatment period with monthly injections at the investigational site.
- A 32-week treatment period with monthly injections at the investigation site when attending a visit (Weeks 24, 32, 40 and 48) or at home between visits (Weeks 20, 28, 36 and 44).

The primary criterion will be evaluated at the end of the 12-week treatment period (i.e. at Week 16). If the investigational drug is judged by the investigator and patient to be beneficial to the patient, the response to treatment will be considered to be favorable and monthly injections will continue to Week 48. In the absence of a favorable response at Week 16, the investigational drug will be discontinued and the patient should attend End of Treatment visit

and will then enter the follow-up period (after EOT visit, the investigator will discuss with the patient the best treatment options).

5.5.5 Extension period

An extension period (only for patient who have received their injection of study drug at W48 before Cosentyx® is marketed in France): period with monthly injections, every 2 months at the investigation site when attending a visit (Weeks 56, 64 to (maximum) 72, visits E1, E2 to (maximum) E3 or at home between visits (Weeks 60 and (maximum) 68).

If the investigational drug is judged by the investigator and patient to be beneficial to the patient, the response to treatment will be considered to be favorable and monthly injections will continue during the extension period. LPLV will be no later than 3 January 2017, therefore the last possible administration of secukinumab during the study can be 3 November 2016 at the latest, whether Cosentyx® is commercialized or not.

In case the commercialization is announced as imminent, subjects will be asked to return at study site on the date of the next scheduled injection where they will receive their last injection of study drug. They will then return to the site for the EOE and follow-up visits.

In the absence of a favorable response at any time during the extension period, the investigational drug will be discontinued and the patient should attend End of Extension visit and will then enter the follow-up period (after EOE visit, the investigator will discuss with the patient the best treatment options).

5.5.6 Permitted dose adjustments and interruptions of investigational drug

Investigational drug dose adjustments are not permitted during this study.

Temporary interruption of investigational drug is permitted in order to keep the patient on the investigational drug if, in the opinion of the investigator, a patient is deemed to be placed at a safety risk unless dosing is temporarily interrupted. In such cases the investigational drug should be interrupted for only the period when this risk is present and on-going. The investigational drug can be resumed at the next scheduled visit when the investigator considers that there is no further safety risk.

The effect of secukinumab on live vaccines is unknown, therefore, live vaccines should not be administered during the study. Any patient receiving a live virus vaccination during the study must discontinue investigational drug and enter the post-treatment follow-up period.

Any interruption, temporary or permanent must be recorded on the Dosage Administration Record CRF.

5.5.7 Rescue medication

Rescue medication is not permitted in this study.

5.5.8 Prior and concomitant treatment

All treatments administered during the 6 months prior to start of study treatment (including any treatments started during the screening period) will be entered in the eCRF.

All systemic treatments and phototherapies for psoriasis administered prior to screening visit will be entered in the eCRF.

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, administered after the patient was enrolled in the study must be recorded.

5.5.8.1 Concomitant medication permitted for psoriasis treatment

Concomitant medication for psoriasis treatment is restricted to bland emollients (not supplied by Novartis) and other non-medicated interventions if not listed in Table 5-1. If the patient experiences intolerable scaling and/or itching after study drug initiation, the use of bland emollients is permitted but must be avoided during the 12 hours preceding a scheduled study visit/injection. Dose adjustment of any concomitant medication should be avoided during the study and any necessary dose adjustment must be recorded in the eCRF.

A mild to moderate potency topical corticosteroid (TCS) will be allowed for treatment on the face, scalp and the anogenital area during the Screening period but must be stopped the day before the first treatment with the investigational drug.

Anti-histamines and inhaled, ocular or auricular corticosteroids are permitted.

5.5.8.2 Concomitant medication permitted for other conditions

Concomitant medications are allowed if not listed in Table 5-1. Dose adjustment should be avoided during the study and, if necessary, must be recorded in the eCRF.

Any treatment known to worsen psoriasis (e.g. beta-blockers, calcium channel blockers, lithium) must be stable for at least 4 weeks prior to study drug initation and throughout the study.

5.5.8.3 Concomitant medication permitted for psoriatic arthritis

Concomitant medications for psoriatic arthritis are allowed if not listed in Table 5-1. Dose adjustments of these medications should be avoided during the study and, if necessary, must be recorded in the eCRF.

5.5.9 Prohibited Treatment

The use of any of the treatments displayed in Table 5-1, or non-respect of the respective wash-out period before starting investigational drug, that could confound efficacy are prohibited during the study for any indication. If any of these treatments are planned the patient cannot participate in the study.

Patients having had previous treatment with any agent targeting IL-17 directly or its receptor (including secukinumab) cannot participate in the study. During the study, only secukinumab will be allowed.

There must be a 7 to 28-day (±2 days) wash-out period after screening visit prior to start of investigational drug. If this period is not respected, the patient cannot be injected with the investigational drug. Use of any of the listed prohibited medications is NOT allowed after the first injection with the investigational drug. The patient should be instructed to notify the study site about any new treatments he/she takes after the start of the investigational drug. All

prohibited medications and significant non-drug therapies administered after the patient starts investigational drug must be recorded in the eCRF. Any patient receiving a prohibited medication during the study must discontinue the investigational drug and enter the post-treatment follow-up period.

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

Administration of a live vaccine during the study will lead to permanent discontinuation of investigational drug and the patient should enter the post-treatment follow-up period. Other types of vaccination should be avoided during the study.

Table 5-1 Prohibited treatment

Treatment[1, 2]	**Wash-out period prior to injection of investigational drug**
Biologic agents targeting IL-17 directly or IL-17 receptor (including secukinumab)	*No prior use allowed*
Other biologic immunomodulating agents: Alefacept, briakinumab, efalizumab, ustekinumab	6 months
Adalimumab, etanercept, infliximab	12 weeks
Other systemic immunomodulating treatments (e.g. methotrexate, cyclosporine A, corticosteroids[3] (oral, i.v., i.m., s.c., intra-articular, transdermal), cyclophosphamide)	4 weeks
Other systemic psoriasis treatments (e.g. retinoids, fumarates)	4 weeks
Photochemotherapy (e.g. PUVA)	4 weeks
Phototherapy (e.g. UVA, UVB)	2 weeks
Topical treatments likely to impact on signs and symptoms of moderate to severe psoriasis (e.g. corticosteroids[4], vitamin D analogs, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, α-hydroxy or fruit acids)	2 weeks
Live virus vaccination	6 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is the longer)
Any treatment known to worsen psoriasis	Stable at least 4 weeks before

Treatment[1, 2]	Wash-out period prior to injection of investigational drug
(e.g. ß-blockers, calcium channel blockers, lithium)	Study drug initiation
Prohibited regimen of topical corticosteroids (TCS)	
TCS with higher than moderate potency	2 weeks
TCS with mild to moderate potency on any body location other than the face, scalp and/or anogenital area	2 weeks
TCS with mild to moderate potency on face, scalp and/or anogenital area	1 day

1 If the prohibited treatment was used during the study, the patient must discontinue use of prohibited treatment if he/she wishes to continue in the study
2 In case of undue safety risk for the patient, the patient should discontinue study treatment at the discretion of the investigator. If the patient received a live virus vaccination during the study, the patient must discontinue study treatment
3 Inhaled CS with only a topical effect (e.g. to treat asthma) are not considered as 'systemic immunomodulating treatments' and are therefore acceptable as concomitant medication
4 Mild to moderate topical CSs are allowed only during the Screening period if used only on the face, scalp and/or anogenital area. These topical CSs must be stopped 12 hours prior to first injection.
After Week 16 and if clinically needed, TCSs are allowed during the study for short-term use (<14 days), for non-psoriasis indications and on areas not affected by psoriasis (see Section 5.5.8)

The use of certain medications will be allowed at the investigator's discretion or for a restricted duration or specific dose (refer to Section 5.5.8).

5.5.10 Discontinuation of investigational drug and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. Patients will be considered as 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 (including during the post-treatment follow-up period), the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information in the eCRF. The investigational drug must be discontinued.

The investigator should discontinue the investigational drug for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

The investigational drug must be discontinued and the patient withdrawn from the study under the following circumstances:

- Emergence of any Adverse Event (AE) judged by the investigator to prevent the patient from continuing treatment.
- Any of laboratory abnormality judged by the investigator to prevent the patient from continuing treatment.

- Pregnancy.
- Any deviation from the prescribed dose regimen of the investigational drug.
- Use of prohibited treatment listed in Table 5-1 and that presents undue safety risk.
- Any other protocol deviation that results in a significant risk to patient safety.
- Any situation in which investigator considers that continuation is not beneficial to the patient.

In all cases, the patient should enter the post-treatment follow-up period with at least an End of treatment visit 4 weeks after last administration of investigational drug.

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 in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

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

5.5.11 Emergency breaking of treatment assignment

Not applicable since this is a single-arm study with no randomization to a treatment group.

5.5.12 Study completion and post-study treatment

Study completion is defined as all patients included at Baseline who completed the study as described in the protocol.

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.

5.5.13 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 the protection of the patient's interests.

6 Visit schedule and assessments

All assessments to be performed are listed in Table 6-1indicated with an 'x' at the visits when they should be performed.

Fifteen (15) visits are planned during the study: an initial Screening visit around one month prior to treatment administration to check eligibility, to obtain signed informed consent and to ensure a wash-out period for prohibited medications, 12 visits during the treatment period and two visits during the follow-up period: an End of treatment visit and a Follow-up visit.

Patients should be seen for all visits as per assessment schedule. Injections at the investigational site, preferably by the patient, are planned at Visit 1 to Visit 8 and the

injections should be performed by the patient at home (Weeks 20, 28, 36 and 44) or on site (Weeks 24, 32, 40 and 48), after W16 as per assessment schedule. The authorized 'visit windows' are as follows:

- Screening (Visit 0) to Visit 1 (1st injection): 1 to 4 weeks ±2 days.
- From Visit 1 (Week 0) until Visit 5 (Week 4): 1 week ±2 days.
- From Visit 6 (Week 8) until Visit 8 (Week 16): 4 weeks ±2 days.
- From Week 20 to Visit 12 (last injection at Week 48): 4 weeks ±5 days. Same visit window will apply to the Extension period.
- After Week 48 (or Week (maximum) 72 for patient entering the extension period), there will be two more visits during the follow-up period: End of treatment visit at Week 52 and Follow-up visit at Week 56 (or End of Extension and Follow-up visits, respectively, 4 and 8 weeks after the last administration of study drug, for patient entering the extension period), each with a 'visit window' of 4 weeks ±5 days.

In addition, during treatment, patients may be seen at an unscheduled visit, e.g. if they experience deterioration of psoriasis or suspected AEs. During these unscheduled visits, investigational drug will NOT be administered.

Patients who discontinue the investigational drug should enter the post-treatment follow-up period with at least an End of treatment visit four weeks after last injection. If they refuse to return for an assessment or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone. Documentation of attempts to contact the patient should be recorded in the patient source documentation.

The reason for discontinuation/withdrawal should be obtained and safety data since the last study visit or since the last administration of investigational drug should be collected if they do not attend any post-treatment follow-up visit.

6.1 Information to be collected on screening failures

If for any reason a patient is a screen failure, the patient may be rescreened. There is no restriction on the number of times a potential patient may be rescreened or on how much time must pass from the date of screen failure and the date of rescreening.

All patients providing signed informed consent but not entering the treatment period will have Screening visit data collected: demographics, inclusion/exclusion criteria and Serious Adverse Events (SAE) data. AEs that are not SAEs will be followed-up by the investigator and reported only in the source data.

All patients providing signed informed consent and entering the treatment period (with at least one Cosentyx® administration) of the study will have all AEs **occurring after signature of informed consent** recorded on the Adverse Event CRF.

Investigators will have the discretion to record abnormal test findings on the Medical History CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

Table 6-1 Assessment schedule

Period		Screening	Treatment[1]												End of treatment	Extension Treatment [15]	End of Extension [16]	Follow-up [17]	Unscheduled visit[3]
			Period 1								Period 2[2]								
Visit		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**E1, E2 and E3**			
Week		**≥- 4 to ≤-1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**56, 64 and 72**		**80 maximum**	
Visit window (days)		**±2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
Inclusion/Exclusion criteria		X	X													Please see details in Table 6-2			
Demographics[4]		X																	
Relevant medical history		X																	
Psoriasis medical history		X																	
Previous treatment for psoriasis		X																	
Smoking history		X																	
Education level		X																	
Physical examination[5]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
Previous medication		X																	
Concomitant medication			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X
QuantiFERON® TB-Gold In-Tube test[6]		X																	X[3]
Chest X-ray, MRI or CT-scan[7]		X																	
BSA[8]		X																	
IGA[8]		X																	
ECG		X																	
Pregnancy test[9:]	Blood	X																	
	Urine		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X[3]
Biochemistry[10]		X	X												X		X		
Hematology[11]		X	X												X		X		

Period	Screening	Treatment[1]												End of treatment	Extension Treatment [15]	End of Extension [16]	Follow-up [17]	Unscheduled visit[3]
		Period 1								Period 2[2]								
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**E1, E2 and E3**			
Week	**≥- 4 to ≤-1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**56, 64 and 72**		**80 maximum**	
Visit window (days)	**±2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	
ProSPI questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
SaSPI questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
DLQI questionnaire		X	X	X	X	X	X	X	X	X	X	X	X	X	Please see details in Table 6-2	X	X	
PASI score	X [12]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
SA-PASI score		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Pain, itching and scaling assessment		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Optional BISF questionnaire		X				X			X									
Administration of investigational drug[13]		X	X	X	X	X	X	X	X	X	X	X	X	X[14]				
Verification of patient drug administration log									X	X	X	X	X	X		X		X[3]
Primary endpoint									X									
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X

1 Patients discontinuing treatment prematurely during the treatment period should attend a visit for data collection (End of treatment visit) and should then enter the post-treatment follow-up period

2 If the investigational drug is judged by the investigator and patient to be beneficial to the patient, the response to treatment will be considered to be favorable and monthly injections will continue to Week 48. In the absence of a favorable response at Week 16, the investigational drug will be discontinued and the patient should attend End of Treatment visit and will then enter the follow-up period.

3 If judged necessary by the investigator

4 Date of birth, gender, race, child-bearing potential

5 Weight and vital signs at all visits and height only at Screening visit

6 A repeat QuantiFERON® TB-Gold In-Tube test is recommended if the result of the first QuantiFERON® TB-Gold In-Tube test is ‘indeterminate’. The patient must be

Period	Screening	Treatment[1]												End of treatment	Extension Treatment [15]	End of Extension [16]	Follow-up [17]	Unscheduled visit[3]
		Period 1								Period 2[2]								
Visit	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**E1, E2 and E3**			
Week	**≥- 4 to ≤-1**	**0**	**1**	**2**	**3**	**4**	**8**	**12**	**16**	**24**	**32**	**40**	**48**	**52**	**56, 64 and 72**		**80 maximum**	
Visit window (days)	**±2**		**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	**±5**	

referred for a follow-up tuberculosis workup (as per local guidelines) if either the first or the repeat test is 'positive' or if the results of both tests are 'indeterminate'. If the first test is 'indeterminate', the investigator may decide not to repeat the test and to proceed directly to the workup, though this is not recommended. The patient will not be eligible for randomization if 'active tuberculosis is present' or if 'latent tuberculosis is present' and is untreated as per local guidelines

7 Exclusion criterion: number 17

8 Inclusion criterion: number 2

9 For all women of child-bearing potential

10 Fast plasma glucose, urea, creatinine, total bilirubin, alanine transaminase (ALT)/ glutamic pyruvate transaminase (SGPT), aspartate transaminase (AST)/glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase, sodium, chloride, potassium, bicarbonate, calcium, phosphorous, total protein, albumin and uric acid

11 Complete blood count : hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, bands neutrophils (optional), lymphocytes, monocytes, eosinophils, basophils) and platelet count12 Additionally patients will self-administer study treatment at home at weeks 20, 28, 36 and 44; these self-administrations will be protocolled by the patient on the self-administration log, which will be brought to the site along with the PFS and outer box for compliance check

12 PASI score at screening visit – V0 needs to be documented in medical source data. PASI scores at following visits (V1 to Follow-up visits) need to be entered into eCRF.

13 The patient will be asked to self administer the injection at the investigation site when attending a site visit (Weeks 24, 32, 40 and 48) or at home between visits (Weeks 20, 28, 36 and 44). If patient is not comfortable with self-injections, injections at home can be performed by a caregiver.

14 Administration of investigational drug need to be done at the Visit 13 only if patient is entering the extension treatment period.

15 The assessments related to the extension treatment period are detailed in table 2 below.

16 The End of Extension (EoE) visit should be performed 4 weeks after the last administration of study drug.

17 The Follow-up (FU) visit should be performed 8 weeks after the last administration of study drug.

Table 6-2 Assessment schedule during extension treatment period only

Period	**Extension Treatment[1]**		
Visit	**E1**	**E2**	**E3**
Week	**56**	**64**	**72**
Visit window (days)	**±5**	**±5**	**±5**
Physical examination[2]	X	X	X
Concomitant medication[3]	X	X	X
Urine Pregnancy test[4]	X	X	X
Administration of investigational drug[5]	X	X	X
Verification of patient drug administration log	X	X	X
Adverse events	X	X	X

1 Only for eligible patients who have received their injection of study drug at W48 before 3 January 2017 or before the commercialization of Cosentyx® in France, whichever occurs first.

2 Weight and vital signs at all visits

3 need to be entered into eCRF only if related to an AE

4 For all women of child-bearing potential

5 The patient will be asked to self administer the injection at home between visits (Weeks 52, 60 and 68). If patient is not comfortable with self-injections, injections at home can be performed by a caregiver.

6.2 Patient demographics/other Screening characteristics

At screening visit, patients must provide signed informed consent. Patient demographic and Baseline characteristics data will be collected (date of birth, gender, race), psoriasis medical history (date of first diagnosis for each form of psoriasis), previous psoriasis treatments (reason for discontinuation), relevant medical history, previous and concomitant medication, smoking history (current/previous, number of packets smoked per week), education level (none, primary education, secondary education, university).

Rationale for collection of race. There are differences in the psoriasis expression in terms of severity and incidence, typically lower in Asian populations, in East Africa (Farber EM, Nall L. Epidemiology of Psoriasis. Roenig and psoriasis Maibach eds. 1998) and also in terms of clinical expression: in Asian populations, psoriasis may be associated with atopy. Furthermore, drugs metabolism and tolerance may vary depending on ethnicity and genetic characteristics (hepatic metabolism, HLA). Finally the registration agencies and particularly the FDA and the EMEA pay attention to the analysis of clinical response based on the race to be sure that the benefit-risk ratio is suitable for all ethnic groups.

A physical examination will be performed (height, weight, vital signs), blood samples will be taken for hematology and biochemistry assessments and a pregnancy test will also be performed for all women of child-bearing potential.

Inclusion and exclusion criteria must be checked at screening visit. PASI score must be ≥12, BSA ≥10 and IGA mod 2011 ≥3 at screening visit.

6.2.1.1 Standard 12-lead ECG

A standard 12-lead ECG must be performed during the 12 weeks preceding study drug initiation. Interpretation of the tracing must be made by a qualified physician and clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study.

6.2.1.2 QuantiFERON®-TB Gold In-Tube assay

A QuantiFERON®-TB Gold In-Tube assay (QFT) will be performed locally at the Screening visit to screen all patients for latent tuberculosis infection in order to determine their eligibility for inclusion in the study. Any patient with a positive QTF result must not be included in the study.

6.2.1.3 X-Ray

An X-ray (or MRI, CT-scan) will be performed if results are not available during the 12 weeks prior to the Screening visit.

6.2.1.4 Investigator's Global Assessment (IGA mod 2011)

The IGA mod 2011 will be conducted for overall psoriatic disease.

Subjects require an IGA mod 2011 score at screening visit of 3 or 4 in order to participate in the study. The IGA mod 2011 rating scale for overall psoriatic disease is shown in Table 6-2.

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

Table 6-2 The IGA mod 2011 rating scale

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

Note: Involvement of nails is not part of the assessment

6.2.1.5 Assessment of total body surface area (BSA)

The total BSA affected by plaque-type psoriasis will be estimated from the percentages of areas affected, including head, trunk, upper limbs and lower limbs. The following calculations will be done: Each reported percentage will be multiplied by its respective body region corresponding factor (head = 0.1, trunk = 0.3, upper limbs = 0.2, lower limbs = 0.4). The resulting four percentages will be added up to estimate the total BSA affected by plaque-type psoriasis.

6.3 Baseline characteristics, questionnaires and scores

All Baseline assessments should be performed prior to the first study treatment administration at Visits 0 and 1. BSA and IGAmod2011 will be assessed at Visit 0 only, PASI at Visits 0 and 1 and all questionnaires at Visit 1 only. Theses assessments were described in Table 6-1 in section 6.

6.4 Treatment exposure and compliance

All injections of secukinumab 300 mg will be recorded by the investigator on the appropriate eCRF page. When injections are performed by the patient or caregiver at home (after Visit 8/Week 16), date and time of administration will be recorded in the patient drug administration log. Patients are required to return the used investigational medication kit (PFSs and packaging) and the patient administration log at each visit to the investigational site in order for the investigator to monitor compliance.
The investigator should emphasize the importance of compliance for patient safety and study validity. The patient should be instructed to attend the study visits as scheduled and to take the investigational drug exactly as prescribed. The patient should be informed to contact the investigator if he/she is unable, for any reason, to attend a study visit as scheduled or to administer the investigational drug at home as prescribed.

6.5 Efficacy

The efficacy assessments listed in Table 6-1 will be performed the specified visits during the treatment period (before each administration of the investigational drug), at each post-treatment follow-up visit. Psoriasis symptoms will be assessed using the following questionnaires: DLQI, SPI, PASI and PSD (pain, itching and scaling assessment).

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

If the occurrence of AEs or SAEs is confirmed, the physician must record the events as per instructions given in Section 7 of the protocol. Investigators should not encourage patients to change the responses reported in the various Patient-Reported Outcome (PRO) questionnaires.

6.5.1 Psoriasis questionnaires and scores

Psoriasis questionnaires and scores should be completed in the following order:

- About scores: 1/pro-SPI, 2/IGA and 3/ PASI
- About questionnaires: 4/saSPI , 5/DLQI, 6/PSD, 7/SA-PASI and 8/optional BISF questionnaires (described in section 6.7).

6.5.1.1 SPI questionnaire

The SPI questionnaire is a new tool developed to provide a concise but holistic summary of psoriasis assessment. The questionnaire consists of 2 complementary versions: one to be completed by the investigator (proSPI) and one by the patient (saSPI). Each version comprises 3 components: current extent and severity of psoriasis plaques (s), psychosocial impact (p), and historical course of disease and intervention (i).

Psoriasis extent and severity (s): part 1

This score is weighted to reflect functional or psychosocial impact of psoriasis, with extra weight given to the scalp, face, hands, feet and anogenital skin. It consists of 2 components:

- Extent of plaques (part 1A): psoriasis plaques visible at 10 unequal critical localizations, each on a 3-point scale: 0=absent or minimal, 0.5='noticeable' or 1=extensive (finger nails are scored with hands and toenails with feet).
- Plaque severity (part 1B): each of the 10 critical locations are scored on a scale of 0 (essentially clear) to 5 (intensely inflamed skin).

The scores for the 2 components, psoriasis plaque extent and severity, are multiplied together to give a maximum score of 50.

Psychosocial impact (p): part 2

Assessed on a VAS of 0 (psoriasis having no effect on patient) to 10 (psoriasis affecting patient very much).

Historical course and intervention (i): part 3

Assessed by means of 10 questions: 4 questions related to disease course and 6 questions about previous interventions (for each question, ticked=1 point) (Chularojanamontri *et al*., J Inv Dermatol 2013).

The SPI questionnaire is included in Appendix 1.

6.5.1.2 PASI score

The PASI score will be used to assess the severity of psoriasis lesions. Various regions of the body: head (including neck: H), upper limbs (U), trunk (including axillae and groin: T) and lower limbs (including buttocks: L) are assessed and lesion surface area is measured. In this questionnaire, the symptoms erythema (E), thickening (plaque elevation, induration: I) and scaling (desquamation: D), are assessed for each body region individually on a scale of 0 (none) to 4 (very severe).

Taking into account that the head, upper limbs, trunk and lower limbs can be estimated as corresponding to approximately 10%, 20%, 30% and 40% of body surface area, respectively, the total PASI score can be calculated using the following 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,

Where A = area score based on true area (%) ranging from 0 (no involvement) to 6 (90%-100%). The total score therefore ranges from 0 (no psoriasis sign) to a theoretical maximum of 72.0.

The PASI scoring system is decribed in Table 6-3 and PASI score is included in Appendix 2 (Fredriksson T and Pettersson U Dermatologica 1978, Weisman S, Pollack CR and Gottschalk RWJ Dermatolog Treat 2003, Gottlieb AB, Griffiths CEM et al. Br J Dermatol 2005).

Table 6-3 The PASI scoring system

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
Head (H)†	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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

Definitions of efficacy variables based on PASI

The following definitions will be used in this study based on the CHMP guidelines for psoriasis (CHMP/EWP/2454/02 2004):

- PASI 50 responders (partial response): patients achieving ≥ 50% improvement (reduction) in PASI score compared to Baseline.

- PASI 75 responders: patients achieving ≥ 75% improvement (reduction) in PASI score, compared to Baseline.
- PASI 90 responders: patients achieving ≥ 90% improvement (reduction) in PASI score, compared to Baseline.
- PASI 100 responders: no psoriasis / remission (PASI=0).

6.5.1.3 SA-PASI score

The SA-PASI score is a PASI-like structured patient self-administered instrument to assess psoriasis severity of the same regions assessed using the PASI score (Section 6.5.1.2). Disease severity is assessed by the patient using 3 modified 120 mm VASs evaluating erythema (on a scale of no redness to dark red), induration (no thickness to very thick) and scaliness (no scale to very flaky).

To estimate the surface area involved, a line-drawing silhouhette of the front and back of a body is presented to patients who shade in the areas currently affected by psoriasis. A single investigator who had not evaluated the patient assigns a numeric value of 0 to 6 based on the silhouette shading and corresponding to 0 to 100% involvement for ech of the following four areas: head, upper extremities, trunk, and lower extremities (Fleischer et al. J Inv Dermatol 1994, Feldman SR et al. J Inv Dermatol 1996).

The total SAPASI score can be calculated using the following formula:

$SAPASI = [(0.1xA_H) + (0.2xA_U) + (0.3xA_T) + (0.4xA_L)] / [0.0333 \times (VAS_E + VAS_I + VAS_S)]$

The SA-PASI score is presented in Appendix 3.

6.5.1.4 Pain, itching and scaling assessment (PSD questionnaire)

A PSD questionnaire completed by the patient will be used to evaluate 3 psoriasis symptoms, pain, itching and scaling, each on a scale of 0 (none) to 10 (worst possible).

The PSD questionnaire is included in Appendix 5.

6.5.2 DLQI questionnaire

The DLQI questionnaire consists of a series of questions related to symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment scored on a scale of 0 (not answered, not relevant, not at all) to 3 (very much or prevented work or studying in the case of question 7). The total DLQI ranges from 0 (minimum) to 30 points (maximum). If the score is 0 or 1, psoriasis is considered as having no effect at all on the patient's life, a score of 2 to 5 indicates a small effect, 6 to 10 indicates a moderate effect, 11 to 20 a very large effect and 21 to 30 indicates an extremely large effect on patient's life. (Finley and Khan Clin Experi Dermato 1994).

Each subscale of the DLQI may also be analyzed separately.

The DLQI questionnaire is included in Appendix 4.

6.5.3 Appropriateness of efficacy assessments

DLQI is a validated questionnaire for evaluating the impact of dermatological diseases on patient QoL. The PASI questionnaire is specific for assessing the area and severity of the signs of psoriasis. PASI is considered acceptable by the health authorities (CHMP/EWP/2454/02 2004) to assess treatment efficacy in combination with the DLQI. The use of questionnaires for the evaluation of the intensity of pain, itching and scaling is a standard method used in clinical studies.

The SPI is a newly developed tool providing a concise but holistic summary of psoriasis assessment. It has several advantages over current tools: 1) it evaluates specifically several critical localizations (scalp, face, hands, feet, anogenital skin); 2) it can be assessed by both the physician (proSPI component) and the patient (saSPI); and 3) it assesses psychological impact and includes historical features.

The efficacy and safety of secukinumab AIN457 have been studied in pivotal Phase III clinical trials employing the PASI and DLQI questionnaires.

6.6 Safety

At each visit, a physical examination should be performed and vital signs must be measured, preferably by the same person at each visit. In addition, any AE must be reported; blood samples will be taken for hematology and biochemistry assessments at inclusion and End of treatment visits (plus unscheduled visits if deemed appropriate). A pregnancy test will be performed for all women of child-bearing potential (Table 6-1).

6.6.1 Physical examination

A physical examination should include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. The investigator can perform other examinations if deemed necessary based on patient's previous medical history.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the eCRF. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded on the Adverse Event section of the eCRF.

6.6.2 Vital signs

Vital signs (including blood pressure and pulse measurements) will be determined after the patient has been sitting for five minutes, with back supported and both feet placed on the floor. Systolic and diastolic blood pressure will be measured using a validated device with an appropriately sized cuff. Two sitting measurements will be made at 1-2 minute intervals and the mean of the two measurements will be used. If a sufficiently large cuff is unavailable, a sphygmomanometer with an appropriately sized cuff may be used. Normal values for vital signs are presented in Appendix 5.

6.6.3 Height and weight

Height in centimeters (cm) will be measured only at the Screening visit. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at each visit, preferably using the same weighing scales throughout the study.

6.6.4 Laboratory evaluations

Collected samples will be analyzed locally.

Clinically notable laboratory findings are defined in Appendix 9.

6.6.4.1 Hematology

Hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differential (neutrophils, bands neutrophils (optional), lymphocytes, monocytes, eosinophils, basophils) and platelet counts will be measured at screening visit, first visit (Week 0) and at End of treatment visit (Week 52).

6.6.4.2 Biochemistry

Fast plasma glucose, urea, creatinine, total bilirubin, alanine transaminase (ALT)/ glutamic pyruvate transaminase (SGPT), aspartate transaminase (AST)/glutamic oxaloacetic transaminase (SGOT), gamma glutamyl transpeptidase (GGT), alkaline phosphatase, sodium, chloride, potassium, bicarbonate, calcium, phosphorous, total protein, albumin and uric acid will be measured at screening visit, first visit (Week 0) and at End of treatment visit (Week 52).

6.6.5 Pregnancy and assessments of fertility

A serum β-hCG test will be performed for all women of child-bearing potential at the Screening visit. A woman with a confirmed positive pregnancy test at Screening is not eligible for participation in the study. A urine pregnancy test will be performed at all other visits (Table 6-1). A positive urine pregnancy test during the treatment period of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, study treatment must be definitively discontinued, as described in Section 5.5.10. An effective contraception method must be used by all women of child-bearing potential during the study. At each study visit, the investigator/qualified site staff will review with the female patients of child-bearing potential requirements for appropriate contraception while participating in the study.

6.6.6 Appropriateness of safety measurements

The safety assessments to be performed during the study are reliable and are standard for the use of a biologic immunomodulating agent in the treatment of psoriasis.

6.7 Other assessments

6.7.1 Sexual function

Data related to sexual dysfunction will be collected only for patients willing to complete sexual function questionnaire. The BISF-w/m will be used to assess sexual dysfunction.

The BISF-m is a brief patient self-reported questionnaire (22 items) related to sexual functioning. It was developed for the specific purpose of assessing key domains of sexual functioning in men (e.g. sexual interest, activity, satisfaction and preference).

The BISF-w is an adaptation of the men's questionnaire specifically for women (22 items). The key domains are sexual thoughts/desire, arousal, activity, pleasure/orgasm, satisfaction, problems affecting sexual function.

BISF-m and BISF-w questionnaires are presented in Appendix 6 and 7, respectively.

7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (i.e. any undesirable sign, abnormal laboratory findings, symptom or medical condition) in a patient after providing signed informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally related to the use of the investigational drug.

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

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

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

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from Baseline or the previous visit, or values which are considered to be non-typical in a patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying AEs. Alert ranges for labs and other test abnormalities are included in Appendix 6.

Information concerning all AEs will be collected and recorded on an Adverse Event Case Report Form and will be followed-up as appropriate.

Medical conditions/diseases present before starting investigational drug will only be considered as AEs if they worsen after starting the investigational drug.

Where possible, each AE should be described by:

- 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.
- Relationship to the investigational drug.
- Duration (start and end dates), or whether the event is ongoing at the final visit.
- Whether it constitutes a SAE.
- Action taken regarding investigational treatment.
- Whether other medication or therapies have been taken (concomitant medication/non-drug therapy).
- Outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, 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 Cosentyx Summary of Product Characteristics. 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 AE (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 a SAE, it must be reported to Novartis.

7.2 Serious Adverse Events

A SAE is any AE (appearance of (or worsening of any pre-existing) undesirable sign, symptom or medical condition which meets any one of the following criteria:

- Is fatal or life-threatening.
- Results in persistent or significant disability/incapacity.
- Constitutes a congenital anomaly/birth defect.
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

  - Elective or pre-planned treatment for a pre-existing condition unrelated to the indication under study that has not worsened since the start of the investigational drug.
  - Social reasons and respite care in the absence of any deterioration in the patient's general condition.
- Is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above (e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission).
- Transmission of an infectious agent via the investigational drug.

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

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

As far as possible, each SAE will also be described by (but not limited to):

- Duration (onset date = date of first signs or symptoms, and end date).
- Severity (mild, moderate, severe).
- Relationship to current investigational drug (suspected / not suspected as judged by the investigator).
- Action(s) taken and investigation results, if applicable.
- Concomitant medication details.
- Outcome.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.3.

7.3 Serious Adverse Event reporting

7.3.1 Notification of an SAE to Novartis Pharmaceuticals Drug Safety & Epidemiology (DS&E) Department

Information related to all SAEs must be collected and recorded on the Serious Adverse Event Report Form and be reported by the investigator to Novartis DS&E Department within 24 hours of knowledge, even if it is not thought to be treatment-related. Follow-up information about a previously reported SAE will also be reported to Novartis DS&E Department within 24 hours of receipt. 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.

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 60 days following the last administration of

investigational drug (i.e. last follow-up visit, 8 weeks after last investigational drug administration) must be reported to Novartis within 24 hours of knowledge. Any SAEs experienced after the 60 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

If the SAE is not previously documented in the Cosentyx Summary of Product Characteristics and is thought to be related to the investigational treatment a DS&E Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3.2 Reporting procedure for an SAE

The investigator must complete the SAE Report Form in English, assess the relationship to study treatment and send the completed and signed form by fax within 24 hours to Novartis DS&E Department [redacted]. The original and the duplicate copies of the SAE Form sheet will be kept at the study site. Should the investigator realize that the number of pages received by Novartis DS&E Department doesn't match the number of pages faxed by the investigator, the SAE form should be re-faxed entirely to Novartis DS&E Department.

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 has resolved or is continuing, if and how the event was treated, and whether the patient continued or discontinued study participation. The form and fax confirmation sheet will be retained by the study site.

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy in a patient will be reported to Novartis within 24 hours of knowledge. Pregnancy will be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis DS&E Department.

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 follow-up will be recorded on the same form and will include an assessment of the possible relationship to the Novartis investigational drug of any pregnancy outcome.

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

Pregnancy outcomes must be collected for the female partners of any males who took investigational drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries in the eCRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that investigational drug 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 in eCRFs 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 must be given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of signed informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for the primary variable. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific monitoring plan. No information in source documents related to 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 eCRFs using fully validated software conforming to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs will check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

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

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

All laboratory samples will be processed locally and the results will be entered on study eCRF by sites staff.

Patients will be provided with the PRO questionnaires on paper to be completed at each visit before injection of the investigational drug.

All completed questionnaires will be collected and checked for completion by the investigator or delegated staff and then a copy will be sent to the CRO working on behalf of Novartis. Answers provided by the patients to the saSPI, SA-PASI, DLQI, PSD, and BISF questionnaires (if available) will be transferred exactly as completed (without any modification or interpretation) by the CRO working on behalf of Novartis on the appropriate screens of the eCRF. Original questionnaires will be filed as source documents on site.

At the study conclusion, the occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made after written agreement by Novartis Development management.

8.4 Data Monitoring Committee

Not required.

8.5 Adjudication Committee

Not required.

9 Data analysis

The Statistical Analysis Plan (SAP) will be written by the CRO in charge of the study and will be validated by Novartis prior to performing the analysis.

All analyses will be performed by the CRO in charge of the study and will be validated by Novartis.

Quantitative variables will be presented in terms of mean, standard deviation, median and extreme values, and in terms of absolute frequency and percentage by modality for qualitative variables. If appropriate, 95% Confidence Intervals (CIs) will be presented.

For statistical analysis, Baseline will be defined as the last available non-missing value collected just prior to the start of treatment. Patients with Screening assessments but not included in the study will only be listed.

Unless otherwise specified, all statistical tests will be two-sided and will use the 0.05 level of significance.

All extension period data will be presented separately from the treatment period and will be outlined in more detail in the SAP.

Analyses will be performed using SAS® software version 9.2 or higher.

Further technical details and discussions of the following statistical considerations will be provided in the SAP.

9.1 Analysis sets

The following analysis sets will be used in this study:

Included Set (IS): The included set will comprise all patients included in the study.

Full Analysis Set (FAS): The FAS will comprise all patients from the IS administered at least one dose of investigational drug during the treatment period with at least one Baseline and one post-Baseline SPI evaluation.

Safety Analysis Set (SAF): The SAF will comprise all patients administered at least one dose of investigational drug during the treatment period.

Per Protocol Set (PPS): The PPS will comprise all patients administered at least one dose of investigational drug during the treatment period without any major protocol deviation.

All analyses will be based on the FAS population, unless otherwise specified.

9.2 Patient demographics and other Baseline characteristics

Descriptive statistics will be provided for patient demographics and baseline characteristics (including the Baseline values of the main efficacy endpoints) on the IS population.

9.3 Medical history

Any condition entered as medical history or current medical condition at the Screening visit will be coded using the MedDRA dictionary and will be summarized by System Organ Class (SOC) and Preferred Term (PT). Summaries for psoriasis-specific medical history will also be presented.

9.4 Treatments

9.4.1 Investigational drug

The analysis of data related to investigational drug administration will be performed on the SAF. The duration of exposure to investigational drug will be summarized.

9.4.2 Prior and concomitant treatment

Previous and concomitant medications will be summarized in separate tables.

A previous medication is defined as a treatment taken but stopped prior to first administration of investigational drug. Any medication administered at least once between the day of first injection of investigational drug and the last day of study visit will be considered as a concomitant medication, including a medication initiated pre-screening and ongoing at the start of the treatment period.

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

In addition, medical procedures and significant non-drug therapies will be summarized as coded in MedDRA.

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

9.5.1 Variable(s)

The primary variables for this study are the changes from Baseline of proSPI (s) and saSPI (s) at Week 16.

The primary analysis of this study will be performed on the FAS population at Week 16 compared to Baseline and will be:

- To evaluate the change from baseline of proSPI (s).
- To evaluate the change from baseline of saSPI (s).

The key secondary variable for this study is the PASI score. The key secondary analysis will be to assess PASI and to evaluate the correlation between PASI and proSPI (s) in the FAS.

9.5.2 Statistical model, hypothesis, and method of analysis

Summary statistics will be presented for changes from Baseline to Week 16 (proSPI (s), saSPI (s)) for all patients in the FAS. Associated 95% CIs will be presented.

To assess the primary objective, the proSPI (s) and saSPI (s) will be analyzed using a paired t-test (baseline vs Week 16). The null hypothesis tested in this model is that there is no difference between means at baseline and Week 16.

As there are co-primary endpoints an adjustment for multiplicity will be performed using the Hochberg procedure and the family-wise type-I-error will be set to α=5% (2-sided). The Hochberg procedure was chosen as the most powerful adjustment due to the positive association between proSPI (s) and saSPI (s) (L Chularojanamontri et al., 2013).

The Hochberg procedure will be applied as follows, if the maximum of the two p-values is rejected at the 5% level (2-sided) then both hypotheses are rejected and statistical significance is claimed for both endpoints. Otherwise if the maximum of the 2 p-values is not rejected, then the minimum p-value is tested at the 2.5% level (2-sided), if rejected then statistical significance is claimed just for this endpoint.

In the event the data is non-normal the Wilcoxon signed rank test will be performed.

Evolution of PASI score and PASI response during the study will be described and associated 95% CIs will be presented. Change from baseline to Week 16 of the PASI score will be analyzed as for the primary analysis.

Spearman's correlation coefficient and the associated test will be used to evaluate the correlation between PASI and proSPI (s) at all weeks.

9.5.3 Handling of missing values/censoring/discontinuations

For the analysis of the primary endpoint in the FAS population and in case of unavailable assessment at Week 16, a LOCF (Last Observation Carried Forward) approach will be used. This approach will consist of replacing the missing Week 16 assessment by the value of the last available primary endpoint assessment. A sensitivity analysis will be conducted by performing two analyses, one using the LOCF completion approach and the other based only on the available data (no missing data replacement). Missing values for all secondary endpoints or other outcomes (e.g. safety or laboratory measurements) will not be replaced.

9.5.4 Supportive analyses

The same analysis will be performed on the PPS population.

Subgroups of interest defined by the scientific committee will be investigated also if required (e.g. psoriasis duration at baseline, baseline bodyweight …) and will be detailed in the SAP before the database lock.

9.6 Analysis of secondary variables

9.6.1 Efficacy variables

Simplified Psoriasis Index

Absolute values and change from baseline (at all assessment periods) for each SPI component will be described and analyzed as for the primary efficacy analysis.

ProSPI (s) and saSPI (s) will be analyzed using a paired t-test at week 16. Descriptive statistics will be presented for each component at each time point.

Dermatology Life Quality Index

The DLQI contains six functional scales (i.e. symptoms and feeling, daily activities, leisure, work and school, personal relationships, treatment). Seven scores will be derived from the DLQI: the total score of each of the six dimensions as well as the total score over all items. The higher the score, the more quality of life is impaired.

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

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

Self-administered PASI

Absolute values and change from baseline of the sa-PASI (at all assessment periods) will be described.

Psoriasis Symptom Diary

For PSD, descriptive summary statistics will be presented for absolute values and change from baseline by visit for intensity of pain, itching and scaling.

Correlations between scores

Relationships between scores will be explored using Spearman's correlation coefficient and the associated test.

Appropriate statistical tests performed on these secondary efficacy variables will be detailed in the SAP.

9.6.2 Safety variables

All safety evaluations will be performed on the SAF.

9.6.2.1 Adverse Events

Treatment-emergent adverse events (TEAEs: events starting after the first dose of investigational drug or events present prior to the first dose of investigational drug but with increased severity) will be summarized by PT.

AEs will be summarized by presenting the number and percentage of patients with:

- An AE.
- An AE by primary SOC.
- An AE by PT.

Summaries will also be presented for AEs by severity and for investigational drug related AEs. If a patient reports more than one AE with the same PT, only the greatest severity will be presented for this AE. If a patient reports more than one AE within the same primary SOC, the patient will be counted only once with the highest severity at the SOC level, where applicable.

All other information collected will be tabulated and listed as appropriate.

Separate summaries will be provided for any death, SAE, any other significant AE leading to investigational drug discontinuation.

These summaries will be presented for the whole study period.

9.6.2.2 Laboratory data

The summary of the data for laboratory evaluations will be presented for both types of laboratory tests (hematology and biochemistry). Descriptive summary statistics for the absolute values and changes from Baseline at each study visit will be presented.

Descriptive summaries will be presented by type and by laboratory test. Changes from Baseline will only be summarized for patients with both Baseline and post-Baseline assessments.

For each parameter, the maximum change from Baseline within each study period will be analyzed. In addition, shift tables will be produced for all parameters in order to compare patient Baseline laboratory evaluation with the observed value at each visit. For these shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value is normal, low, or high at each visit relative to whether or not the Baseline value

was normal, low, or high. These summaries will be presented by laboratory test. Shifts will be presented by visit as well as post-Baseline for the most extreme values.

9.6.2.3 Vital signs

Analysis of the vital sign measurements using summary statistics for the absolute values and changes from Baseline at each post-Baseline visit will be performed. These descriptive summaries will be presented by vital sign. Change from Baseline will be summarized only for patients with both Baseline and post-Baseline values. All information collected will be listed by patient, by visit, and abnormal values will be flagged.

9.6.3 Resource utilization

Data relating to resource utilization will not be analyzed in this study.

9.6.4 Health-related Quality of Life

QoL is a secondary endpoint (DLQI) and as such is described in Section 9.6.1.

9.6.5 Pharmacokinetics

Not applicable.

9.6.6 Pharmacogenetics/pharmacogenomics

Not applicable.

9.6.7 Biomarkers

Not applicable.

9.6.8 PK/PD

Not applicable.

9.7 Exploratory analyses

Correlations between scores

Correlations between saSPI and DLQI, between saSPI (s) and PASI, and between proSPI and saSPI (component s and p) will be evaluated using the Spearman correlation coefficient. The associated p-value will be presented.

Sexual dysfunction

To explore sexual dysfunction (only in patients willing to complete sexual function questionnaire), descriptive summary statistics will be presented for absolute values and change from baseline of BISF-m and BISF-w scores.

Sexual dysfunction analysis will be performed if a sufficient number of patients agreed to participate.

Responsiveness to change

An analysis of the SPI responsiveness to change will be led in order to investigate if reductions in psoriasis severity resulting from treatment would be accompanied by corresponding reductions in proSPI–s and saSPI–s scores. This analysis will be performed by the calculation of receiver operating characteristic (ROC) area under the curve (AUC). Three criteria of response will be examined to evaluate each score: ≥75, ≥90, and 100% reduction in PASI score.

9.8 Interim analyses

No interim analysis is planned in this study.

9.9 Sample size calculation

All sample size calculations were performed using EAST 6.0.

The primary objective of this study is to evaluate the benefit of secukinumab on the severity and psychosocial burden of psoriasis based on SPI change at Week 16 compared to Baseline in patients suffering from moderate to severe plaque psoriasis.

The sample size calculation is based upon the SPI variable which is the primary endpoint.

A similar study by Chularojanamontri *et al.* J Inv dermatol 2013 showed that it is possible to detect responsiveness and a minimum clinically important difference (an absolute change of 5 and 7 for proSPI (s) and saSPI (s), respectively) derived from PASI changes with n=100 patients. The study showed a standard deviation at week 10 in change from baseline of 7.35 in proSPI (s) and 10.35 in saSPI (S) as the standard deviation at week 16 is expected to be higher, conservative standard deviation estimates of 14 and 19 will be assumed for change at week 16 for proSPI (s) and saSPI (s) respectively.

Based on an analysis of paired differences, in order to have at least 90% power to detect a significant clinical difference for each index at the 2.5% level (2-sided), it can be estimated that a sample size of 100 evaluable patients would be sufficient.

Taking into account an anticipated drop-out of 20 patients, 120 patients will need to be included in the study.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient.

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

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

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

10.3 Responsibilities of the investigator and IRB/IEC

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

10.4 Publication of study protocol and results

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

11 Protocol adherence

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

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstance should an investigator collect additional data or conduct any additional procedure 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 as 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 Appendices

13.1 Appendix 1: SPI questionnaire

SIMPLIFIED PSORIASIS INDEX (SPI)

A practical tool for assessing psoriasis

Leena Chularojanamontri
Christopher Griffiths
Robert Chalmers

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University of Manchester and
Manchester Academic Health Science Centre

Salford Royal NHS Foundation Trust
Manchester M6 8HD
UK

Contact: r.chalmers@manchester.ac.uk

Date:

For completion by doctor or nurse

LABEL or Record no: Sex:

First name:

Surname:

PART 1A Circle the option which most closely describes the current extent of psoriasis in each body area

0	±	+

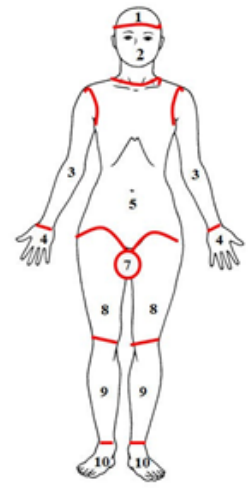
0	clear or minimal with no more than a few scattered thin plaques (0)
±	obvious but still leaving plenty of normal skin (0.5)
+	widespread and involving much of the affected area (1.0) §

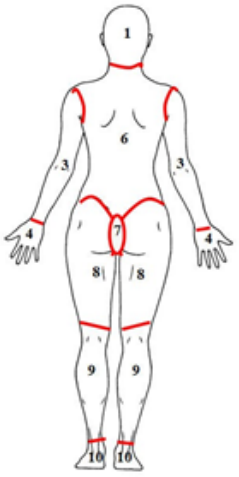
§ Please note that this is not the same as percentage body surface area (BSA) involvement: the extent score takes into account how dispersed the plaques are

		0	½	1
1	Scalp & hairline	0	±	+
2	Face, neck & ears	0	±	+
3	Arms & armpits	0	±	+
4	Hands, fingers & fingernails*	0	±	+
5	Chest & abdomen (stomach)	0	±	+
6	Back & shoulders	0	±	+
7	Anogenital area	0	±	+
8	Buttocks & thighs	0	±	+
9	Knees, lower legs & ankles	0	±	+
10	Feet, toes & toenails*	0	±	+

* score severe dystrophy of ≥ 2 nails as 0.5 and ≥ 6 nails as 1.0

Total extent score: maximum 10 points 1A





PART 1B Select the option which best describes the current average severity of psoriasis. This should take into account all affected areas identified above, not just the worst areas. Please refer to photographic severity key if available.

0	Essentially clear: with faint erythema or residual pigmentation only
1	Mild: erythema and/or scale with focal slight palpable thickening
2	Mild-to-moderate: erythema and/or scale with majority of affected skin palpably thickened
3	Moderate: erythema and/or scale and/or skin thickening
4	Marked: erythema and/or scale and/or skin thickening
5	Intensely inflamed skin: with or without pustulation

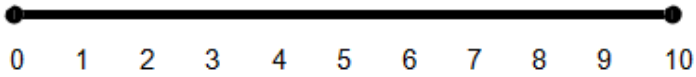
Average severity score : maximum 5 points 1B

Current extent and severity score = 1A x 1B (max. 50) 1A X 1B

Please turn over

PART 2 Ask patient to mark the line below in response to the question:

"How much is your psoriasis affecting you in your day-to-day life today?"



Guide: 0 = my psoriasis is not affecting me at all
5 = my psoriasis is affecting me quite a lot
10 = my psoriasis is affecting me very much (I could not imagine it affecting me more)

PART 3 Give one point for each true statement / for each therapy received (whether currently or in the past).	Point
About patient's psoriasis	
Patient has had psoriasis for more than ten years	
Patient has had psoriasis for more than 20 years (additional point)	
Patient has had erythrodermic or generalised pustular psoriasis	
Patient has been admitted to hospital for psoriasis	
About patient's treatment	
Patient has had at least one course of ultraviolet treatment or PUVA	
Patient has been treated with methotrexate (now or in past)	
Patient has been treated with acitretin or etretinate (now or in past)	
Patient has been treated with ciclosporin (now or in past)	
Patient has been treated with a "biological" drug (now or in past) Biological drugs include Remicade/infliximab; Enbrel/etanercept; Raptiva/efalizumab; Humira/adalimumab; Stelara/ustekinumab	
Patient has been treated with another systemic agent for psoriasis (now or in past) Name of treatment:	
History and interventions score: maximum 10 points	SUM

Please enter scores for each part

S	P	I
SEVERITY (0-50)	PSYCHOSOCIAL (0-10)	INTERVENTION (0-10)

Simplified Psoriasis Index
Self-Assessment Form

Date:

LABEL or Record no: Sex:

First name:

Surname:

Thank you for completing this questionnaire which will help us understand more about you and your psoriasis. If you need help with filling in the form please ask the nurse or researcher present. The questions are in three parts and tell us a little about how your psoriasis is now, how it is affecting you personally and how it has behaved in the past.

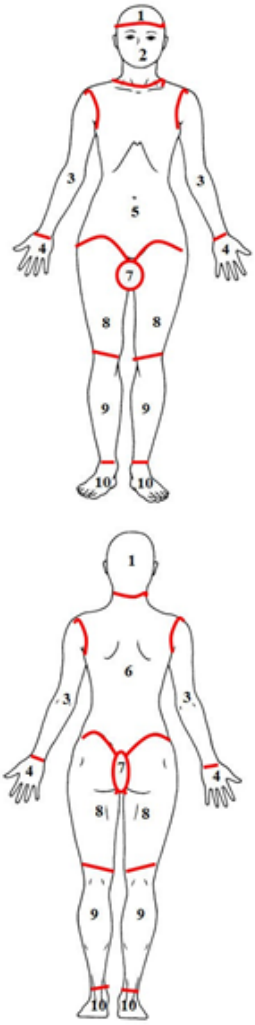
Please mark how you think your psoriasis is today

PART 1A For each of these 10 body areas please circle one choice which best describes your psoriasis today

0	±	+

0	clear or so minor that it does not bother me (0)
±	obvious but still leaving plenty of normal skin (0.5)
+	widespread and involving much of the affected area (1.0)

1	Scalp & hairline	0	±	+
2	Face, neck & ears	0	±	+
3	Arms & armpits	0	±	+
4	Hands, fingers & fingernails*	0	±	+
5	Chest & abdomen (stomach)	0	±	+
6	Back & shoulders	0	±	+
7	Genital area and/or around anus (back passage)	0	±	+
8	Buttocks & thighs	0	±	+
9	Knees, lower legs & ankles	0	±	+
10	Feet, toes & toenails*	0	±	+
*PSORIASIS OF THE NAILS: even if the skin of the hands or feet is unaffected you can score ± for severe psoriasis of at least 2 and + for 6 or more finger or toenails		SUM		



PART 1B Please circle whichever of these choices best describes the overall state of your psoriasis today. Your score should reflect the average of all of your psoriasis, not just the worst areas.

0	Clear or just slight redness or staining
1	Mild redness or scaling with no more than slight thickening
2	Definite redness, scaling or thickening
3	Moderately severe with obvious redness, scaling or thickening
4	Very red and inflamed, very scaly or very thick
5	Intensely inflamed skin with or without pustules (pus spots)

You may be given some photographic images to help you score your psoriasis.

PRODUCT 1A X 1B

please turn over

PART 2 Please make a mark on the line below to show us how much your psoriasis is affecting you in your day-to-day life today.

0 1 2 3 4 5 6 7 8 9 10

Guide: 0 = my psoriasis is not affecting me at all
5 = my psoriasis is affecting me quite a lot
10 = my psoriasis is affecting me very much (I could not imagine it affecting me more)

PART 3 Please tick each statement you think is true. Leave blank if you have not heard of the treatment or are not sure.	Tick
About your psoriasis	
I have had psoriasis for more than ten years	
I have had psoriasis for more than 20 years (additional point)	
I have had very inflamed psoriasis of all my skin (erythrodermic or pustular)	
I have been admitted to hospital for my psoriasis	
About your psoriasis treatment	
I have had at least one course of ultraviolet light treatment or PUVA	
I have been treated with methotrexate (now or in past)	
I have been treated with acitretin (Neotigason, etretinate) (now or in past)	
I have been treated with ciclosporin (Neoral) (now or in past)	
I have been treated with a "biological" drug given by injection or drip (now or in past) Biological drugs include Remicade/infliximab; Enbrel/etanercept; Raptiva/efalizumab; Humira/adalimumab; Stelara/ustekinumab	
I have been treated with another tablet/injection treatment for my psoriasis (now or in the past). If so, can you remember the name of the treatment? Name of treatment:	
	SUM

To be completed by doctor or nurse

PART 1 S	PART 2 P	PART 3 I
SEVERITY (0-50)	PSYCHOSOCIAL (0-10)	INTERVENTION (0-10)

Simplified Psoriasis Index

Date: 6 / 6 / 13

For completion by doctor or nurse

LABEL or Record no: 84726 Sex: M

First name: John

Surname: Smith

PART 1A Circle the option which most closely describes the current **extent** of psoriasis in each body area

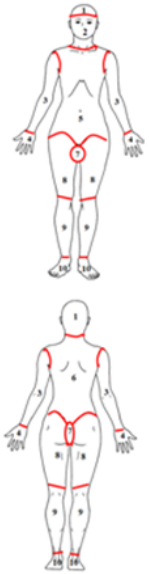
0	clear or minimal with no more than a few scattered thin plaques (0)
±	obvious but still leaving plenty of normal skin (0.5)
+	widespread and involving much of the affected area (1.0) §

§ Please note that this is not the same as percentage body surface area (BSA) involvement: the extent score takes into account how dispersed the plaques are

		0	½	1
1	Scalp & hairline	0	±	+
2	Face, neck & ears	0	±	+
3	Arms & armpits	0	±	+
4	Hands, fingers & fingernails*	0	±	+
5	Chest & abdomen (stomach)	0	±	+
6	Back & shoulders	0	±	+
7	Anogenital area	0	±	+
8	Buttocks & thighs	0	±	+
9	Knees, lower legs & ankles	0	±	+
10	Feet, toes & toenails*	0	±	+

* score severe dystrophy of ≥ 2 nails as 0.5 and ≥ 6 nails as 1.0

Total extent score: maximum 10 points 1A 3



PART 1B Select the option which best describes the current **average severity** of psoriasis. This should take into account **all** affected areas identified above, not just the worst areas. Please refer to photographic severity key if available.

0	**Essentially clear:** with faint erythema *or* residual pigmentation only
1	**Mild: erythema** *and/or* **scale** with focal slight palpable thickening
2	**Mild-to-moderate: erythema** *and/or* **scale** *with* majority of affected skin palpably thickened
3	**Moderate: erythema** *and/or* **scale** *and/or* **skin thickening**
4	**Marked: erythema** *and/or* **scale** *and/or* **skin thickening**
5	**Intensely inflamed skin:** with or without pustulation

Average severity score: maximum 5 points 1B 3

Current extent and severity score = 1A x 1B (max. 50) 1A*1B 9

Please turn over

PART 2 Ask patient to mark the line below in response to the question:

"How much is your psoriasis affecting you in your day-to-day life today?"

0 1 2 3 4 5 6 7 8 9 10

Guide: 0 = my psoriasis is not affecting me at all
5 = my psoriasis is affecting me quite a lot
10 = my psoriasis is affecting me very much (I could not imagine it affecting me more)

PART 3 Give **one point** for each true statement / for each therapy received (whether currently or in the past).	**Point**
About patient's psoriasis	
Patient has had psoriasis for more than ten years	
Patient has had psoriasis for more than 20 years (additional point)	
Patient has had erythrodermic or generalised pustular psoriasis	
Patient has been admitted to hospital for psoriasis	
About patient's treatment	
Patient has had at least one course of ultraviolet treatment or PUVA	
Patient has been treated with methotrexate (now or in past)	
Patient has been treated with acitretin or etretinate (now or in past)	
Patient has been treated with ciclosporin (now or in past)	
Patient has been treated with a "biological" drug (now or in past) Biological drugs include Remicade/infliximab; Enbrel/etanercept; Raptiva/efalizumab; Humira/adalimumab; Stelara/ustekinumab	
Patient has been treated with another systemic agent for psoriasis (now or in past) Name of treatment:	
History and interventions score: maximum 10 points	I 8

Please enter scores for each part

S	P	I
9	3	8
SEVERITY (0-50)	PSYCHOSOCIAL (0-10)	INTERVENTION (0-10)

13.2 Appendix 2 : PASI score

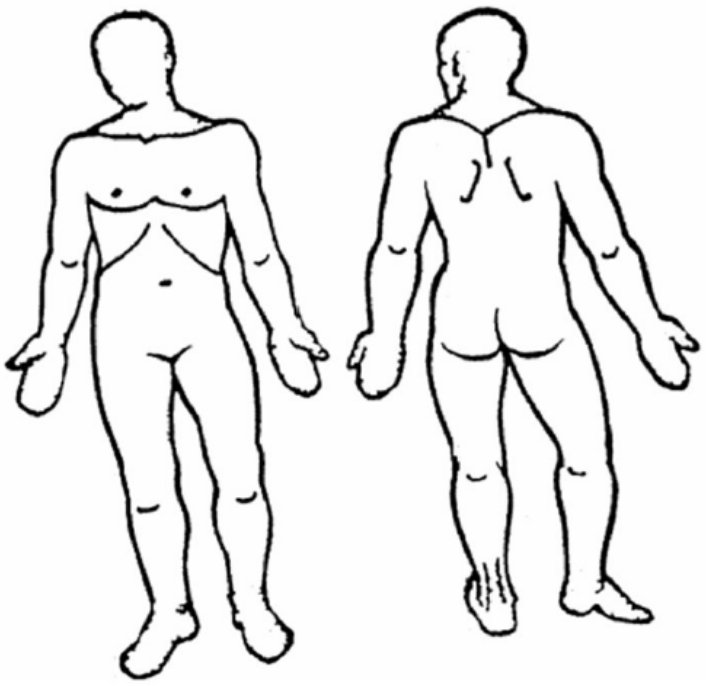
Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
Head (H)†	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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=no involvement 1=>0-<10% 2=10-<30% 3=30-<50% 4=50-<70% 5=70-<90% 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

13.3 Appendix 3: SA-PASI score

How bad is your psoriasis TODAY?

1. As best you can, please shade in on the drawing exactly where you have psoriasis.



2. Answer each question by placing a mark anywhere on the line to show how red, thick, and scaly an average spot of your psoriasis is (see example).

EXAMPLE: Great | Good | OK | Bad | Terrible

A. What color is an average spot of your psoriasis?

No redness | Slight Pink | Pink | Red | Dark Red

B. How thick is an average spot of your psoriasis?

No thickness | Feels Firm | Raised | Thick | Very Thick

C. How scaly is an average spot of your psoriasis?

No scale | Slight Scale | Scaly | Flaky | Very Flaky

13.4 Appendix 4 : DLQI questionnaire

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

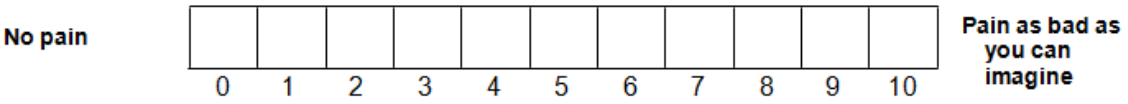
Please check you have answered EVERY question. Thank you.

13.5 Appendix 5 : Pain, itching and scaling assessment

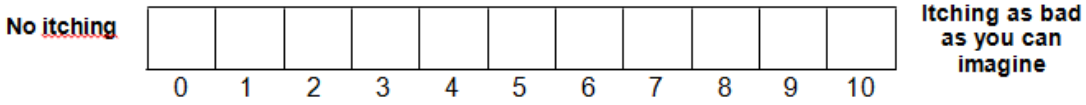
Select the number that best describes your symptoms in the past 24 hours.

Please check (x) one box.

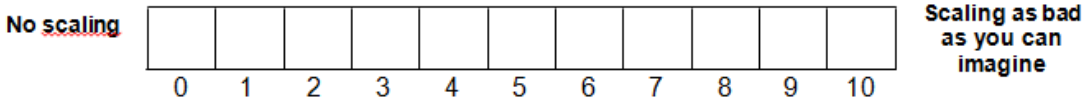
Pain : Overall, how severe was your psoriasis-related pain over the past 24 hours ?



Itching : Overall, how severe was your itching over the past 24 hours ?



Scaling : Overall, how severe was your psoriasis scaling over the past 24 hours ?



13.6 Appendix 6 : BISF-M

ID#_____ Date _____

This index covers material that is sensitive and personal. Your responses will be kept completely confidential. If you are unable or do not wish to answer any question, you may leave it blank.

Answer the following questions by choosing the most accurate response *for the past month.*

1, Do you currently have a sex parnter? _____Yes _____ No

2. Have you been sexually active during the past month? _____ Yes _____ No

3. During the past month, how frequently have you had sexual thoughts, fantasies, or erotic dreams? *(Please circle the most appropriate response.)*

(0) Not at all
(1) Once
(2) 2 or 3 times
(3) Once a week
(4) 2 or 3 times per week
(5) Once a day
(6) More than once a day

4. Using the scale to the right, indicate how frequently you have felt a desire to engage in the following activities during the past month? *(An answer is required for each, even if it may not apply to you.)*

Kissing	_____	(0) Not at all
Masturbation alone	_____	(1) Once
Mutual masturbation	_____	(2) 2 or 3 times
Petting and foreplay	_____	(3) Once a week
Oral sex	_____	(4) 2 or 3 times per week
Vaginal penetration or intercourse	_____	(5) Once a day
Anal sex	_____	(6) More than once a day

5. Using the scale to the right, indicate how frequently you have become aroused by the following sexual experiences during the past month. *(An answer is required for each, even if it may not apply to you.)*

Kissing	_____	(0) Have not engaged in this activity
Dreams or fantasy	_____	(1) Not at all
Masturbation alone	_____	(2) Seldom, less than 25% of the time
Mutual masturbation	_____	(3) Sometimes, about 50% of the time
Petting and foreplay	_____	(4) Usually, about 75% of the time
Oral sex	_____	(5) Always became aroused
Vaginal penetration or intercourse	_____	
Anal sex	_____	

6. Overall, during the past month, how frequently have you become anxious or inhibited during sexual activity with a partner? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Not at all anxious or inhibited
(2) Seldom, less than 25% of the time
(3) Sometimes, about 50% of the time
(4) Usually, about 75% of the time
(5) Always became anxious or inhibited

7. Using the scale to the right, indicate how frequently you have engaged in the following sexual experiences during the past month? *(An answer is required for each, even if it may not apply to you.)*

Kissing	_____	(0) Not at all
Sexual fantasy	_____	(1) Once
Masturbation alone	_____	(2) 2 or 3 times
Mutual masturbation	_____	(3) Once a week
Petting and foreplay	_____	(4) 2 or 3 times per week
Oral sex	_____	(5) Once a day
Vaginal penetration or intercourse	_____	(6) More than once a day
Anal sex	_____	

8. During the past month, who has usually initiated sexual activity? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) I have not had sex with a partner during the past month
(2) I usually have initiated activity
(3) My partner and I have equally initiated activity
(4) My partner usually has initiated activity.

9. During the past month, how have you usually responded to your partner's sexual advances? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Has not happened during the past month
(2) Usually refused
(3) Sometimes refused
(4) Accepted reluctantly
(5) Accepted, but not necessarily with pleasure
(6) Usually accepted with pleasure
(7) Always accepted with pleasure

10. During the past month, have you felt pleasure from any forms of sexual experience? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Have had no sexual experience during the past month
(2) Have not felt any pleasure
(3) Seldom, less than 25% of the time
(4) Sometimes, about 50% of the time
(5) Usually, about 75% of the time
(6) Always felt pleasure

11. Using the scale to the right, indicate how often you have reached orgasm during the past month with the following activities. *(An answer is required for each, even if it may not apply to you.)*

In dreams or fantasy	(0) I have not had a partner
Kissing	(1) Have not engaged in this activity
Masturbation alone	(2) Not at all
Mutual masturbation	(3) Seldom, less than 25% of the time
Petting and foreplay	(4) Sometimes, about 50% of the time
Oral sex	(5) Usually about 75% of the time
Vaginal penetration or intercourse	(6) Always reached orgasm
Anal sex	

12. During the past month, has the frequency of your sexual activity with a partner been: *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Less than you desired
(2) As much as you desired
(3) More than you desired

13. Using the scale to the right, indicate the level of change, if any, in the following areas during the past month? *(An answer is required for each, even if it may not apply to you.)*

Sexual interest	(0) Not applicable
Sexual arousal	(1) Much lower level
Sexual activity	(2) Somewhat lower level
Sexual satisfaction	(3) No change
Sexual anxiety	(4) Somewhat higher level
	(5) Much higher level

14. During the past month, how frequently have you experienced the following? *(An answer is required for each, even if it may not apply to you.)*

Ejaculation too fast	(0) Not at all
Difficulty obtaining and / or maintaining an erection	(1) Seldom, less than 25% of the time
No penetration or report painful ejaculation or ejaculation obtained with difficulty	(2) Sometimes, about 50% of the time
involuntary urination	(3) Usually, about 75% of the time
Headaches after sexual activity	(4) Always
urogenital infection	

15. Using the scale to the right, indicate the frequency with which the following factors have influenced your level of sexual activity during the past month. *(An answer is required for each, even if it may not apply to you.)*

My own health problems	(0) I have not had a partner
(for example, infection, illness)	(1) Not at all
My partner's health problems	(2) Seldom, less than 25% of the time
Conflict in the relationship	(3) Sometimes, about 50% of the time
Lack of privacy	(4) Usually, about 75% of the time
Other (please specify):	(5) Always
_____	

16. How satisfied are you with the overall appearance of your body? *(Please circle the most appropriate response.)*

(0) Very satisfied
(1) Somewhat satisfied
(2) Neither satisfied nor dissatisfied
(3) Somewhat dissatisfied
(4) Very dissatisfied

17. During the past month, how frequently have you been able to communicate your sexual desires or preferences to your partner? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) I have been unable to communicate my desires or preferences
(2) Seldom, about 25% of the time
(3) Sometimes, about 50% of the time
(4) Usually, about 75% of the time
(5) I was always able to communicate my desires or preferences

18. Overall, how satisfied have you been with your sexual relationship with your partner? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Very satisfied
(2) Somewhat satisfied
(3) Neither satisfied nor dissatisfied
(4) Somewhat dissatisfied
(5) Very dissatisfied

19. Overall, how satisfied do you think your partner has been with your sexual relationship? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Very satisfied
(2) Somewhat satisfied
(3) Neither satisfied nor dissatisfied
(4) Somewhat dissatisfied
(5) Very dissatisfied

20. Overall, how important a part of your life is your sexual activity? *(Please circle the most appropriate response.)*

(0) Not at all important
(1) Somewhat unimportant
(2) Neither important nor unimportant
(3) Somewhat important
(4) Very important

21. Circle the number that corresponds to the statement that best describes your sexual experience.

(1) Entirely heterosexual
(2) Largely heterosexual, but some homosexual experience
(3) Largely heterosexual, but considerable homosexual experience
(4) Equally heterosexual and homosexual
(5) Largely homosexual, but considerable heterosexual experience

(6) Largely homosexual, but some heterosexual experience
(7) Entirely homosexual

22. Circle the number that corresponds to the statement that best describes your sexual desires.

(1) Entirely heterosexual
(2) Largely heterosexual, but some homosexual desire
(3) Largely heterosexual, but considerable homosexual desire
(4) Equally heterosexual and homosexual
(5) Largely homosexual, but considerable heterosexual desire
(6) Largely homosexual, but some heterosexual desire
(7) Entirely homosexual

13.7 Appendix 7 : BISF-W

ID#_____ Date _____

This index covers material that is sensitive and personal. Your responses will be kept completely confidential. If you are unable or do not wish to answer any question, you may leave it blank.

Answer the following questions by choosing the most accurate response *for the past month.*

1, Do you currently have a sex parnter? _____Yes _____ No

2. Have you been sexually active during the past month? _____ Yes _____ No

3. During the past month, how frequently have you had sexual thoughts, fantasies, or erotic dreams? *(Please circle the most appropriate response.)*

(0) Not at all
(1) Once
(2) 2 or 3 times
(3) Once a week
(4) 2 or 3 times per week
(5) Once a day
(6) More than once a day

4. Using the scale to the right, indicate how frequently you have felt a desire to engage in the following activities during the past month? *(An answer is required for each, even if it may not apply to you.)*

Kissing	_____	(0) Not at all
Masturbation alone	_____	(1) Once
Mutual masturbation	_____	(2) 2 or 3 times
Petting and foreplay	_____	(3) Once a week
Oral sex	_____	(4) 2 or 3 times per week
Vaginal penetration or intercourse	_____	(5) Once a day
Anal sex	_____	(6) More than once a day

5. Using the scale to the right, indicate how frequently you have become aroused by the following sexual experiences during the past month. *(An answer is required for each, even if it may not apply to you.)*

Kissing	_____	(0) Have not engaged in this activity
Dreams or fantasy	_____	(1) Not at all
Masturbation alone	_____	(2) Seldom, less than 25% of the time
Mutual masturbation	_____	(3) Sometimes, about 50% of the time
Petting and foreplay	_____	(4) Usually, about 75% of the time
Oral sex	_____	(5) Always became aroused
Vaginal penetration or intercourse	_____	
Anal sex	_____	

6. Overall, during the past month, how frequently have you become anxious or inhibited during sexual activity with a partner? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Not at all anxious or inhibited
(2) Seldom, less than 25% of the time
(3) Sometimes, about 50% of the time
(4) Usually, about 75% of the time
(5) Always became anxious or inhibited

7. Using the scale to the right, indicate how frequently you have engaged in the following sexual experiences during the past month? *(An answer is required for each, even if it may not apply to you.)*

Kissing	_____	(0) Not at all
Sexual fantasy	_____	(1) Once
Masturbation alone	_____	(2) 2 or 3 times
Mutual masturbation	_____	(3) Once a week
Petting and foreplay	_____	(4) 2 or 3 times per week
Oral sex	_____	(5) Once a day
Vaginal penetration or intercourse	_____	(6) More than once a day
Anal sex	_____	

8. During the past month, who has usually initiated sexual activity? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) I have not had sex with a partner during the past month
(2) I usually have initiated activity
(3) My partner and I have equally initiated activity
(4) My partner usually has initiated activity.

9. During the past month, how have you usually responded to your partner's sexual advances? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Has not happened during the past month
(2) Usually refused
(3) Sometimes refused
(4) Accepted reluctantly
(5) Accepted, but not necessarily with pleasure
(6) Usually accepted with pleasure
(7) Always accepted with pleasure

10. During the past month, have you felt pleasure from any forms of sexual experience? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Have had no sexual experience during the past month
(2) Have not felt any pleasure
(3) Seldom, less than 25% of the time
(4) Sometimes, about 50% of the time
(5) Usually, about 75% of the time
(6) Always felt pleasure

11. Using the scale to the right, indicate how often you have reached orgasm during the past month with the following activities. *(An answer is required for each, even if it may not apply to you.)*

In dreams or fantasy	_____	(0) I have not had a partner
Kissing	_____	(1) Have not engaged in this activity
Masturbation alone	_____	(2) Not at all
Mutual masturbation	_____	(3) Seldom, less than 25% of the time
Petting and foreplay	_____	(4) Sometimes, about 50% of the time
Oral sex	_____	(5) Usually about 75% of the time
Vaginal penetration or intercourse	_____	(6) Always reached orgasm
Anal sex	_____	

12. During the past month, has the frequency of your sexual activity with a partner been: *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Less than you desired
(2) As much as you desired
(3) More than you desired

13. Using the scale to the right, indicate the level of change, if any, in the following areas during the past month? *(An answer is required for each, even if it may not apply to you.)*

Sexual interest	_____	(0) Not applicable
Sexual arousal	_____	(1) Much lower level
Sexual activity	_____	(2) Somewhat lower level
Sexual satisfaction	_____	(3) No change
Sexual anxiety	_____	(4) Somewhat higher level
		(5) Much higher level

14. During the past month, how frequently have you experienced the following? *(An answer is required for each, even if it may not apply to you.)*

Bleeding or irritation after vaginal penetration or intercourse	_____	(0) Not at all
Lack of vaginal lubrication	_____	(1) Seldom, less than 25% of the time
Painful penetration or intercourse	_____	(2) Sometimes, about 50% of the time
Difficulty reaching orgasm		(3) Usually, about 75% of the time
Vaginal tightness	_____	(4) Always
Involuntary urination	_____	
Headaches after sexual activity	_____	
Vaginal infection	_____	

15. Using the scale to the right, indicate the frequency with which the following factors have influenced your level of sexual activity during the past month. *(An answer is required for each, even if it may not apply to you.)*

My own health problems (for example, infection, illness)	_____	(0) I have not had a partner
My partner's health problems	_____	(1) Not at all
Conflict in the relationship	_____	(2) Seldom, less than 25% of the time
Lack of privacy	_____	(3) Sometimes, about 50% of the time
Other (please specify):	_____	(4) Usually, about 75% of the time
_____	_____	(5) Always

16. How satisfied are you with the overall appearance of your body? *(Please circle the most appropriate response.)*

(0) Very satisfied
(1) Somewhat satisfied
(2) Neither satisfied nor dissatisfied
(3) Somewhat dissatisfied
(4) Very dissatisfied

17. During the past month, how frequently have you been able to communicate your sexual desires or preferences to your partner? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) I have been unable to communicate my desires or preferences
(2) Seldom, about 25% of the time
(3) Sometimes, about 50% of the time
(4) Usually, about 75% of the time
(5) I was always able to communicate my desires or preferences

18. Overall, how satisfied have you been with your sexual relationship with your partner? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Very satisfied
(2) Somewhat satisfied
(3) Neither satisfied nor dissatisfied
(4) Somewhat dissatisfied
(5) Very dissatisfied

19. Overall, how satisfied do you think your partner has been with your sexual relationship? *(Please circle the most appropriate response.)*

(0) I have not had a partner
(1) Very satisfied
(2) Somewhat satisfied
(3) Neither satisfied nor dissatisfied
(4) Somewhat dissatisfied
(5) Very dissatisfied

20. Overall, how important a part of your life is your sexual activity? *(Please circle the most appropriate response.)*

(0) Not at all important
(1) Somewhat unimportant
(2) Neither important nor unimportant
(3) Somewhat important
(4) Very important

21. Circle the number that corresponds to the statement that best describes your sexual experience.

(1) Entirely heterosexual
(2) Largely heterosexual, but some homosexual experience
(3) Largely heterosexual, but considerable homosexual experience
(4) Equally heterosexual and homosexual
(5) Largely homosexual, but considerable heterosexual experience

(6) Largely homosexual, but some heterosexual experience
(7) Entirely homosexual

22. Circle the number that corresponds to the statement that best describes your sexual desires.

(1) Entirely heterosexual
(2) Largely heterosexual, but some homosexual desire
(3) Largely heterosexual, but considerable homosexual desire
(4) Equally heterosexual and homosexual
(5) Largely homosexual, but considerable heterosexual desire
(6) Largely homosexual, but some heterosexual desire
(7) Entirely homosexual

13.8 Appendix 8: Normal ranges of values for vital signs

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

13.9 Appendix 9: Clinically notable laboratory findings

The following criteria will be used to define expanded limits and notable abnormalities of key laboratory tests. Notable values for blood pressure and pulse are presented in Section 6.6.2. Whether action needs to be taken to address notable laboratory or vital signs values will be decided by the investigator, taking into account the overall status of the patient. No specification is foreseen as part of the study protocol.

Variable	Limit
Liver Function and Related Variables	
Alanine transaminase (ALT) (SGPT)	> 3 x ULN
Aspartate transaminase (AST) (SGOT)	> 3 x ULN
Total bilirubin	> 2 x ULN
Alkaline phosphatase	> 2.5 x ULN
Renal Function and Electrolyte Variables	
Creatinine (serum)	> 1.5 x ULN

Potassium	> 6 mmol/L or < 3 mmol/L
Sodium	> 160 mmol/L or < 115 mmol/L
Hematology Variables	
Hemoglobin	≥ 20 g/dL decrease from Baseline
Platelet count	< 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	++*

ULN: Upper Limit of Normal
LLN: Lower Limit of Normal
* ++ corresponds to ≥ 100 mg/dL

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

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