NOVARTIS

Clinical Research Germany, Therapeutic Area Dermatology, Allergology, Rheumatology

Non-Interventional Study Protocol

CAIN457ADE07

Title	PROSPECT: Observational, descriptive study of **PR**ior and c**O**ncomitant p**S**oriasis treatments in **P**atients receiving S**EC**ukinumab in the routine **T**reatment of moderate to severe plaque-type psoriasis
Protocol version identifier	v01
Date of last version of protocol	13 May 2016
EU PAS register number	ENCEPP/SDPP/10715
Active substance	Secukinumab (AIN457), pharmacotherapeutic group: immunosuppressants, interleukin inhibitors, ATC code: L04AC10

Medicinal product and product reference

Name of the medicinal product	**Marketing authorization number (centrally authorized medicinal product)**
Cosentyx 150 mg solution for injection in pre-filled syringe	
• 2 pre-filled syringes	EU/1/14/980/003
• 6 (3 x 2) pre-filled syringes (multipack)	EU/1/14/980/006
Cosentyx 150 mg solution for injection in pre-filled pen	
• 2 pre-filled pens	EU/1/14/980/005
• 6 (3 x 2) pre-filled pens (multipack)	EU/1/14/980/007

Procedure	EMEA/H/C/3729

number

Name of marketing authorization holder(s)	Marketing authorization holder: Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom Local representative of the marketing authorisation holder: Novartis Pharma GmbH, Roonstraße 25, 90429 Nuernberg, Germany
Sponsor:	Novartis Pharma GmbH, Roonstraße 25, 90429 Nuernberg, Germany
Joint PASS	No
Research question and objectives	The objective of this descriptive study is to assess prior and concomitant psoriasis treatments in patients receiving Secukinumab in the routine treatment of moderate to severe plaque-type psoriasis, focusing on duration of transition periods from prior treatments to Secukinumab and on the use of concomitant treatments. Furthermore, effectiveness as assessed in clinical routine as well as safety will be described.
Country (-ies) of study	Germany
Authors	[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited, Frimley Business Park, Camberley GU16 7SR, United Kingdom
MAH contact person	[redacted]

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List of abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BSA	Body Surface Area
CRO	Contract Research Organization
DLQI	Dermatology Life Quality Index
DS&E	Drug Safety and Epidemiology
eCRF	Electronic Case Report/Record Form
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food & Drug Administration
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HA	Health Authority
ICD-9-CM	The International Classification of Diseases, 9th Revision, Clinical Modification
ICF	Informed Consent Form
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NIS	Non-Interventional Study
NVS	Novartis
PAS	Post-Authorization Study
PASI	Psoriasis Area and Severity Index
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
WHO	World Health Organisation

Glossary of terms

Transition period	If a treatment is stopped before the initial dose of a new treatment, the time between the last dose of the prior and the first dose of the latter treatment is defined as transition period.
Treatment category	All treatment groups that are used alternatively in the same line of treatment and/or the same group of patients are summarized into one treatment category.
Treatment group	All treatment types that have the same or a similar target are summarized into one treatment group. As exceptions, the different TNF-antagonists are defined as distinctive treatment groups and some rare treatment types are summarized to treatment groups despite different targets.
Treatment type	All treatments with the same pharmacologically active ingredient or physically active component (e.g. UVB) and with similar galenic forms and/or administration routes are summarized into the same treatment type. Some rare treatments may be summarized to one treatment type if they have similar targets but not identical active ingredients.

1 Responsible parties

Table 1-1 Main responsible parties

Role	Person
Main protocol authors	[redacted]
Principal investigator (PI)	The studies principal investigators constitute a steeting committee. The steering committee chair is: Prof. Dr. Diamant Thaçi University Hospital Schleswig-Holstein, Campus Lübeck Ratzeburger Allee 160 23538 Lübeck, Germany phone: +49 (0)451 500 4130 fax: +49 (0)451 500 4129
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2 Abstract

Title

PROSPECT: Observational, descriptive study of PRior and cOncomitant pSoriasis treatments in Patients receiving SECukinumab in the routine Treatment of moderate to severe plaque-type psoriasis

Version and date

Non-interventional Study Protocol CAIN457ADE07 v01 released on 13 May 2016

Name and affiliation of main author

[redacted]

Rationale and background

It is expected that in routine treatment of psoriasis, due to the current recommendations and medical practice, transition periods before administration of Secukinumab will be short. Also, some concomitant treatments with pharmacologically active substances will be given in parallel, tapered or stopped only after the effectiveness of Secukinumab in the individual patient becomes evident, despite lack of experience in their combined application.

Research question and objectives

The objective of this descriptive study is to assess prior and concomitant psoriasis treatments in patients receiving Secukinumab in the routine treatment of moderate to severe plaque-type psoriasis, focusing on duration of transition periods from prior treatments to Secukinumab and on the use of concomitant treatments. Furthermore, effectiveness as assessed in clinical routine as well as safety will be described.

Study design

This is a single-cohort, non-interventional study with a study duration of 24 weeks recruiting patients for whom the decision of treatment with Secukinumab for plaque-psoriasis has been made before inclusion. It is expected that most patients are likely to be seen at the regular visits at weeks 0, 4, 12, 16, and 24 and that some patients may also be seen at some of the additional visits at weeks 1, 2, 3, 8, and 20.

Population

The study population will consist of a representative group of adults with moderate to severe plaque type psoriasis who are candidates for systemic therapy and for whom routine treatment with Secukinumab is planned. The goal is to recruit a total of approximately 2504 patients in approximately 300-400 sites in Germany.

Variables

Variables related to patient demographics, psoriasis and other medical history, prior and concomitant treatments, PASI and other routine effectiveness and quality of life assessments and safety will be documented.

Data sources

This study involves a primary data collection. Therefore the sources of data are the treating physicians and the patients. All these data should be documented as well in the individual patient charts at the physicians office.

Study size

The duration of the transition period shall be estimated with sufficient precision for all groups of previous treatments, especially for Methotrexate due to its international significance as a first-line treatment. A total of 2504 patients are expected to result in 283 patients who underwent transition from Methotrexate to Secukinumab. With 283 patients in this group the mean duration of the transition period can be estimated with an adequate precision [95% CI] of about 7 days assuming a standard deviation of 60 days.

Data analysis

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the treating physician(s) should be submitted to Novartis before publication or presentation. All data will be analyzed descriptively. Exploratory subgroup and correlation analyses will be applied to identify factors that may influence primary and secondary endpoints.

Milestones

Start of data collection	01 September 2015
End of data collection	31 March 2018
Interim Analysis Study Report	31 December 2016
Final report of study results	30 September 2018
Registration in the EU PAS register	01 September 2015

3 Amendments and updates

Amendment 1

The original protocol is amended to increase sample size and and site number, and prolong the recruitment period based on the predefined interim analysis (see section 8.6). Moreover, reconciliation of adverse events data with the national registry PsoBest was removed after clarification of the collaboration with PsoBest.

- As the standard deviation of the duration of the transition period in Methotrexate pre-treated patients was much higher in interim analysis data than expected during the planning of the study, sample size was increased to 2504 patients to obtain an acceptable precision (see section 7.5).
- Recruitment period was extended until 30-Sep-2017 to be able to recruit 2504 patients. Accordingly, the end of data collection had to be shifted to 31-Mar-2018, and the date of final study report had to be moved to 30-Sep-2018 (see sections 4, 7.2.4 and 7.5).
- The number of sites was increased to 300-400 in order to be able to recruit 2504 patients (see section 7.2.1).
- Recruitment limitations to control for sample sizes of subgroups patients with higher disease severity or disease impact and patients without prior conventional systemic treatments or phototherapy or biologic treatments were removed as it is expected that sufficient samples sizes are obtained with the increased overall sample size of 2504 patients (see sections 7.1 and 7.2.2).
- A further interim analysis of baseline data will be conducted after recruitment of 2000 patients to reassess the precision for all groups of previous treatments, given the high variability of data obtained in the first interim analysis (see section 8.6.).
- Reconciliation of adverse events data with the national registry PsoBest was removed as the collaboration with PsoBest was clarified and reconciliation of safety events between PROSPECT and PsoBest is no longer required (see section 10). Consequently, the prerequisite for patients from PsoBest to provide informed consent for reconciliation of adverse event reports with PsoBest was removed as well (see section 7.2.2.).

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

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities. The changes described in this amended protocol require IRB/IEC approval prior to implementation.

4 Milestones

Table 4-1 Study milestones

Milestone	Planned date
Start of data collection	01 September 2015
End of data collection	31 March 2018
Interim Analysis Study Report	31 December 2016
Final report of study results	30 September 2018
Registration in the EU PAS register	01 September 2015

5 Rationale and background

In Germany, treatment of moderate to severe psoriasis usually involves the following treatment categories and treatment groups, some of which include more than one individual treatment type:

Table 5-1 Psoriasis treatment categories and groups in Germany

Treatment Categories	Topical treatments	Conventional systemic treatments (and phototherapy):	Biologic treatments:
Treatment Groups (one or with one or more types per group)	- Topical steroids - Vitamin D3 analogues - Calcineurin inhibitors - all other topical treatments (e.g. dithranol, tar, laser)	- Fumaric acid esters - Methotrexate - Photo- and Photochemotherapy - Ciclosporin - Acitretin - Apremilast - all other systemic treatments (e.g. systemic steroids)	- Ustekinumab - Adalimumab - Etanercept - Infliximab - Secukinumab

The German treatment guidelines for psoriasis recommend combinations of some of these treatments for selected patients and purposes. Therefore, especially topical treatments are often combined with both conventional systemic treatments and biologics, and conventional systemic treatments are sometimes combined with biologics [1]. Moreover, an international consensus group recently recommended switching psoriasis treatments with minimal transition periods if switching is done due to lack of efficacy [2]. As a consequence some patients experience short term and low dose exposure to two biologics after the transition from a failing to a new biologic. This is a result of the potentially long elimination half-life of the respective failing biologic.

Cosentyx (Secukinumab) was recently approved in Europe for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Extensive phase III study data have shown that Secukinumab is an effective and safe treatment in this indication [3-7]. However, in these studies patients were required to have washed out all conventional systemic, biologic and topical treatments during long transition periods and only bland emollients were allowed as concomitant psoriasis treatments. Therefore, there is a lack of data

on the effect of shorter transition periods and concomitant psoriasis treatment with other pharmacologically active substances on the effectiveness and safety of Secukinumab.

It is, however, expected that in routine treatment of psoriasis, due to the current recommendations and medical practice, transition periods before administration of Secukinumab will be short, and some concomitant treatments with pharmacologically active substances will given in parallel, tapered or stopped only after the effectiveness of Secukinumab in the individual patient becomes evident, despite lack of precedent.

The goal of this short-term, descriptive, observational study is to determine the transition periods of prior treatments and the use of concomitant treatments of patients who receive Secukinumab in routine treatment of psoriasis.

6 Research question and objectives

The objective of this descriptive study - without any formal a priori hypothesis - is to assess prior and concomitant psoriasis treatments in patients receiving Secukinumab in the routine treatment of moderate to severe plaque-type psoriasis, focusing on duration of transition periods from prior treatments to Secukinumab and on the use of concomitant treatments. Furthermore, effectiveness as assessed in clinical routine as well as safety will be described. Moreover, exploratory analytical objectives of this study are subgroup differences and correlations between effectiveness and safety and prior and concomitant psoriasis treatments.

6.1 Primary endpoint

The descriptive primary endpoint of the study is the assessment of the duration of the transition periods from prior treatments to Secukinumab with adequate precision for the following prior treatment categories and groups:

- All topical treatments
- All conventional systemic treatments (and phototherapy)
- All biologic treatments
- Fumaric acid esters
- Methotrexate
- Ciclosporin

The study is powered to determine the duration of the transition period of the Methotrexate treatment group with a precision of 7 days (see section 7.5).

6.2 Secondary endpoints

- The assessment of the duration of the transition periods from prior treatments to Secukinumab per prior treatment group with adequate precision for the following prior treatment groups:
    - Topical steroids
    - Vitamin D3 analogues
    - Calcineurin inhibitors
    - All other topical treatments (e.g. dithranol, tar, laser)

  - Photo- and Photochemotherapy
  - Retinoids
  - Apremilast
  - Ustekinumab
  - Adalimumab
  - Etanercept
  - Infliximab

- The proportion of patients with a transition period of ≤ 1 treatment interval, > 1 and ≤ 3 treatment intervals, > 3 and ≤ 5 treatment intervals, and > 5 treatment intervals per treatment group.
- The proportion of patients with a transition period of ≤ 1 systemic terminal half-life, > 1 and ≤ 3 systemic terminal half-lives, > 3 and ≤ 5 systemic terminal half-lives and > 5 systemic terminal half-lives for the following treatment groups:
  - Fumaric acid esters
  - Methotrexate
  - Ciclosporin
  - Retinoids
  - Apremilast
  - Ustekinumab
  - Adalimumab
  - Etanercept
  - Infliximab
- Relative dose tapering of concomitant treatments per treatment group for all treatment groups defined in Table 5-1
- Dose of concomitant treatments per individual treatment type
- Clinical effectiveness of Secukinumab as assessed by PASI:
  - Raw PASI and the number of patients with a PASI of 0, and a PASI below 1, 2, 3, 5, and 10 will be assessed over time.
  - For patients who have a PASI > 10 at the first visit, PASI 50, 75, 90, and 100 response rates will be assessed, which correspond to the number of patients achieving at least a 50, 75, 90 or 100% reduction in PASI.
- Clinical effectiveness of Secukinumab, as assessed in routine treatment (e.g. IGA, PGA, DLQI, or other assessments only if performed during clinical routine)
- Clinical safety as assessed in routine treatment (AEs and SAEs)

6.3 Exploratory endpoints

- Subgroup analyses for patients who did not receive Secukinumab in a clinical trial prior to inclusion in this NIS, patients with higher disease severity or impact, and patients without prior systemic treatments

- Assessments of correlations of durations of transition periods and of concomitant medication with effectiveness parameters and adverse events, if feasible

7 Research methods

7.1 Study design

This is a single-cohort, non-interventional study with a study duration of 24 weeks recruiting patients for whom the decision of treatment with Secukinumab for plaque-psoriasis has been made before inclusion. The study will collect data from patients during routine Secukinumab treatment and will be representative of the prior and concomitant treatment categories and groups used in Germany. This study is a voluntary post authorization safety study (PASS).

The descriptive primary endpoint of the study is the assessment of the transition periods from prior treatments to Secukinumab per treatment group with adequate precision. This endpoint will be assessed retrospectively, due to the inclusion of patients at the initiation of routine Secukinumab treatment. Furthermore, the relative dose of concomitant treatments per treatment group and the absolute dose of concomitant treatments per individual treatment type will be assessed prospectively.

PASI is part of the guideline definition of both, treatment severity and treatment goals, for patients with plaque psoriasis. Therefore it is expected that PASI will be assessed for all patients as part of the clinical routine. In order to describe the effectiveness and safety of Secukinumab in routine clinical treatment and in the context of routine transition periods and concomitant medication, PASI will be documented. Moreover, IGA-, PGA- and DLQI-results and other results of measures of clinical effectiveness, if used by the treating physician during routine clinical practice, as well as adverse events, will be documented prospectively. This may also allow for exploratory analysis of correlations between effectiveness and safety and prior and concomitant psoriasis treatments.

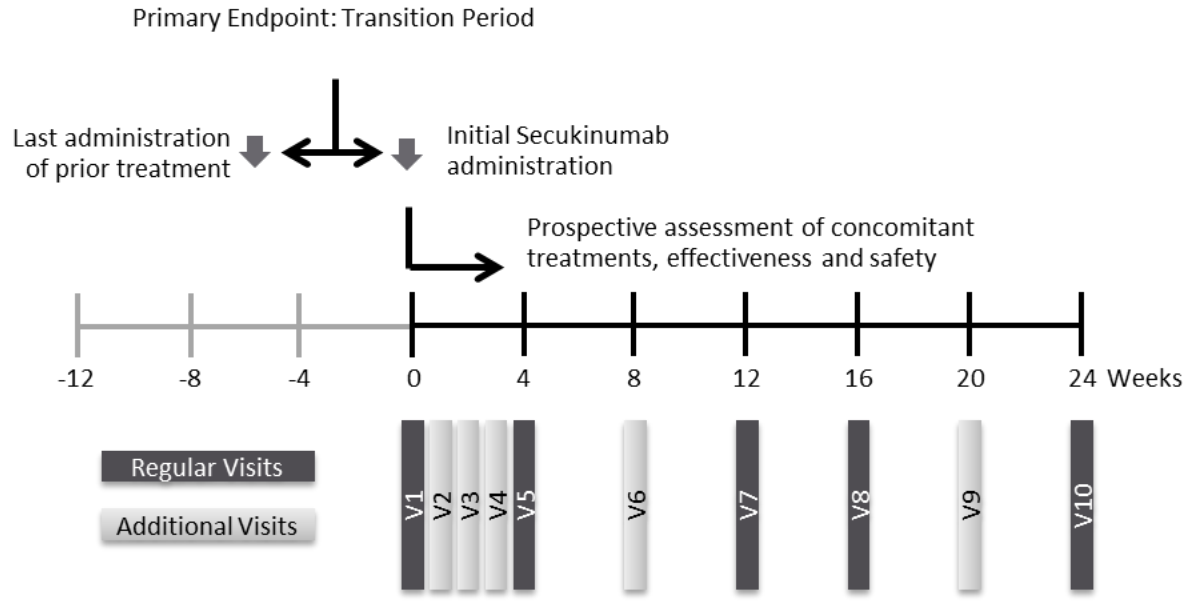
For exploratory subgroup analyses, the following subgroups' sample sizes will be analyzed. Overlap between the subgroups is expected, since their definitions are not mutually exclusive.

a. Patients who did not receive Secukinumab in a clinical trial prior to inclusion in this NIS.

b. Patients with higher disease severity or disease impact, potentially affecting transition periods and concomitant treatments as evidenced by one of the following at baseline: severe psoriasis, affected scalp, face, palms, soles, nails, joints, diagnosis of psoriatic arthritis or signs and symptoms of psoriatic arthritis including but not limited to joint pain, swelling, redness, dactylitis or enthesitis.

c. Patients without prior conventional systemic treatments or phototherapy or biologic treatments.

Figure 7-1 Study design



7.2 Setting

7.2.1 Population

The study population will consist of a representative group of adults with moderate to severe plaque type psoriasis who are candidates for systemic therapy and for whom routine treatment with Secukinumab is planned. The goal is to recruit a total of approximately 2504 patients in approximately 300-400 sites in Germany.

7.2.2 Inclusion Criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria at baseline (Visit 1, week 0):

1. Patients must give a written, signed and dated informed consent before documentation in the study will be commenced.
2. Men or women must be at least 18 years of age.
3. Diagnosis of clinically moderate to severe plaque-psoriasis. Other forms of psoriasis may be present if moderate to severe plaque-psoriasis is the reason for Secukinumab treatment.
4. Candidates for systemic therapy.
5. Documented decision for treatment with marketed Secukinumab in compliance with the prescribing information and the summary of product characteristics.
6. Initial treatment with marketed Secukinumab planned for the day of the baseline visit.

7.2.3 Exclusion Criteria

Patients fulfilling any of the following criteria at baseline (Visit 1, week 0) are not eligible for inclusion in this study. Conditional exclusion criteria will be activated during the course of the study as soon as predefined recruitment criteria have been met without the need for a protocol amendment. No additional exclusion criteria may be applied by the treating physician, in order to ensure that the study population will be representative of all eligible patients.

1. Initial treatment with marketed Secukinumab prior to the day of informed consent.
2. Parallel enrollment in any interventional clinical trial.
3. Parallel enrollment in a non-interventional study sponsored by Novartis or one of her divisions or affiliates.
4. After 300 patients who had participated in a clinical trial with Secukinumab prior to inclusion in this NIS have been recruited, no further patients who have participated in a clinical trial with Secukinumab will be included.

7.2.4 Study period

The study is scheduled to recruit patients between 01-Sep-2015 and 30-Sep-2017. Study completion of the last patient is planned to be no later than 31-Mar-2018. This study period will cover the initial period of routine clinical use of Secukinumab in Germany (available as marketed drug since 01-Jun-2015)

7.2.5 Study time frames

The study data relate to two study time frames:

1. The prospective time frame consists of 24 weeks starting with the baseline visit (week 0) and ending with the end of study visit (week 24). Data from the prospective time frame will be captured at baseline and during the regular and additional study visits.
2. The retrospective time frame consists of the time prior to the baseline visit (week 0). Data from the retrospective time frame will be captured at baseline. It is intended to cover all of the patients psoriasis history and prior psoriasis treatment as well as detailed information about disease severity and treatment types and doses during the 6 months preceeding the baseline visit if possible. Importantly the day of the last treatment with the last prior psoriasis therapy must be documented as precisely as possible.

7.2.6 Source and method of primary data collection

The treating physicians and site staff will be responsible for primary data collection by capturing the data in electronic case report forms (eCRF). The primary data captured in the eCRF must be based on written site files and documents, i.e. source data.

7.3 Variables

7.3.1 Patient demographics

Patient demographic and baseline characteristic data to be collected on all patients include: year of birth, sex, race, body height, body weight.

7.3.2 Psoriasis and other medical history

The psoriasis disease history will be recorded for all patients including: date of first psoriasis symptoms, date of first psoriasis diagnosis, signs of higher disease severity or disease impact (severe psoriasis, symptoms of psoriasis in one of the following areas: scalp, face, palms, soles, nails, signs and symptoms of psoriatic arthritic including but not limited to joint pain, enthesitis, bursitis).

Significant non-psoriasis medical history being active and or treated during the last up to 6 months prior to inclusion will be recorded including but not limited to malignancies, cardiovascular diseases, psychological diseases, chronic infectious, inflammatory or degenerative disorders. Moreover, all non-psoriasis medical history related to recorded prior and concomitant treatments will be recorded.

7.3.3 Prior and concomitant treatments

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

The primary outcome variable is the duration of the transition period (in days) between the last dose of a prior psoriasis treatment and the first dose of secukinumab.

Prior and concomitant psoriasis treatments will be documented including start date, end date, dose and reason for discontinuation (with a distinction between at least failure to respond, contraindication or intolerance). Administration and dose of Secukinumab will be captured by individual administration records. Other significant prior and concomitant treatments will be documented up to 6 month before the baseline visit.

7.3.4 PASI

PASI is part of the guideline definition of both, treatment severity and treatment goals, for patients with plaque psoriasis. Therefore it is expected that PASI will be assessed for all patients as part of the clinical routine.

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 (see below for full details of the PASI assessment). 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.

A PASI score will be derived as indicated in Table 6-3. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation).

The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details to help with the assessment are provided below:

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

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

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

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

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0. The baseline value for analysis of the PASI is collected at the baseline visit.

Table 7-1 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 CRF
[†]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

7.3.5 Routine effectiveness and quality of life assessments

If in addition to PASI, other measures of effectiveness and quality of life such as IGA, PGA and/or DLQI are used during clinical routine, the resulting scores will be documented in the eCRF. If available from the medical history, assessments conducted up to 6 months before informed consent should also be recorded in eCRFs.

7.3.6 Safety

Information about AEs and SAEs should be collected as described in chapter 10 and assessed and treated as in routine clinical practice (see chapter 10 for further details).

7.4 Data sources

This study involves a primary data collection. Therefore the sources of data are the treating physicians and the patients. Records from routine clinical documentation are used for SDV. These include electronical and paper-based patients charts, hospital discharge files, prescription drug files and doctor's letters.

Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Safety data will be transferred to Novartis at a frequency as defined in section 10 of this protocol. Clinical data will be transferred to Novartis on an ongoing basis.

Data collection schedule

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete if possible at every patient visit the appropriate CRF.

However, below is the recommended data collection schedule that most likely mirrors the patterns of routine clinical care of most patients being treated with Secukinumab. It is expected that most patients are likely to be seen at the regular visits and that some patients may also be seen at some of the additional visits. A visit window is not applied. If a visit occurs in between the predefined visit timepoints it may be recorded as the next visit that is closest, unless another visit up to that point in time is already scheduled. The date of the visit should be documented accurately.

Table 7-2 Data collection

Type of visit	Baseline	Regular visits	Additional visits	Regular end of study visit
Time of visit (week)	**0**	**4, 12, 16**	**1, 2, 3, 8, 20**	**24**
Informed consent	X			
Inclusion/Exclusion criteria	X			
Baseline characteristics	X			
Psoriasis disease history	X			
Prior psoriasis treatments (duration of treatment, last dose and day of discontinuation)	X			
Prior results of assessments (e.g. PASI, IGA, PGA)	X			
Prior results of questionnaires (e.g. DLQI)	X			
Documentation of Secukinumab treatment	X	X	X	X
Documentation of concomitant treatments	X	X	X	X
PASI assessment	X	X	X	X
Results of other routine assessments (e.g. IGA, PGA)	X	X	X	X
Results of routine questionnaires (e.g. DLQI)	X	X	X	X
Adverse Events	X	X	X	X

For patients who discontinue prematurely, the reason for discontinuation should be determined.

7.5 Study size

The duration of the transition period shall be estimated with sufficient precision for all groups of previous treatments, especially for Methotrexate due to its international significance as a first-line treatment. Data from the PsoBest registry (online on http://www.psobest.de/einschlusszahlen/, retrieved 04-April-2015) suggest that about 20% of systemic treatments in Germany are Methotrexate. Thereof at least 50% (i.e., 10% of the included patients) are expected to stop prior to treatment with Methotrexate before starting treatment with Secukinumab. Therefore, a total of 1200 patients would result in 120 patients who previously underwent transition from Methotrexate to Secukinumab. With 120 patients in this group the mean duration of the transition period can be estimated with an adequate precision [95% CI] of about 4 days assuming a standard deviation of 3 weeks (21 days).

The pre-defined interim analysis of baseline data after enrollment of 800 patients (see section 8.6) suggests that the proportion of patientes transitioning from Methotrexate to Secukinumab is slightly higher than expected (11,3% instead of 10,0%). However, based on the interim analysis data, we have to expect a much higher standard deviation of the duration of the transition period in those patients than estimated during the planning of the study (60 days instead of 21 days). To obtain a precision [95% CI] of +/- 4 days for the mean duration of the transition period with this high standard deviation, a total of 7655 patients would be required. Targeting a precision [95% CI] of +/- 7 days - which reflects the dosing interval of

Methotrexate - instead of +/-4 days, this would lead to 283 patients who previously underwent transition from Methotrexate to Secukinumab and an overall sample size of 2504 patients. This seems to be an acceptable compromise between feasible sample size and an adequate precision.

7.6 Steering Committee

Between four and six external experts and between one and two Novartis associates will be appointed to the steering committee. The scope of the steering committee's mandate is:

- Make recommendations for the non-interventional study protocol and amendments
- Make recommendations for operational questions of study conduct including but not limited to site selection, local study meetings and newsletters
- Review recruitment data, data from the interim analysis and final study data
- Make recommendations for the publication of the data

7.7 Data management

Novartis will supply the study site with access to an online eCRF that has been fully validated. Novartis personnel will train designated study site staff on the eCRF system. Alternatively, self-administered online trainings may be applied. Study site staff will not be given access to the eCRF until they have been trained. Designated investigator staff will enter the data required by the protocol into the Novartis eCRFs using a computer. Novartis will not provide computers for documentation. Data entry by designated study site staff occur exclusively via eCRF system. Automatic validation programs check for data discrepancies and plausibility in the eCRF and generate appropriate error messages or queries. If entered data is modified to a plausible value, error messages will disappear or queries will be resolved automatically by the eCRF system, respectively. Values that do not meet the plausible ranges must be commented by the study site staff by answering the respective query. The treating physician must approve that the data are complete and accurate and that all adverse events were documented by signing the eCRF electronically.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the end of data collection, there will be three additional months to complete the data entry and respond to open queries through the site staff, to sign the data by the treating physician electronically. After these actions have been completed, the database will be locked for data analysis. All documented data will be used for analysis regardless of implausibilities/discrepancies (i.e. open queries at data base lock) and signature status. During data analysis it will be verified, if further follow up of implausibilities/discrepancies is needed. In that case, further queries will be sent to the study sites to resolve these

implausibilities/discrepancies. Any changes to the database after database lock can only be made by joint written agreement between the Study Statistician and the Medical Advisor.

8 Data analysis

The data will be analyzed by Novartis and/or by the designated CRO. Any data analysis carried out independently by the treating physician(s) should be submitted to Novartis before publication or presentation.

All data will be analyzed descriptively. Exploratory subgroup and correlation analyses will be applied to identify factors that may influence primary and secondary endpoints.

8.1 Patient demographics

Summary statistics will be presented for continuous demographic and baseline characteristic variables. The frequency and percentage of subjects in each category will be presented for categorical variables for each treatment group and for all subjects. Summary statistics will include n (number of observations), mean, standard deviation, median, minimum and maximum values for continuous variables.

8.2 Psoriasis and other medical history

All psoriasis medical history variables will be summarized descriptively. Any condition entered as non-psoriasis medical history at baseline will be coded using the medical dictionary for regulatory activities (MedDRA) dictionary. Non-psoriasis medical history will be summarized by system organ class and preferred term in the MedDRA dictionary.

8.3 Treatments

8.3.1 Secukinumab

The mean dose, mean treatment interval, total number of injections administered and duration of exposure to Secukinumab will be presented using summary statistics.

8.3.2 Prior and concomitant treatments

Prior and concomitant treatments will be summarized separately. Prior treatments are defined as treatments taken and stopped prior to first dose of Secukinumab during the study. Any treatment given at least once between the day of first dose of Secukinumab during the study and the last day of study visit will be a concomitant treatment, including those which were started pre-baseline and continued into the treatment period.

The primary outcome variable is the duration of the transition period (in days) between the last dose of a prior psoriasis treatment and the first dose of secukinumab.

The duration of transition periods will be descibed by the arithmetic mean, standard deviation, median, inter-quartile range and 95% confidence interval for all relevat treatment categories and groups (as defined by primary and secondary objectives). In addition, histograms and box-and-whiskers-plots will be generated. Proportions of patients within certain categories of

transition periods (as defined by secondary objectives) will be calculated with 95% confidence intervals and displayed by stacked bar plots.

The frequency of prior and concomitant psoriasis treatment categories, groups and individual types (according to Table 5.1) will be summarized. Relative dose calculations of concomitant psoriasis treatments will be done as % of the dose at the day of first dose of study treatment or of the initial dose of the concomitant treatment if initiated later. The dosage of prior psoriasis treatments will be presented by the highest and last dose before the first dose of study treatment. In addition treatment durations will be summarized. For prior and discontinued concomitant treatments, the reason for discontinuation will be analysed with a distinction between at least failure to respond, contraindication or intolerance, and the treatment duration.

Non-psoriasis prior treatments if administrered no more than 6 months prior to informed consent 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 subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

8.4 Effectiveness

PASI and all other assessment of effectiveness and quality of life will be analyzed descriptively. Statistical tests for comparisons to baseline and between subgroups may be used where appropriate, but their results will be interpreted exploratively only. For the evaluation of (cor-)relations between measurements (e.g. concomitant treatment – effectiveness), (partial) correlation coefficients will be calculated and graphical methods will be used as far as possible. Details will be specified in a statistical analysis plan (SAP) prior to data base lock.

8.5 Safety

Adverse events

AEs will be summarized by presenting, the number and percentage of subjects

- having any AE,
- having an AE in each primary system organ class and
- having each individual AE (preferred term).

Summaries will also be presented for AEs by severity and for AEs related to Secukinumab therapy. If a subject reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a subject reported more than one adverse event within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable.

In addition, AEs will be summarized by presenting the total number of events in each primary system organ class and in each preferred term.

These summaries will be presented with the total number of patients exposed in that respective phase as a denominator. Separate summaries will be provided for death, serious

adverse event, other significant adverse events leading to discontinuation and adverse events leading to dose adjustment (including Secukinumab treatment discontinuation).

Statistical tests for comparisons to baseline and in between subgroups may be used where appropriate, but their results will be interpreted as explorative only. For the evaluation of (cor-)relations between measurements (e.g. transition time – safety), graphical methods will be used as far as possible. Details will be specified in a statistical analysis plan (SAP) prior to data base lock.

8.6 Interim analysis

After 800 patients have been recruited, an interim analysis of the baseline data will determine, whether sufficient precision for all groups of previous treatments is likely to be achieved. After the increase of sample size via protocol amendement 1 based on the first interim analysis, a further interim analysis of the baseline data will be conducted after 2000 patients have been enrolled to reassess the precision for all groups of previous treatments. If necessary, the study sample size will be adjusted via a protocol amendment to obtain adequate and representative coverage of all previous treatment groups.

8.7 Quality control

8.7.1 Data quality management

To assure database quality, edit checks will be programmed in accordance with the data validation plan. The data entered into the eCRF will be checked automatically for completeness and accuracy. In case of missing relevant data or discrepancies, error messages or queries will be generated automatically by the system.

8.7.2 Data recording and document retention

In all scenarios, the physician 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, and the results of any other tests or assessments. All information entered in the eCRF must be traceable to these source documents in the patient's file.

The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the eCRF entries.

8.7.3 Site monitoring

At the site initiation visit, a Novartis representative will review the protocol and eCRFs with the treating physicians and their staff. Alternatively, self-administered online trainings may be applied for eCRF training. During the study, the field monitor will visit the site at least once to verify the completeness of patient records, the accuracy of entries on the eCRFs compared to the original patient chart entries and the adherence to the protocol. Key study personnel must be available to assist the field monitor during these visits.

The treating physician must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries. Novartis monitoring standards require full

verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of (S)AEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan.

8.8 Limitations of the research methods

Site specific preferences may bias towards misrepresentation of prior and concomitant treatment types and transition periods and concomitant treatments if the site selection process or the recruitment is imbalanced. To limit this bias, a balanced selection of sites and a balanced recruitment will be sought. Specifically, it is intended to include a significant proportion of study sites who were not involved in Secukinumab clinical trials. Furthermore, the retrospective documentation of transition periods is an inherent limitation of this study design. Analysis of confounding factors and effect modifications shall be covered in the exploratory analyses. Other limitations such as information bias, selection bias, and limitations of feasibility are expected to be similar to other multicentric prospective non-interventional trials.

8.9 Other aspects

None.

9 Protection of human subjects

The treating physician must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

For audits,inspections or routine monitoring, source data and signed informed consent forms as well as patient enrollment log must be available to Novartis representative or Health Authorities.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke, et al 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a ‘European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study’ and follows the ‘ENCePP Code of Conduct’ (European Medicines Agency 2010).

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board / Independent Ethics Committee (IRB/IEC) before study start. Approval letters concerning protocol and informed consent will be filed by Novartis.

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. The patient should assent by personally signing and dating two copies of the written informed consent document or of a separate assent form. Informed consent must be obtained before any data are collected. The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

The physician must keep one of two copies of the informed consent form signed by the patient.

10 Management and reporting of adverse events/adverse reactions

All adverse events (AEs) – including serious adverse events (SAEs) and safety endpoints (where relevant) – must be collected and recorded in the study database, irrespective of causal association. All AEs, including SAEs occurring in association with exposure to the Novartis drug of interest, also have to be recorded in the Novartis safety database.

Adverse Drug Reactions (ADRs) occurring in association with exposure to a Novartis drug other than the Novartis drug of interest, must be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting and Novartis DS&E as a spontaneous report.

All adverse reactions identified for non-Novartis products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

Adverse event reporting

An adverse event is any untoward medical occurrence in a patient administered Secukinumab that does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug of interest, whether or not related to the medicinal product(s).

Drug of interest includes the drug under evaluation and the comparator drug(s) if specified as part of the research objective, given at any time during the study. The drug of interest of this study is Cosentyx®/Secukinumab.

If patient starts with the drug of interest during the study medical conditions/diseases present before starting the drug of interest are only considered adverse events if they worsen after first intake of the drug of interest. If patient had already started therapy with the drug of interest before he signed informed consent medical conditions/diseases which worsen after signing informed consent are considered as adverse events. The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. All adverse events must be recorded on the Adverse Events case report/case record form (CRF) with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the drug(s) of interest (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

As the drug under evaluation is a biological drug (monoclonal antibody) the documentation of the batch number of the drug which was used at the time of the occurrence of the (S)AE is necessary, in addition to the before mentioned information.

In addition, all reports of the following special scenarios are also considered an adverse event irrespective if a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug exposure during pregnancy
- Drug use during breast-feeding
- Lack of effectiveness

Reports of lack of effectiveness without an associated clinical event must be recorded on the AE page of the eCRF even if lack of efficacy parameters are being collected and recorded elsewhere within the study database.

- Overdose
- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / Medication errors

Reports of overdose, drug abuse and misuse, drug maladministration or accidental exposure and dispensing errors/medication errors without an associated clinical event must be recorded on the AE page of the eCRF irrespective of whether or not the information is recorded elsewhere within the study database.

- Withdrawal or rebound symptoms

Any treatment of any adverse event should be recorded on the Adverse Event page of the eCRF. Some examples of treatment to be recorded are: no action taken (i.e., further observation only); drug of interest dosage adjusted/temporarily interrupted; drug of interest permanently discontinued due to this adverse event; treatment medication introduced or adjusted; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged.

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

Information about common adverse effects already known about the medicinal product can be found in the locally available labeling document for the approved indication under evaluation in this study. This information will be included in the patient informed consent and should be discussed with the patient prior to study start and during the study as needed.

Non-serious adverse events associated with the Novartis drug of interest must also be recorded in the safety database:

Serious adverse event reporting

A SAE is defined as an event which:

- Is fatal or life-threatening

  Life-threatening is an event which constitutes a fatal risk for the patient at the time of the event and which not only may become fatal by hypothetical worsening or further complications.

- 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 (not applicable for psoriasis)
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest (Secukinumab)
  - 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

Note: Transmission of infectious agent via medicinal product is considered to be a serious adverse reaction and should be reported and assessed as medically significant in the absence of other seriousness criteria.

The assessment whether an adverse event constitues an SAE is only dependent on the presence of one of the above mentioned formal criteria and independent from the assessment whether a causal relationship between the drug and the occurrence of the SAE has been suspected.

Causality assessment

For the assessment of causality between the drug and the event there exist the options "no causal relationship" and "causal relationship suspected". A medical causality assessment is absolutely necessary and has to be documented in any case. It should be taken into account that many different aspects should be considered for causality assessment. These aspects can concern the individual patient, the underlying disease, comorbidities, concomitant medication (if applicable) or also non-medicinal factors.

No causal relationship: there exists no reasonable possibility of a causal relationship between drug and AE.

Causal relationship suspected: there exists a reasonable possibility of a causal relationship between drug and AE.

•

Disease progression

A progression of the underlying disease during treatment with the drug under evaluation (Secukinumab) only has to be documented as adverse event if a causal relationship with the drug under evaluation has been suspected *or* if as a result of the disease progression one or more of the formal criteria for an SAE apply.

Abnormal laboratory values and test results

Abnormal laboratory values or test results only should be documented as adverse event if they

- constitute a change in terms of a worsening of the respective parameter in comparison to the baseline value (baseline visit). This term becomes invalid if there is no baseline value

AND

- the changed laboratory parameters
    - are assessed as clinically relevant OR
    - are accompanied by clinical signs or symptoms OR
    - require therapeutic intervention OR
    - lead to a dosage reduction and/or temporary interruption or permanent discontinuation of the drug under evalution.

In these cases, they have to be documented on the adverse event page.

Changes of quantifiable parameters have to be documented as serious adverse events if formal criteria for an SAE apply (see SAE definition).

Notification timelines for SAE

ToTo ensure patient safety, every SAE, regardless of causality assessment, occurring after the patient has provided informed consent (applicable to patients who already took Secukinumab before start of the study) or has started therapy with Secukinumab(applicable to patients who start Secukinumab therapy during this study) and until 30 days after the patient has stopped study participation (defined as time of last dose of the Novartis drug of interest taken or last visit whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the treating physician or other involved health care professional suspects a causal relationship to the Novartis drug of interest.

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 by the treating physician or other involved health care professional after receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all (S)AEs is collected and recorded on the Serious Adverse Event page in the eCRF. The treating physician or other involved health care professional must assess the relationship to the Novartis drug of interest, complete the (S)AE page and save the completed page in the eCRF within 24 hours. Follow-up information is reported in the same manner as the initial report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, When a patient withdraws from study participation, the 'End of Observation'-Page must be completed in the eCRF.

If the SAE is not previously documented in the SmPC a local DS&E Department associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

Reporting of SAE and AE

Information on any AE (non-serious, serious) is documented in the individual eCRF of the respective patient in the study database. The study centre documents every SAE within 24 hours after becoming aware of it, non-serious AE within 10 days. The information on SAE will be forwarded to Novartis and the CRO automatically via eCRF system/e-mail (PDF format) after saving of the data by the study centre. Information on non-serious AE will be transferred from the study database to Novartis DS&E by CRO on a periodic basis, but not less frequently than every week.

Exception: if documentation of an SAE in the eCRF is not possible for technical or other reasons the SAE can be documented on paper and faxed directly to the CRO:

Winicker Norimed GmbH Medizinische Forschung
Deutschherrnstraße 15-19
D-90429 Nürnberg
Fax: +49 (0) 911 92680 4444

The original report form has to be dated with the fax date and will be stored in the study documentation until forwarding to CRO. The original copy of the SAE form and the fax confirmation has to be stored at the study centre, together with the CRF documentation.

In case that documentation of an nsAE in the eCRF is not possible for technical or other reasons the AE can be documented on paper and faxed directly to the CRO.

If information about adverse event is of preliminary nature information has to be completed as soon as possible and sent as follow-up to Novartis. The follow-up report has to be sent in the same manner as the initial report and should be clearly stated as follow-up report and contain the date of the initial report. If known, the missing information of the initial report should be completed and newly received information (e.g. if and which treatment was given, outcome (recovered/continuing) or further study participation of the patient (further participation/discontinuation of study)) should be reported.

If information is incomplete or queries are necessary for other reasons Novartis DS&E or the contracted CRO will contact the treating physician or other involved health care professional. In special cases, e.g. if SAE is not listed in the summary of product characteristics, urgent response to the query by the physician can be necessary to fulfill legal reporting obligations to the authorities. In these cases, the physician participating at this NIS or other involved health care professional is obliged to appropriate cooperation so that reporting obligations can be fulfilled.

Hospital reports and other findings or laboratory results in context of adverse events should be sent to Novartis **only upon request**.

Pregnancies

To ensure patient safety, any occurrence of a pregnancy in a patient on the Novartis drug of interest must be reported to the local Novartis Drug Safety & Epidemiology (DS&E) Department within 24 hours.. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Pharmacovigilance Pregnancy Form and reported by the treating physician or other involved health care professional to Novartis. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug of interest should be reported.

This has to be documented on the pregnancy form with the initial report or as follow-up report if pregnancy was already reported. The pregnancy form has to be filled in completely with the

recent information, including information about birth and child, and the completed and signed form has to be forwarded to the local Novartis Drug Safety & Epidemiology (DS&E) Department via fax. Additionally, any SAE experienced during pregnancy must be reported on the SAE Report Form.

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

11 Plans of disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study may be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines. An early publication of the interim analysis may be sought if appropriate.

The interim and final study report will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

12 References

1. Nast A et al 2011 S3 - Leitlinie zur Therapie der Psoriasis vulgaris, Update 2011 [German S3 Guideline for the treatment of psoriasis vulgaris]

2. Mrowietz U et al. A consensus report on appropriate treatment optimization and transitioning in the management of moderate-to-severe plaque psoriasis. J Eur Acad Dermatol Venereol. 2014 Apr;28(4):438-53.

3. Langley RG et al 2014 Secukinumab in plaque psoriasis--results of two phase 3 trials. N Engl J Med. 2014 Jul 24;371(4):326-38.

4. Blauvelt A et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol. 2015 Feb;172(2):484-93.

5. Paul et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol. 2015 Jun;29(6):1082-1090.

6. Thaçi D et al. Secukinumab in psoriasis: randomized, controlled phase 3 trial results assessing the potential to improve treatment response in partial responders (STATURE). Br J Dermatol. 2015 Mar 30

7. Mrowietz et al. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: A randomized, double-blind, noninferiority trial (SCULPTURE). J Am Acad Dermatol. 2015 May 13.

13 Annexes

13.1 Annex 1 – List of stand-alone documents

Table 13-1 List of stand-alone documents

Number	Document reference number	(Planned) Date	Title
1	1	30 Jun 2015	ENCePP Checklist, annex 2 to the study protocol
2	2	01 Sep 2015	Monitoring Plan
3	3	01 Sep 2015	Steering Committee Charter
4	4	01 Mar 2016	Statistical Analysis Plan
7	7	31 Dec 2016	Interim Analysis Study Report
8	8	30 Sep 2018	Final Study Report

13.2 Annex 2 – ENCePP checklist for study protocols

See separate ENCePP Checklist.