NOVARTIS

Clinical Development

AIN457/Secukinumab/Cosentyx®

CAIN457A3401 / NCT02752776

An open-label, prospective, non-randomized, multicenter study to evaluate clear skin effect on health-related quality of life outcomes at 16 and 52 weeks in patients with moderate to severe plaque psoriasis treated with secukinumab 300 mg s.c. with or without previous exposure to systemic therapy

Statistical Analysis Plan (SAP)

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Document type: SAP Documentation

Document status: Amendment 1

Release date: 13-June-2017

Number of pages: 33

Document History – Changes compared to previous final version of SAP

Date	Time point	Reason for update	Outcome for update	Section and title impacted (Current)
13-June-2017	Prior to Interim DBL	Creation of Amendment 1	Removed "side effects" as TSQM scale score, as this is not part of TSQM-9. Added visit 10 to visit window for vital signs and safety laboratory Section 5.4.5 added clarification on derivation of HAQ-DI.	General definitions Section 5.4

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List of abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BSA	Body Surface Area
CSR	Clinical Study report
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
eCRF	Electronic Case Report Form
EQ-5D	EuroQoL 5-Dimension Health Questionnaire©
[redacted]	[redacted]
GGT	Gamma-glutamyl transferase
LFT	Liver Function Test
LLN	Lower Limit of Normal
LOCF	last observation carried forward
LPFT	Last Patient First Treatment
FAS	Full Analysis Set
HAQ©-DI	Health Assessment Questionnaire©-Disability Index
HR-QoL	health-related Quality of Life
IGA mod 2011	Novartis Investigator's Global Assessment modified 2011
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NRS	Numeric Rating Scale
PASI	Psoriasis Area and Severity Index
PBI	Patient Benefit Index
PRO	Patient-reported Outcomes
PsA	Psoriatic Arthritis
QoL	Quality of Life
SAP	Statistical Analysis Plan
SOC	System Organ Class
TBL	Total bilirubin
TFLs	Tables, Figures, Listings
TSQM	Treatment Satisfaction Questionnaire for Medication
ULN	Upper Limit of Normal

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the Clinical Study Report (CSR) of study CAIN457A3401, a Phase 4, open-label, prospective, non-randomized, multicenter study to evaluate clear skin effect on health-related quality of life outcomes at 16 and 52 weeks in patients with moderate to severe plaque psoriasis treated with secukinumab 300 mg s.c. with or without previous exposure to systemic therapy.

In addition the SAP describes all planned analyses for the interim analysis which will be performed for this study after last patient first treatment (LPFT).

The content of this SAP is based on the final version of protocol CAIN457A3401 (release date 21-Oct-2015). All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock and unblinding of the study data.

1.1 Study design

The study is an open-label, prospective, non-randomized but stratified multicenter study to evaluate clear skin effect on health-related quality of life outcomes at 16 and 52 weeks in patients with moderate to severe plaque psoriasis treated with secukinumab 300 mg s.c. with or without previous exposure to systemic therapy.

A total of 1615 patients will be enrolled into the study. Eligible patients will be categorized at baseline according to previous exposure to treatment in one of the following 3 subpopulations:

- **Subpopulation A:** Patients who are **naïve to any systemic treatment**, e.g. patients failing or intolerant to previous topical treatment, including narrow band UVB, but never exposed to any systemic treatment, with or without contraindications to the use of conventional systemic treatment and in a need of a first systemic treatment.
- **Subpopulation B:** Patients who have been **previously exposed to at least one conventional systemic therapy**; either because of failure or intolerance to their previous conventional systemic treatment, they are in a need of a first biologic systemic treatment;
- **Subpopulation C:** Patients who have been **previously exposed to at least one biologic systemic therapy**; either because of failure or intolerance to their previous biologic systemic treatment, they are in a need of a different biologic systemic treatment.

The primary endpoint of this study is the proportion of patients achieving a Dermatology Life Quality Index (DLQI) 0/1 response at Week 16 in the 3 subpopulations and in the overall study population.

One interim analysis will be performed after LPFT. The purpose of the interim analysis is to describe the self-reported baseline characteristics and health-related Quality of Life (HR-QoL) of patients prior to treatment.

1.2 Study objectives and endpoints

Primary objective:

- To assess the proportion of patients achieving a DLQI 0/1 response at Week 16 in the 3 subpopulations and in the overall study population.

Secondary objectives:

- To assess the proportion of patients achieving a DLQI 0/1 response at Week 52 in the 3 subpopulations and in the overall study population.
- To assess the effects of treatment with secukinumab 300 mg with respect to changes in EuroQoL 5-Dimension Health Questionnaire© (EQ-5D), Health Assessment Questionnaire©-Disability Index (HAQ-DI), Numeric Rating Scale (NRS), Treatment Satisfaction Questionnaire for Medication (TSQM) and Patient Benefit Index (PBI) response over time up to Week 16 and Week 52 compared to baseline in the 3 subpopulations and in the overall study population.
- To assess the proportion of patients achieving Psoriasis Area and Severity Index (PASI) 50, PASI 75, PASI 90, PASI 100 and Novartis Investigator's Global Assessment modified 2011 (IGA mod 2011) 0/1 responses at Week 16 and Week 52 in the 3 subpopulations and in the overall study population.
- To assess the proportion of patients with DLQI scores 2-5, 6-10, 11-20, 21-30 at Week 16 and Week 52 compared to baseline in the 3 subpopulations and in the overall study population.
- To assess the overall safety and tolerability of treatment with secukinumab 300 mg in the 3 subpopulations and in the overall study population.

[redacted]

2 Statistical methods

Statistical methods are based on study protocol section 9 with more details given in this SAP.

2.1 Data analysis general information

The statistical analysis of the study (including the interim analysis) will be performed by [redacted], a designated Contract Research Organization (CRO).

SAS version 9.3 or later will be used to perform all data analyses and to generate tables, figures and listings.

Qualitative data (e.g., gender, race, etc.) will be summarized by means of contingency tables; a missing category will be included as applicable. Percentages will be calculated using the number of patients in the relevant population or subgroup as the denominator.

Quantitative data (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics, i.e., n, mean, standard deviation (SD), first quartile (Q1), median, third quartile (Q3), minimum, and maximum.

Data from all study centers will be pooled for the analysis.

2.1.1 General definitions

Investigational drug and study treatment

The same study drug will be given to all patients recruited in the 3 subpopulations: secukinumab/AIN457 300 mg s.c. No reference therapy will be given.

Date of first and last administration of study drug

The date/time of first administration of secukinumab is defined as the first date/time of administration as per Study drug administration eCRF. The date/time of last administration of secukinumab is defined as the last date/time when a dose is administered as per Study drug administration eCRF.

Study day

The study day, describes the day of the event or assessment date, relative to the reference start date which is the date of first administration of secukinumab.

The study day is defined as:

- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date + 1 if event is on or after the reference start date;
- The date of the event (visit date, onset date of an event, assessment date etc.) − reference start date if event precedes the reference start date.

Baseline

For safety and efficacy evaluations, the last available assessment before the first administration of secukinumab is defined as "baseline" assessment. If patients have no value prior to first administration of secukinumab the baseline result will be missing.

Post-baseline

For safety and efficacy evaluations all assessments after the first administration of secukinumab are defined as "post-baseline" assessment.

Change and percent change from baseline for continuous parameter.

Change from baseline and percent change from baseline will only be summarized for subjects with both baseline and post-baseline values and will be calculated as:

change from baseline = post-baseline value – baseline value

percent change from baseline = 100 * change from baseline / baseline value

Study periods and date of last contact

The overall observation period will be divided into three mutually exclusive segments:

- A screening phase of 4 weeks
- A treatment phase 1 starting with first dose of study drug at Visit 2 and covering the first 16 weeks of treatment.
- A treatment phase 2 starting with the dosing at Visit 9 (Week 16) and lasting until end of the study, Visit 14 (Week 52).

According to the protocol for patients not achieving a PASI 50 response at the Week 16, i.e. at the end of treatment phase 1, considerations should be given to discontinuing study drug. Thus patients can complete treatment phase 1 without entering treatment phase 2.

For patients entering treatment phase 2, the treatment phase 2 date of discontinuation/study phase completion will be used as the date of last contact. For subjects not entering treatment phase 2, the treatment phase 1 date of discontinuation/study phase completion will be used.

Visit windows

Visit-windows will be used for the data that is summarized by visit; they are based on the study evaluation schedule and comprise a set of days around the nominal visit day. For any assessment, there are the protocol defined scheduled visits around which visit windows were created to cover the complete range of days within the study. When visit windows are used, all visits will be re-aligned, i.e., they will be mapped into one of the visit windows.

In general, if two consecutive visits V_t and V_s are x days apart, the upper limit of the visit window for V_t will be V_t+x/2 and the lower limit for the visit V_s will be V_s-x/2 (if x is even, the lower limit for V_s will be V_s-x/2+1, and the upper limit for V_t will be V_t+x/2). The algorithm needs to ensure that visit windows are not overlapping and that there are no gaps, such that each assessment can be uniquely allocated to one visit window.

The visit windows are shown in Table 2-1.

Table 2-1: Visit windows

Analysis visit	Week	Sched. Day	Visit window – assessments [a] scheduled at all visits	Visit window - assessments [b] scheduled at visits 2, 6, 8, 9, 10, 11, 12, 13 and 14	Visit window - assessments [c] scheduled at visits 2, 6, 8, 9, 11, 12, 13 and 14	[redacted]	Visit window – assessments [e] scheduled at visits 2, 9 and 13 and 14	Visit window – assessments [f] scheduled at visits 2, 9 and 14
Base-line	BL	1	Day -99 to Day 1 (pre-dose)	Day -99 to Day 1 (pre-dose)	Day -99 to Day 1 (pre-dose)		Day -99 to Day 1 (pre-dose)	Day -99 to Day 1 (pre-dose)
3	1	8	Day 1 (post dose) – Day 11					
4	2	15	Day 12 – Day 18					
5	3	22	Day 19 – Day 25					
6	4	29	Day 26 – Day 43	Day 1 (post dose) – Day 57	Day 1 (post dose) – Day 57			
7	8	57	Day 44 – Day 71					
8	12	85	Day 72 – Day 99	Day 58 – Day 99	Day 58 – Day 99			
9	16	113	Day 100 – Day 127	Day 100 – Day 127	Day 100 – Day 141		Day 1 (post dose) – Day 225	Day 1 (post dose) –Day 239
10	20	141	Day 128 – Day 155	Day 128 – Day 155				
11	24	169	Day 156 – Day 211	Day 156 – Day 211	Day 142 – Day 211			
12	36	253	Day 212 – Day 295	Day 212 – Day 295	Day 212 – Day 295			
13	48	337	Day 296 – Day 351	Day 296 – Day 351	Day 296 – Day 351		Day 226– Day 351	
14	52	365	Day 352 – Day 379	Day 352 – Day 379	Day 352 – Day 379		Day 352 – Day 379	Day 240 – Day 379

a: Body Surface Area (BSA), PASI, IGA mod 2011
b: laboratory sampling (Hematology, Chemistry and Urinalysis) and vital signs
c: NRS, DLQI, EQ-5D, HAQ-DI, TSQM, PBI
[redacted]
e: Fasting laboratory
f: (weight, waist and hip circumference)

In the case of major deviations from the visit schedule, or due to unscheduled visits, several assessments of a subject may fall in a particular visit window (either scheduled or unscheduled). In this case, the following rules are applied to select one value “representing”

the subject in summary statistics in a visit window. For baseline assessment definition see Section for Baseline above. For post-baseline visit windows the following applies:

- for *quantitative variables and qualitative efficacy variables*, the closest to the actual visit is chosen (if two assessments have the same distance, then the earlier one will be chosen);
- for *qualitative safety variables*, the worst record is selected. It is noted that in the analyses performed, worst case is always well defined (e.g., for urine dipstick values "+" and "++", the worst case is defined as "++"),
- in case *qualitative variables are based on quantitative variables*, e.g. PASI 75 response, the visit will be assigned to the quantitative variable, and this visit will be used for the derived qualitative variable.

For the analysis of assessments done at Screening, the Screening visit will be analyzed as reported on the eCRF.

2.2 Analysis sets

The following analysis sets will be used in the analyses:

- Enrolled set: All patients who are enrolled, i.e. who signed informed consent, are included in the Enrolled set.
- Safety set: The Safety set includes all patients who received at least one dose of study drug.
- Full Analysis set (FAS): The FAS includes all patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment.

2.2.1 Subgroup of interest

All analyses will be performed by the following subpopulations:

- **Subpopulation A:** Patients who are **naïve to any systemic treatment**, e.g. patients failing or intolerant to previous topical treatment, including narrow band UVB, but never exposed to any systemic treatment, with or without contraindications to the use of conventional systemic treatment and in a need of a first systemic treatment.
- **Subpopulation B:** Patients who have been **previously exposed to at least one conventional systemic therapy**; either because of failure or intolerance to their previous conventional systemic treatment, they are in a need of a first biologic systemic treatment;
- **Subpopulation C:** Patients who have been **previously exposed to at least one biologic systemic therapy**; either because of failure or intolerance to their previous biologic systemic treatment, they are in a need of a different biologic systemic treatment.

2.3 Patient disposition, demographics and other baseline characteristics

Demographics and other baseline characteristics will be collected at Screening (Visit 1) or at Baseline (Visit 2) prior to first study drug administration for the efficacy and Patient-reported

Outcome (PRO) measurements. Summary statistics will be provided for demographic and baseline characteristics overall and by subpopulations for the Safety set.

Demographics include age, sex, race, ethnicity, height, weight, body mass index (BMI), waist and hip circumference at Screening. Age will be presented as continuous variable in years and also as categorical variable with the categories <65, >=65 and >=75 years.

Demographic data of screen failures and violated inclusion and exclusion criteria of all patients will be listed only.

Baseline disease characteristics include duration of psoriasis (in years), presence of PsA, duration of PsA, IGA mod 2011 response categories, PASI score and BSA score at Screening. PASI score will be presented as continuous variable and also as categorical variable with the categories <20, >=20.

Other baseline characteristics include smoking history and presence of tuberculosis, vital signs at Screening (i.e. systolic and diastolic blood pressure, pulse rate).

In addition baseline IGA mod 2011 response categories, PASI score, BSA score and PROs NRS (pain, itching and scaling) scores , DLQI score, DLQI subsection scores, [redacted] EQ-5D (question and answer categories, VAS and Crosswalk Index Value) and HAQ-DI will be summarized. The DLQI score will be summarized as continuous variable and as categorical variable categorized into 0-1 no effect on patient's life, 2-5 small effect on patient's life, 6-10 moderate effect on patient's life, 11-20 very large effect on patient's life, 21-30 extremely large effect on patient's life. PASI score will be presented as continuous variable and also as categorical variable with the categories <20, >=20.

Baseline vital signs and laboratory values will be summarized within the safety section.

Cardiovascular history will be summarized by predefined history term overall and by subpopulation. Other medical history and current medical conditions will be summarized by MedDRA primary system organ class (SOC) and preferred term overall and by subpopulations.

2.3.1 Patient disposition

If not stated otherwise the Safety set will be used for the summary and listing of patient disposition.

The number of patients in the Safety set will be summarized by country, center and subpopulation.

The number of patients with protocol deviations will be tabulated by deviation category overall and by subpopulation. Protocol deviations will be listed with date and study day of occurrence and the population codes which show the exclusion from analysis sets.

The number of patients included in each analysis set will be tabulated.

For each study phase (i.e., screening, treatment phase 1 and treatment phase 2), the overall number of patients who entered, completed, and discontinued that phase will be summarized including the reasons for discontinuation. The summary of the screening phase will be done

for the Enrolled set, the summaries of the treatment phase 1 and 2 will be done on the Safety set overall and by subpopulation.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

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

Duration (days) of exposure to study drug will be summarized. Duration of exposure is defined as:

- End of treatment phase 1 date - date of first dose of study drug + 1 for subjects discontinuing during treatment phase 1
- End of treatment phase 2 date - date of first dose of study drug + 1 for subjects completing the study or discontinuing during treatment phase 2

In addition, the number of subjects with exposure of at least certain time thresholds ("any exposure", "≥ 1 week", "≥ 2 weeks", "≥ 3 weeks", "≥ 4 weeks", "≥ 8 weeks", >=12 weeks, >=16 weeks, >=20, weeks, >=24 weeks, >=28 weeks, >=32 weeks, >=36 weeks, >=40 weeks, >=44 weeks, >=48 weeks, >=52 weeks) will be displayed.

The number of secukinumab injections will be presented cumulatively.

Compliance (%) will be calculated in percent as the total number of injections administered divided by the number of injections scheduled according to the protocol multiplied by 100.

2.4.2 Prior, concomitant and post therapies

Prior medications and non-drug therapies will be summarized overall and by subpopulation separately for Psoriasis therapies and non-indication medications / non-drug therapies. The same analysis as described for prior medications and non-drug therapies will be repeated for concomitant medications and non-drug therapies.

Prior therapies are defined as treatments taken and stopped prior to first dose of study drug. Concomitant therapies are defined as therapies given at least once between the day of first dose of study drug and the last day of study, including those which were started prior to first dose of study drug and continued into the treatment period or beyond.

Psoriasis therapies and non-indication medications / non-drug therapies will be presented overall, by ATC codes (level 4) and preferred term. Medications will be presented in alphabetical order of the ATC code and preferred term. Tables will also show the overall number and percentage of patients receiving at least one treatment of a particular ATC code.

In addition psoriasis therapies will be summarized by type of psoriasis therapy (biologic systemic, non-biologic systemic, topical, phototherapy, and photochemotherapy) and preferred term.

2.5 Analysis of the primary objective

2.5.1 Primary endpoint

The primary analysis variable is the proportion of patients achieving a DLQI 0/1 response at Week 16 in 3 pre-defined subpopulations and in the overall study population.

The analysis of the primary variable will be based on the FAS.

2.5.2 Statistical hypothesis, model, and method of analysis

The primary analysis of this study will be descriptive without any formal group comparisons or hypothesis testing. The absolute and relative frequencies of patients achieving a DLQI 0/1 response, i.e. a DLQI score of 0 to 1, at Week 16 will be calculated for the subpopulations as well as for the overall study population. For the proportions, (descriptive) 95% CIs will additionally be reported.

The proportion of DLQI 0/1 response at Week 16, overall and by subpopulation, will be presented graphically.

Details how to derive the DLQI score are given in the Appendix 5.4.1.

2.5.3 Handling of missing values/censoring/discontinuations

The last observation carried forward (LOCF) method will be applied to the continuous variables of DLQI score that are missing after baseline regardless to the reason for missing data (e.g. premature study discontinuation, missed visit, administrative issues). The binary response variable based on DLQI score will be derived from these imputed values, this means that a patient with missing values will be counted as a non-responder unless he already achieved the respective response criterion at the last available measurement. Baseline values will not be carried forward. LOCF will be applied to all post-baseline visits.

LOCF imputation:

1. Assign analysis visit windows as described in Section 2.1.1 per assessment date for unscheduled visits.
2. If no eCRF visit is assigned to an analysis visit as per Section 2.1.1, impute with LOCF

Any missing individual items are treated as missing data. Handling of missing items within the DLQI questionnaire is described in the Appendix 5.4.1.

The percentage of missing items in the DLQI questionnaire and will be presented over visits. In addition the percentage of scores/index values imputed with LOCF will be presented by visit.

2.5.4 Supportive analyses

No sensitivity analysis will be performed.

2.6 Analysis of the key secondary objective

There is no key secondary objective defined for this study.

2.7 Analysis of secondary efficacy objective(s)

2.7.1 Secondary endpoints

- To assess the proportion of patients achieving a DLQI 0/1 response at Week 52 in the 3 subpopulations and in the overall study population.
- To assess the effects of treatment with secukinumab 300 mg with respect to changes in EQ-5D, HAQ-DI, NRS, TSQM and PBI response over time up to Week 16 and Week 52 compared to baseline in the 3 subpopulations and in the overall study population.
- To assess the proportion of patients achieving PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responses at Week 16 and Week 52 in the 3 subpopulations and in the overall study population.
- To assess the proportion of patients with DLQI scores 2-5, 6-10, 11-20, 21-30 at Week 16 and Week 52 compared to baseline in the 3 subpopulations and in the overall study population.
- To assess the overall safety and tolerability of treatment with secukinumab 300 mg in the 3 subpopulations and in the overall study population.

The analyses of the secondary efficacy endpoints will be performed on the FAS, overall and by subpopulation.

The analysis of the secondary endpoint regarding safety will be described in the safety section 2.8.

2.7.2 Statistical hypothesis, model, and method of analysis

As the analysis of the primary endpoint all analyses of the secondary endpoints will be descriptive without any formal group comparisons or hypothesis testing.

Summaries by visit will include the corresponding scheduled visits with missing data imputed using LOCF.

Details how to derive the respective index values and scores are given in Appendix 5.4.

2.7.2.1 DLQI

The absolute and relative frequencies (including 95% CI) of patients achieving a DLQI 0/1 response will be presented by visit, overall and by subpopulation. The proportion of DLQI 0/1 response will presented graphically over visits.

The absolute and relative frequencies (including 95% CI) of patients achieving a 0 response in a subsection will by analyzed similarly to the DLQI 0/1 response separately for each subsection.

The number and percentages (including 95% CI) of patients in each DLQI score category of 0-1, 2-5, 6-10, 11-20, 21-30 will be presented by visit, overall and by subpopulation. In

addition a shift table using these categories will be presented to compare baseline and Week 16/Week 52 respectively.

The DLQI score and the DLQI subsection scores will be summarized by visit, overall and by subpopulation presenting the baseline value, post-baseline value, change from baseline and percent change from baseline.

2.7.2.2 BSA, PASI and IGA mod 2011

The absolute and relative frequencies (including 95% CI) of patients achieving PASI 50, PASI 75, PASI 90, PASI 100 and IGA mod 2011 0/1 responder will be presented by visit, overall and by subpopulation. The proportion of response over visits will be presented graphically.

The number and percentages (including 95% CI) of patients in each IGA mod 2011 category will be presented by visit, overall and by subpopulation.

BSA score and PASI score will be summarized similarly to the DLQI score. The mean percent change from baseline in PASI score will be displayed graphically over visits by subpopulation.

2.7.2.3 EQ-5D

The number and percentages (including 95% CI) of patients in each The EQ-5D answer and response category will be presented by visit, overall and by subpopulation.

The EQ-5D VAS and crosswalk index value will be similarly analyzed to the PASI score, presenting the absolute change from baseline in the figure.

2.7.2.4 HAQ-DI

The HAQ-DI disability index will be analyzed similarly to the EQ-5D.

2.7.2.5 NRS

The NRS scales (pain, itching and scaling) will be analyzed similarly to the EQ-5D. The absolute and relative frequencies (including 95% CI) of patients achieving a complete relief of symptom will be presented by symptom (pain, itching, scaling), visit, overall and by subpopulation. The proportion of symptom relief over visits will be presented graphically. A complete relief of symptom is defined as a reply of 0 for the respective symptom.

2.7.2.6 TSQM

The TSQM scale scores (Effectiveness, Convenience and Global satisfaction) will be summarized by visit. A summary of TSQM scale scores will be presented graphically over visits overall and by subpopulation.

2.7.2.7 PBI

The PBI global score will be summarized by visit. A summary of the PBI will be displayed graphically over time by subpopulation.

2.7.3 Handling of missing values/censoring/discontinuations

The last observation carried forward (LOCF) method will be applied to all secondary variables.

Any missing individual items will not be imputed. Handling of missing items within each questionnaire is described in the Appendix 5.4.

For each questionnaire, where it is allowed to skip questions (DLQI, HAQ-DI, PBI, TSQM [redacted]), the percentage of missing items and will be presented over visits. In addition the percentage of scores/index values imputed with LOCF will be presented by visit.

2.8 Safety analyses

One of the secondary objectives is to assess the overall safety and tolerability of treatment with secukinumab 300 mg in 3 pre-defined subpopulations and in the overall study population.

All safety analyses will be performed on the Safety set, overall and by subpopulation.

2.8.1 Adverse events (AEs)

AE summaries will include all treatment emergent AEs (TAES), i.e. AEs starting after first dose study drug.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their overall frequency.

The following adverse event summaries will be produced; overview of AEs and deaths, AEs by SOC and PT, summarized by relationship to study, severity, leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, SAEs will be summarized by SOC and PT overall and for those leading to treatment discontinuation.

All AEs collected in the AE eCRF page will be listed along with the information collected on those AEs e.g. AE relationship to study drug, AE outcome etc. AEs with start date prior to first dose of study drug will be flagged in the listings. AEs for screen failures will be listed separately.

2.8.1.1 AEs of special interest / grouping of AEs

Not applicable.

2.8.2 Deaths

The primary reason for death will be summarized by system organ class and preferred term. All deaths will be listed. Deaths for screen failures will be listed separately.

2.8.3 Laboratory data

Hematology, clinical chemistry, and fasting laboratory tests parameter will be summarized with standard descriptive statistics by visit, overall and by subpopulation presenting the baseline value, post-baseline value and change from baseline. Change from baseline will only be summarized for subjects with both baseline and post-baseline values.

For each parameter, the maximum change (maximum decrease and maximum increase) from baseline will be analyzed analogously.

Shift tables will be provided for all parameters to compare a patient's baseline laboratory evaluation relative to the worst observed value during the treatment phase. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the baseline value was normal, low, or high. These summaries will be presented by laboratory test overall and by subpopulation. Shifts will be presented by visit and for most extreme values post-baseline.

For urinalysis dipstick results a frequency table will be produced by parameter and visit.

The following laboratory parameters will be analyzed with respect to numerical Common Terminology Criteria for Adverse Events (CTCAE) grades, given in Appendix 5.3: hemoglobin, platelets, white blood cell count, neutrophils, lymphocytes, creatinine, total bilirubin (TBL), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP).

The number and percentage of patients with CTCAE grade newly occurring or worsening after baseline will be presented. These summaries will be split into hematology and chemistry.

Shift tables will be presented comparing baseline laboratory result (CTCAE grade) with the worst results (expressed in CTCAE grade) post-baseline.

For a patient to meet the criterion of a newly occurring clinically notable value, the patient needs to have a baseline value which is not clinically notable for that parameter. For a patient to meet the criterion of a worsening clinically notable value, the patient needs to have a baseline value which is clinically notable and also have a worse post-baseline value.

Listings of patients with laboratory values meeting CTCAE grades will be provided by treatment group, patient, and laboratory parameter.

Serum and urine pregnancy test results will be listed only.

Liver function tests (LFT)

To evaluate potential drug-induced liver injury, the number and percentage of patients with newly occurring or worsening abnormalities in liver function tests at any time post-baseline will be summarized by treatment based on the following criteria:

Table Notable liver function test values

Criterion
ALT > 3 x the upper limit of normal range (ULN) ALT > 5 x ULN ALT > 8 x ULN ALT > 10 x ULN ALT > 20 x ULN
AST > 3 x ULN AST > 5 x ULN AST > 8 x ULN AST > 10 x ULN AST > 20 x ULN
ALT or AST > 3 x ULN ALT or AST > 5 x ULN ALT or AST > 8 x ULN ALT or AST > 10 x ULN ALT or AST > 20 x ULN
Total bilirubin > 1.5 x ULN Total bilirubin > 2 x ULN Total bilirubin > 3 x ULN
ALP > 2 x ULN ALP > 3 x ULN ALP > 5 x ULN
ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 5 x ULN and total bilirubin > 2 x ULN ALT or AST > 8 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN and total bilirubin > 2 x ULN
ALP > 3 x ULN and total bilirubin > 2 x ULN ALP > 5 x ULN and total bilirubin > 2 x ULN
ALT or AST > 3 x ULN and Total Bilirubin > 2 x ULN and ALP < 2 x ULN (Hy's law)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase

When a criterion contains multiple laboratory parameters, the criterion will only be considered to have been met when all conditions occur at the same time (i.e., within the same sample). A case where all criteria are met at a post-baseline time point will be considered as newly occurring if the criteria are not met at baseline and will be considered as worsening if the criteria are met at baseline and at least one component is worsening from baseline irrespective of whether the other(s) are better.

Listings of patients with clinically notable LFT values will be provided.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

No ECG data are collected in this study.

2.8.4.2 Vital signs

Vital signs (blood pressure, pulse rate, weight, waist circumference and hip circumference) will be summarized with standard descriptive statistics by visit, overall and by subpopulation presenting the baseline value, post-baseline value and change from baseline.

Newly occurring notable values for vital signs will be summarized. Notable values are defined as

- Systolic blood pressure (mmHg) >= 140 mmHg or < 90 mmHg
- Diastolic blood pressure (mmHg) >=90 mmHg or <60 mmHg
- Pulse (bpm) > 100 bpm or <60 bpm

Data of subjects with newly occurring notable vital signs abnormalities will be listed in an additional listing.

2.9 Pharmacokinetic endpoints

Not applicable.

2.10 PD and PK/PD analyses

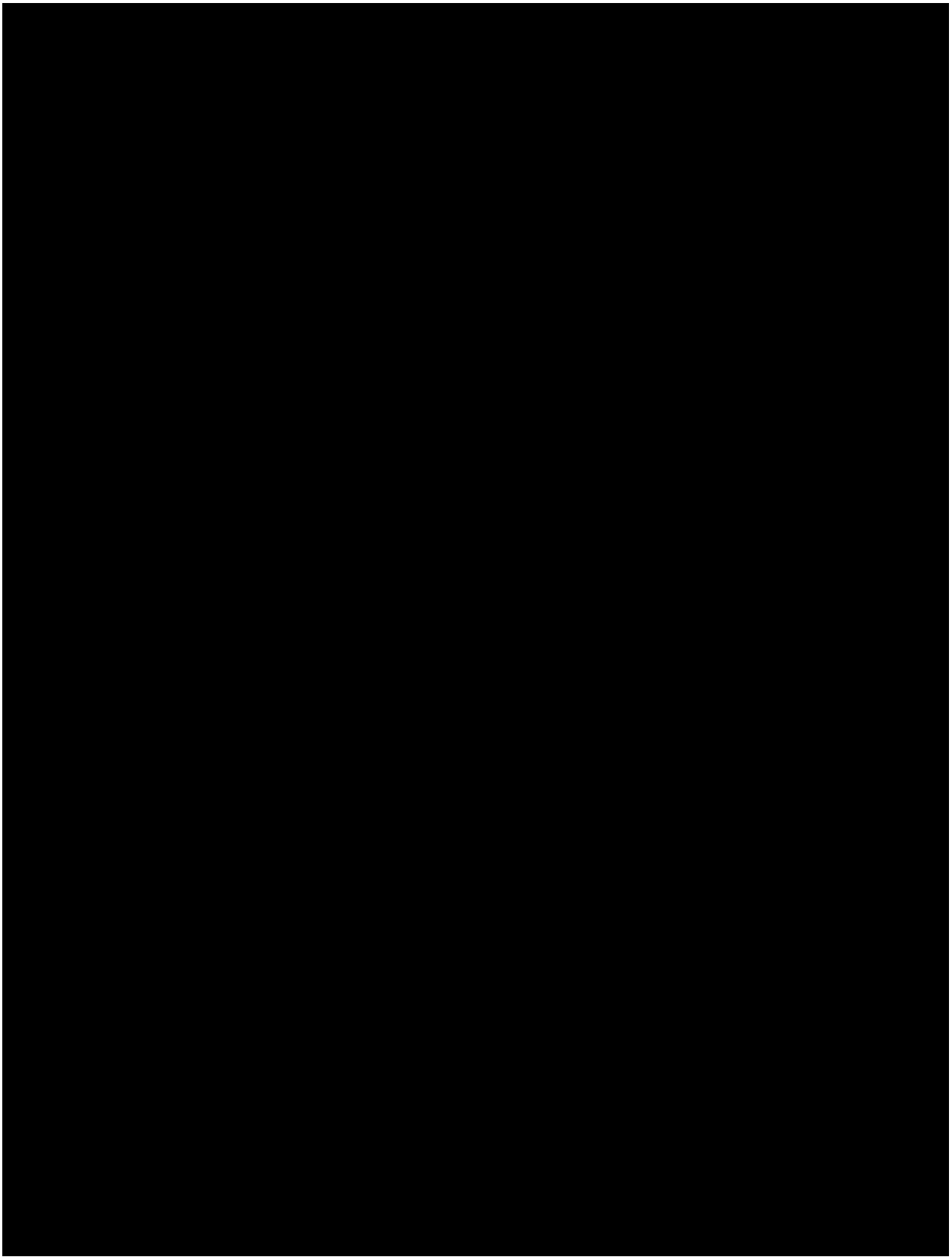
Not applicable.

2.11 Patient-reported outcomes

See Section 2.5 for primary endpoint and Section 2.7 for secondary endpoints as well as Section 2.13 for other exploratory analysis.

2.12 Biomarkers

If a biomarker substudy is performed, details will be described in a separate study protocol and SAP.



2.14 Interim analysis

An interim analysis describing the self-reported baseline characteristics and HR-QoL of patients prior to treatment will be performed for this study after LPFT.

The interim analysis will be based on the Safety set.

Patient screening phase disposition, demographics, baseline disease characteristics, baseline IGA mod 2011, PASI and PROs will be presented as described in Section 2.3.

Other medical history and prior medications and non-drug therapies will not be part of the interim analysis.

3 Sample size calculation

The study aims to estimate primarily the effect of 16 weeks treatment with secukinumab 300 mg on the QoL of the overall study population as well as within the 3 pre-defined subpopulations. It is expected that 40% of the overall study population will fulfil the criteria

for the definition of subpopulation A; 40% will fulfil the criteria for subpopulation B; and 20% will fulfil the criteria for subpopulation C.

The DLQI 0/1 response rate in the overall population treated with secukinumab 300 mg s.c. is expected to be around 70% at Week 16; however, it may vary within those pre-defined subpopulations. A total of 323 patients are required to estimate the response rate of DLQI 0/1 with a precision (= 95% CI) of 5% if the true response rate is about 70% in the smallest subpopulation. To ensure that this precision is achieved in the 3 subpopulations (defined in Section 3.1), which consist of 20% to 40% of the overall study population, 1 615 patients in total should be recruited into this trial.

4 Change to protocol specified analyses

According to the protocol all data from physical examinations should be summarized and listed. As these data are only collected in the source data (see Section 6.5.1 of the protocol) this will not be analyzed.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Not applicable as complete dates for AEs must be reported in the eCRF.

5.1.3 Concomitant medication date imputation

Rules for imputing the prior/concomitant medication (CMD) start date:

1. If the CMD start date year value is missing, the imputed CMD start date is set to one day prior to treatment start date, if not after the CMD end date. Thus the imputed CMD start date will be the minimum of one day prior to treatment start date and the CMD end date.
2. If the CMD start date year value is less treatment start date year value, the CMD started before treatment start. Therefore:
    a) If the CMD year is less than treatment start year and the CMD month is missing, the imputed CMD start date is set to 01JulYYYY.
    b) Else if the CMD year is less than the treatment start year and the CMD month is not missing, the imputed CMD start date is set to 15MONYYYY.
3. If the CMD start date year value is greater than treatment start date year value, the CMD started after treatment start. Therefore:

a) If the CMD year is greater than the treatment start year and the CMD month is missing, the imputed CMD start date is set to 01JanYYYY.

b) Else if the CMD year is greater than the treatment start year and the CMD month is not missing, the imputed CMD start date is set to 01MONYYYY.

4. If the CMD start date year value is equal to treatment start date year:

   a) If the CMD month is missing or the CMD month is equal to treatment start month, then the imputed CMD start date is set to the minimum of one day prior to treatment start date and the CMD end date.

   b) Else if the CMD month is less than the treatment start month, the imputed CMD start date is set to 15MONYYYY.

   c) Else if the CMD month is greater than the treatment start month, the imputed CMD start date is set to 01MONYYYY.

Rules for imputing the CMD end date:

1. If the CMD end date is completely missing (and "Ongoing at final examination" was not answered "Yes"), the CMD end date will be the maximum of treatment end date + 1 day and CMD start date.
2. If a partial CMD end date is reported (day is missing or day and month are missing), the CMD end date will be imputed by the maximum possible date, i.e., the end of the reported month if day is missing, or the end of the reported year if day and month are missing provided that the imputed date is not before the CMD start date, otherwise CMD end date will be equal to CMD start date.

5.2 AEs coding/grading

AEs are coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

5.3 Laboratory parameters derivations

The following table shows the CTCAE grades for laboratory parameter. Not all parameters have CTCAE grades defined.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
HGB decreased (Anemia)	<LLN – 100 g/L	<100 – 80 g/L	<80 g/L	-
Platelet count decreased	<LLN – 75.0 x10e9 /L	<75.0 - 50.0 x10e9 /L	<50.0 – 25.0 x10e9 /L	<25.0 x 10e9 /L
White blood cell decreased	<LLN - 3.0 x 10e9 /L	<3.0 - 2.0 x 10e9 /L	<2.0 - 1.0 x 10e9 /L	<1.0 x 10e9 /L
Neutrophil count decreased	<LLN - 1.5 x 10e9 /L	<1.5 - 1.0 x 10e9 /L	<1.0 - 0.5 x 10e9 /L	<0.5 x 10e9 /L
Lymphocyte count decreased	<LLN - 0.8 x 10e9/L	<0.8 - 0.5 x 10e9 /L	<0.5 - 0.2 x 10e9 /L	<0.2 x 10e9 /L
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 6.0 x ULN	>6.0 x ULN
TBL increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALT increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
AST increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
ALP increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

5.4 Derivation of index values and scores

5.4.1 DLQI

The **DLQI**© is a 10-item general dermatology disability index. Each item has 4 response categories ranging from "not at all" to "very much". “Not relevant” is also a valid response. The scoring for each question is as follows:

Response	Score
Very much	3
A lot	2
A little	1
Not at all	0
Not relevant	0
Question unanswered	0
Question 7: “prevented work or studying” is answered as "Yes"	3
Question 7: “prevented work or studying” is answered as "No" and "problem at working or studying" is answered as "A lot"	2
Question 7: “prevented work or studying” is answered as "No" and "problem at working or studying" is answered as "A little"	1
Question 7: “prevented work or studying” is answered as "No" and "problem at working or studying" is answered as "Not at all", "Not relevant" or unanswered.	0

The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The higher the score, the more quality of life is impaired. If more than one question left unanswered the score will not be calculated and set to missing.

The DLQI 0/1 response is defined as a DLQI total score of 0-1.

The DLQI subsection scores will be calculated as by summing the scores of specific questions as follows:

Subsection	Questions	Maximum Score
Symptoms and feelings	Questions 1 and 2	6
Daily activities	Questions 3 and 4	6
Leisure	Questions 5 and 6	6
Work and school	Question 7	3
Personal relationships	Questions 8 and 9	6
Treatment	Question 10	3

The DLQI subsection response of 0 is defined as a DLQI subsection score of 0.

5.4.2 IGA mod 2011

IGA mod 2011 consist of 4 response items, each response lead to an IGA mod 2011 score as follows:

Response (short description)	Score
Clear	0
Almost clear	1
Mild	2
Moderate	3
Severe	4

An IGA mod 2011 0/1 responder is defined as a patient achieving a score of 0 or 1 and improve by at least 2 points on the IGA scale at post-baseline compared to baseline.

5.4.3 BSA and PASI

The **BSA** score and the **PASI** score will be analyzed as calculated by the tablet. The PASI improvement and PASI responder status will be derived as follows, based on the baseline value as defined in Section 2.1.1.

PASI improvement ratio (%) = percent change from baseline = (baseline PASI score – post-baseline PASI score)/(baseline PASI score)*100

A PASI xx responder is defined a patient achieving a PASI improvement ratio of at least xx % with xx = 50, 75, 90 and 100.

5.4.5 HAQ-DI

The HAQ-DI consists of 20 items in 8 categories of functioning including dressing and grooming, arising (getting up), eating, walking, hygiene, reach, grip, and usual activities. Responses to each item are scored as follows:

Response	Score
Unable to do	3
With much difficulty	2
With some difficulty	1
Without any difficulty	0

Each of the 8 categories has a companion question about the use of ‘aids or equipment’ and 'help from another person' to supplement the answers given to the items of the respective category.

Category	Items "Aids or equipment"	Help from another person
A: Dressing & Grooming	Aids used for dressing	Dressing & Grooming
B: Getting up	Specially adapted chair	Getting up
C: Eating	Specially adapted utensils	Eating
D: Walking	Walking stick	Walking
	Walking frame	
	Crutches	
	Wheelchair	
Categories A - D	Other A - D	
E: Hygiene	Bath seat	Hygiene
	Raised toilet seat	
	Long-handled appliances in bathroom	
	Bath rail	
F: Reach	Long-handled for reaching things	Reaching
G: Grip	Jar opener	Gripping and opening things
H: Activities		Shopping and housework
Categories E - H	Other E - H	

The score for each of the 8 categories is the maximum score of the corresponding items. If items are missing the category score is derived from the remaining answered items. If an item of 'aids or equipment' or 'help required from another person' is ticked and this item is not 'other', the score for the corresponding category is the maximum out of 2 and the maximum score of the items of that category.

The disability index will be calculated as the mean score of the 8 category scores. If one of the 8 scores is missing the mean over the 7 available scores will be derived. If more than two category scores are missing the disability index not be calculated.

5.4.6 EQ-5D

The EQ-5D consists of an EQ-5D© descriptive system and the EQ-5D© VAS.

The EQ-5D© descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 dimensions have 5 response levels scored from 1 to 5. The first 3 dimensions have the response levels lasting from no problems, slight problems, moderate problems, severe problems to unable, the last 2 dimensions have the 5 response levels lasting from no, slight, moderate, severe to extreme.

From these 5 dimensions the Crosswalk-index will be calculated by concatenating the responses and choosing the corresponding country specific index value from the EQ-5D-5L_Crosswalk_Index_Value_Calculator.v2 excel file. For countries where the Crosswalk index value is not defined, the index value of the country as specified below will be used.

Country	Crosswalk index country to use
Belgium	UK
Bulgaria	UK
Czech Republic	UK
Estonia	UK
France	France
Germany	Germany
Greece	UK
Hungary	UK
Israel	UK
UK	UK
Italy	UK
Latvia	UK
Lithuania	UK
Poland	UK
Portugal	UK
Romania	UK
Russia	UK
Slovakia	UK
Spain	Spain

The any of the 5 dimensions is missing the Crosswalk index will not be calculated.

The VAS is a continuous scale starting from 0 (worst possible health state) to 100 (best possible health state). The VAS will be analyzed as entered by the patient.

5.4.7 TSQM

The TSQM consists of 9 questions. The responses are scored are scored as follows:

Response	Score	Response	Score	Response	Score
Extremely dissatisfied	1	Extremely difficult	1	Extremely inconvenient	1
Very dissatisfied	2	Very difficult	2	Very inconvenient	2
Dissatisfied	3	difficult	3	Inconvenient	3
Somewhat satisfied	4	Somewhat easy	4	Somewhat convenient	4
Satisfied	5	Easy	5	Convenient	5
Very satisfied	6	Very easy	6	Very convenient	6
Extremely satisfied	7	Extremely easy	7	Extremely convenient	7
Not at all confident	1	Not at all certain	1		
A little confident	2	A little certain	2		
Somewhat confident	3	Somewhat certain	3		
Very confident	4	Very certain	4		
Extremely confident	5	Extremely certain	5		

The TSQM scale scores for effectiveness, convenience and global satisfaction will be derived. If more than one question for a score remains unanswered the corresponding score will not be calculated.

Effectiveness score = ([Score question 1 + score question 2 + score question 3) – 3]/18)*100

If one of the questions remains unanswered the score will be derived as

= ([Score question 1 or 2 + score question 2 or 3) – 2]/12)*100

Convenience score = ([Score question 4 + score question 5 + score question 6) – 3]/18)*100

If one of the questions remains unanswered the score will be derived as

= ([Score question 4 or 5 + score question 5 or 6) – 2]/12)*100

Global satisfaction score

= ([Score question 7 + score question 8 + score question 9) – 3]/14)*100

If one of the questions 7 or 8 remains unanswered the score will be derived as

= ([Score question 7 or 8 + score question 9) – 2]/10)*100

If question 9 remains unanswered the score will be derived as

= ([Score question 7 + score question 8) – 2]/8)*100

5.4.8 PBI

The questionnaire includes 27 items on patient-relevant therapy needs and benefits. The first part of the instrument, the 'Patient Needs Questionnaire' (PNQ), is filled in by the patients before therapy. A 5-step Likert scale (0 = 'not important at all' to 4 = 'very important') records the individual relevance of the different items to the patients. The second part, the PBQ, is filled in by the patients during or after therapy. It comprises the same items as the PNQ, but in contrast, the patients evaluate the extent to which the treatment needs have been fulfilled by therapy (scaled from 0 = 'treatment did not help at all' to 4 = 'treatment helped a lot'). In addition, the Likert scale contains the option 'does not apply to me' in the PNQ and the option 'did not apply to me' in the PBQ. The needs prior to treatment (PNQ) and the benefits achieved by treatment (PBQ) are converted to a weighted index value, the PBI.

$$PBI = \sum_{i=1}^{k} \frac{PNQ_i}{\sum_{i=1}^{k} PNQ_i} PBQ_i$$

Algorithm for the computation of the PBI global benefit value with k preference items (PNQ) and benefit items (PBQ); possible range of item values and global score values: 0-4.
[PBI Short Manual]

For the score calculation, both "does not apply" and "question unanswered" will be treated as missing values. The global score will be calculated using all items pairs (importance + benefit) for which the patient has given a response other than "does not apply". If more than 6 item pairs are missing the PBI will not be calculated.

5.5 Metabolic syndrome

Metabolic syndrome is defined if the patient is fulfilling the criteria for obesity and 2 of the following 4 additional criteria [International Federation of Diabetes, 2006]:

- raised triglycerides >= 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality (Note: defined as intake of any medication of ATC class C10 at the time point of the evaluation)
- reduced HDL cholesterol <40 mg/dL (<1.03 mmol/L for men) or
  < 50 mg/dL(<1.29 mmol/L for women, or specific treatment for this lipid abnormality (Note: defined as intake of any medication of ATC class C10 at the time point of the evaluation)
- raised blood pressure >= 130 mmHg (systolic) and / or >= 85 mmHg (diastolic), or treatment of previously diagnosed hypertension (Note: defined as intake of any medication of ATC classes C02, C03, C07, C08, C09 and reason for use is one of the terms selected by clinical review as per project-specific excel spreadsheet at the time point of the evaluation)
- raised fasting plasma glucose >100 mg/dL (5.6 mmol/L), or previously diagnosed diabetes mellitus type 2

- Obesity is assumed when BMI is >30 kg/m² or in the following cases

Ethnic group	Waist circumference
Europids; Sub-Saharan Africans; Eastern Mediterranean and Middle East (Arab populations) – defined as subjects of Caucasian race and	Male >= 94 cm Female >=80 cm
South Asians, Chinese, Japanese, Ethnic South and Central Americans	Male >= 90 cm Female >=80 cm

In the present study the following rules for assignments to the above ethnic groups will be followed:

Ethnic group	Assignment using race from eCRF
Europids; Sub-Saharan Africans; Eastern Mediterranean and Middle East (Arab populations)	Race Caucasian, Black or Other.
South Asians, Chinese, Japanese, Ethnic South and Central Americans	Race Asian

5.6 Statistical models

5.6.1 Primary analysis

The primary analysis of this study will be descriptive without any formal group comparisons or hypothesis testing.

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies. Confidence intervals will be derived as well based on the score method including continuity correction [Newcombe (1998)]:

With z as (1-alpha/2)-quantile of the standard normal distribution (SAS: z=PROBIT(1-alpha/2), n as total number of subjects (i.e. number of subjects in the denominator), and p as estimated crude incidence (number of subjects with event / n) it is $q = 1-p$.

Then the lower limit is for $p > 0$, (L = 0 for $p = 0$),

$$L = \max\left(0, \frac{2np + z^2 - 1 - z\sqrt{z^2 - 2 - 1/n + 4p(nq+1)}}{2(n+z^2)}\right)$$

and the upper limit is for $p < 1$, $(U = 1 \text{ for } p = 1)$

$$U = \min\left(1, \frac{2np + z^2 + 1 + z\sqrt{z^2 + 2 - 1/n + 4p(nq-1)}}{2(n+z^2)}\right)$$

5.6.2 Key secondary analysis

Not applicable.

5.7 Rule of exclusion criteria of analysis sets

The following protocol deviations lead to exclusion from analysis sets:

Deviation ID	Description of Deviation	Exclusion in Analyses
INCL01	Informed consent missing or not signed prior to initiating study procedures.	Excluded from all analysis

6 Reference

1. Newcombe RG (1998) Two-sided confidence intervals for the single proportion: comparison of seven methods. Statistics in Medicine; 17: 857-872.
2. PBI Short Manual: Patient Benefit Index (PBI), Questionnaire on Patient-Defined Treatment Objectives and Benefits in Skin Diseases, Short Manual, Date August 20th 2015
3. Castela E, Archier E, Devaux S et al (2012): Topical corticosteroids in plaque psoriasis: a systematic review of efficacy and treatment modalities. Journal of the Europan Academy of Dermatology and Venereology; 26 (Suppl 3): 36-46.
4. International Federation of Diabetes (2006), The IDF consensus worldwide definition of the METABOLIC SYNDROME, http://www.idf.org/webdata/docs/IDF_Meta_def_final.pdf (Accessed 25 August 2016).

Approval signatures for SAP - CSR deliverables

Name	Function	Date, Signature
[redacted]	[redacted]	13 Jun 2017 [redacted]