STATISTICAL ANALYSIS PLAN AMENDMENT 1

Study: PS0016

Product: Bimekizumab (UCB4940)

A MULTICENTER, RANDOMIZED, SUBJECT-BLIND, INVESTIGATOR-BLIND STUDY TO EVALUATE THE TIME COURSE OF PHARMACODYNAMIC RESPONSE, SAFETY AND PHARMACOKINETICS OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

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LIST OF ABBREVIATIONS

ACP	above cut point
ADA	anti-drug (bimekizumab) antibody
ADAE	analysis data adverse events
ADaM	analysis data model
AE(s)	adverse event(s)
AESM	adverse events of special monitoring
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALQ	above the limit of quantification
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
BCP	below cut point
BKZ	bimekizumab
BLQ	below the limit of quantification
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CCR	chemokine receptor
CD	cluster of differentiation
CI	confidence interval
CP	confirmed positive

CRF	case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CXCR	CXC chemokine receptor
DAP	data analysis plan
DC	dendritic cell
DEM	data evaluation meeting
DMC	Data Monitoring Committee
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EWD	early withdrawal visit
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
geoCV	geometric coefficient of variation
GGT	gamma glutamyltransferase
HADS	Hospital Anxiety and Depression Scale

HADS-A	HADS-Anxiety
HADS-D	HADS-Depression
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C virus antibody
HIV1-Ab	human immunodeficiency virus 1 antibody
HIV2-Ab	human immunodeficiency virus 2 antibody
HLT	high level term
HLGT	high level group term
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IL	interleukin
IMP	investigational medicinal product
LCL	lower confidence limit
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LLT	lower level term
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov chain Monte Carlo
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
n	number of subjects

NCP	not confirmed positive
NK	natural killer
NRI	nonresponder imputation
NSAIDs	non-steroidal anti-inflammatory drugs
PASI	Psoriasis Area and Severity Index
PBO	placebo
PCS	potentially clinically significant
PD	pharmacodynamic
PD-PPS	Pharmacodynamic Per-Protocol Set
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PPS	Per-Protocol Set
PT	preferred term
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
RS	Randomized Set
SAEs	serious adverse events
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	standard deviation
SDTM	Study Data Tabulation Model
SFU	safety follow-up
SMQ	standardized MedDRA query

SOC	system organ class
SS	Safety Set
TB	tuberculosis
TBNK	T cell, B cell and NK cell assay
Tc	T cytotoxic
TEAE(s)	treatment-emergent adverse event(s)
TEMA	treatment-emergent markedly abnormal
TFLs	tables, figures and listings
Th	T helper
UCL	upper confidence limit
ULN	upper limit of normal
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of study PS0016. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol.

This SAP Amendment 1 is based on, and assumes familiarity, with the following documents:

- Final protocol, dated 06 June 2016
- Protocol amendment 1, dated 04 August 2016
- Protocol amendment 2, dated 06 September 2016
- Protocol amendment 3, dated 23 September 2016
- Statistical analysis plan, dated 23 February 2017

Unless specified in the sections below, the study will be analyzed as described in the most recent version of the protocol. If a future protocol amendment necessitates a substantial change to the statistical analysis of the study data, this SAP amendment will be updated accordingly. In addition, if analysis definitions have to be modified or updated prior to database lock, a further SAP amendment will be required. If, after database lock, additional analyses are required to supplement the planned analyses described in this SAP amendment, these changes will be described in the CSR together with the associated rationale.

The content of this SAP amendment is compatible with the International Council for Harmonisation (ICH)/Food and Drug Administration (FDA) E9 Guidance documents.

UCB is the Sponsor and PAREXEL is the Contract Research Organization (CRO) for this study.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this study is to evaluate the time-course of Psoriasis Area and Severity Index (PASI) over a 28-week period following the administration of bimekizumab given at Baseline and Week 4 to subjects with moderate to severe chronic plaque psoriasis.

2.1.2 Secondary objectives

The secondary objectives of the study are to:

- To evaluate the time-course of PASI over a 28-week period following the administration of bimekizumab given at Baseline and Weeks 4 and 16 in subjects with moderate to severe chronic plaque psoriasis
- Assess the pharmacokinetics (PK) and immunogenicity of bimekizumab
- Assess the safety and tolerability of bimekizumab

2.1.3 Other objectives

The other objectives of the study are to:

- Assess the effect of bimekizumab on gene and protein expression, and explore the relationship between genomic, genetic, and proteomic biomarkers and disease biology, drug treatment and inflammatory/immune responses

2.2 Study variables

2.2.1 Primary variables

2.2.1.1 Primary efficacy variable

The primary endpoint of this study is change from Baseline in PASI at Week 28.

2.2.1.2 Primary pharmacokinetic variable

The primary PK variable is plasma concentration of bimekizumab.

2.2.1.3 Primary immunogenicity variable

The primary immunological variable is anti-drug (bimekizumab) antibody (ADA) detection prior to and following study treatment.

2.2.1.4 Primary safety variable

The primary safety variable is incidence of adverse events (AEs).

2.2.2 Secondary variables

The secondary efficacy variables are:

- PASI75, PASI90 and PASI100 response at Week 16
- Investigator's Global Assessment (IGA) response (Clear or Almost Clear with at least a 2-category improvement from Baseline) at Week 16

2.2.3 Other variables

2.2.3.1 Other efficacy variables

The other efficacy variables are listed below and will be evaluated at all scheduled visits in accordance with the schedule of assessments in Table 5-1 of the clinical study protocol. This excludes the primary and secondary variables as previously specified in Section 2.2.1 and Section 2.2.2.

- Absolute and percentage change from Baseline in PASI with time (Week 2 to Week 36)
- PASI75, PASI90 and PASI100 response at Weeks 2, 4, 8, 12, 20, 24, 28 and 36
- PASI25 and PASI50 response (Week 2 to Week 36)
- IGA response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Weeks 2, 4, 8, 12, 20, 24, 28 and 36
- Change from Baseline in IGA score with time (Week 2 to Week 36)
- Change from Baseline in the body surface area (BSA) affected by psoriasis with time (Week 2 to Week 36)
- Change from Baseline in Hospital Anxiety and Depression Scale (HADS) HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) scores with time (Week 4 to Week 36)

- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores) at each post-Baseline visit (Week 4 to Week 36)

2.2.3.2 Other pharmacodynamic variable

The pharmacodynamic (PD) variable is to determine the blood or blood derivative (eg, plasma) concentrations of cytokines of relevance to interleukin (IL)-17A/F signaling pathway and psoriasis biology, including but not limited to serum complement concentrations, mononuclear cell subtypes (flow cytometry), cytokines and other candidate biomarkers.

Only the results for the flow cytometry will be included in the TFLs. The results arising from the analysis of other PD variables will be reported separately, if applicable. These are not described further in this SAP.

2.2.3.3 Other safety variables

Other safety variables to be assessed are:

- Change from Baseline in clinical laboratory variables (chemistry, hematology and urinalysis)
- Change from Baseline in vital signs
- Change from Baseline in physical examination
- Electrocardiogram (ECG) results

2.2.4 Ribonucleic acid, proteins, and metabolite variables

Blood and tissue biopsy samples will be collected at specified timepoints and stored for up to 20 years to allow for potential exploratory analyses of ribonucleic acid (RNA), proteins and metabolites biomarkers relevant to psoriasis and the inflammatory and immune response process.

The nature and format of these tentative analyses will be determined at a later stage.

These results will not form part of the TFLs and therefore are not discussed further in this SAP.

2.2.5 Immunological variable

The immunological variable is ADA detection following study treatment.

2.3 Study design and conduct

This is a Phase 2a, multicenter, randomized, subject-blind and investigator-blind study to evaluate the PD, PK, and safety of bimekizumab administered via subcutaneous (sc) injection to subjects with psoriasis. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe chronic plaque psoriasis (Baseline PASI ≥12 and BSA affected by psoriasis ≥10% and IGA score ≥3 [on a 5-point scale]) who are candidates for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy.

This study will include 3 periods: a Screening Period (up to 4 weeks), a Treatment Period (28 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the last dose of study medication). Between Week 20 and the end of the 28-week Treatment Period, eligible subjects will be allowed to enroll in an extension study.

Screening Period

The Screening Period will last up to a total of 4 weeks in the event that applicable laboratory screening tests require retesting if the initial results are in error, borderline, or indeterminate. During this time, laboratory data (hematology, urine, and biochemistry tests) will be obtained, the doses of non-steroidal anti-inflammatory drugs (NSAIDs) (if used to treat psoriatic arthritis), will be verified as stable.

Treatment Period

During the Treatment Period, subjects will be randomized 2:1 to receive one of the following blinded study treatment regimens:

- Treatment arm A: Bimekizumab 320mg administered sc at Baseline and Week 4, and placebo administered at Week 16
- Treatment arm B: Bimekizumab 320mg administered sc at Baseline and Weeks 4 and 16

There will be approximately 30 subjects in treatment arm A and 15 subjects in treatment arm B. Bimekizumab will be administered in the clinic at Baseline and Week 4, and at Baseline, Week 4, and Week 16 for those in treatment arm A and treatment arm B, respectively. Additional nondosing study visits will occur at Week 2, Week 8, Week 12, Week 20, Week 24, and Week 28.

From Week 20 through Week 28, subjects who were previously PASI25 responders (defined as described in Section 8.3.1) but subsequently relapse (defined as returning to a less than PASI25 response) will undergo the study assessments for that visit (ie, Week 20, Week 24, or Week 28) before receiving their first dose of study treatment in the extension study at Week 20, Week 24, or Week 28. Subjects eligible for the extension study must have the assessments for SFU (for PS0016) conducted prior to entering the extension study. Subjects may also enter the extension study after the SFU Visit at Week 36. Subjects who have not achieved a PASI25 response at any visit prior to Week 20 will not be eligible to enter the extension study. All subjects not enrolling in the extension study will continue in PS0016 until the SFU Visit at Week 36.

Subjects withdrawing early from the study will undergo the Early Withdrawal Visit (EWD) assessments (ie, the same assessments as for Week 36) and will enter the SFU Period, completing study participation with the SFU Visit 20 weeks after the last dose of investigational medicinal product (IMP).

Safety Follow-Up Period

All subjects not continuing in the extension study, including those withdrawn from study treatment, will have a SFU Visit 20 weeks after their last dose of IMP (ie, bimekizumab or placebo).

2.4 Determination of sample size

No formal statistical sample size estimation has been performed due to the exploratory nature of this study. This clinical study is not powered for any conclusive statistical analysis of efficacy, PK, safety or immunological variables. The sample size has been determined based on the number of subjects required in the current study to provide reliable PK/PD model parameter estimates when the data is combined with PS0010. Reliable estimates of PK/PD parameters are

defined as number of subjects required to achieve a relative standard error of ≤30% for fixed effects parameters and ≤50% for all random effects parameters.

In order to determine the sample size required for the PK/PD model, Markov chain Monte Carlo (MCMC) simulations were performed. Five hundred trials were simulated with the proposed design, and including 240 subjects from PS0010. The simulated data were re-estimated using the same model. These simulations indicated that reliable estimates will be possible with a total number of 45 subjects (30 subjects in Treatment arm A and 15 subjects in Treatment arm B).

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical evaluation will be performed by PAREXEL. The datasets will follow the UCB analysis data model (ADaM) data specifications.

All analyses will be performed using SAS version 9.3 or higher (SAS Institute, Cary, North Carolina, United States). Continuous variables will be summarized by treatment group, visit and timepoint (where applicable) including number of subjects (n), mean, standard deviation (SD), median, minimum, maximum and confidence intervals (CI) where stated in the SAP. Categorical variables will be summarized by treatment, visit and timepoint (where applicable) with frequency counts and percentages. Coefficient of variation (CV), geometric mean and 95% CI for the geometric mean will also be presented in the descriptive statistics for the PK concentration data. In all outputs the confidence limits will be restricted to the possible values that the variable can take.

When reporting relative frequencies or other percentage values, the following rules apply:

- For values where all subjects fulfill certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is zero, there will be no percentage displayed at all
- All other percentage displays will use 1 decimal place

Percentages displayed based on continuous data (eg, percentage changes from baseline) will be displayed to 1 decimal place. Unless otherwise stated, the denominator for the percentages will be based on the number of subjects in the respective analysis set and treatment group.

When reporting descriptive statistics, the following rules will apply in general (with the exception of PK concentration data, for which additional rules are stated below):

- n will be an integer
- Mean (arithmetic and geometric), SD and median will use 1 decimal place more than the original data
- Coefficient of variation (CV) will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places as the original value

- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. If n<3, then only the n, minimum and maximum will be presented. If n=3, then only n, median, minimum and maximum will be presented. The other descriptive statistics will be left blank.

When reporting individual values and descriptive statistics for PK concentration data, the following rules will apply with regard to rounding and precision:

- Individual values for PK concentration data will be reported to the same level of precision as received from the bioanalytical laboratory
- Descriptive statistics for PK concentration data will be reported to the same level of precision as the individual data for the minimum and maximum, and to 1 additional significant figure for the mean (arithmetic and geometric), median, SD and 95% CI for the geometric mean
- Geometric CV (geoCV) will be reported as a percentage to 1 decimal place

All tabulations will be performed by treatment group, visit and timepoint (where applicable). In the TFLs the treatment groups will be displayed as follows where BKZ refers to bimekizumab and PBO refers to placebo:

- BKZ 320mg + PBO
- BKZ 320mg

Data listings containing all documented data and all derived data will be generated.

3.2 General study level definitions

3.2.1 Analysis timepoints

3.2.1.1 Relative day

Relative day for an event will be derived with the date of the first sc injection of IMP as reference.

Relative days for an event of measurement occurring before the date of first sc injection are calculated as follows:

$$Relative\ Day = Event\ Date - Date\ of\ First\ Injection \quad [1]$$

The relative day for an event or measurement occurring on or after the reference date to the date of the last injection is calculated as follows:

$$Relative\ Day = (Event\ Date - Date\ of\ First\ Injection) + 1 \quad [2]$$

For events or measurements occurring after the date of the last injection, relative day will be prefixed with '+' in the data listings and will be calculated as follows:

$$Relative\ Day = Event\ Date - Date\ of\ Last\ Injection \quad [3]$$

There is no relative Day 0. Relative day is not calculated for partial dates in cases where relative day is shown in a subject data listing. In such cases, relative day should be presented as '-' in the subject data listings.

3.2.1.2 Study periods

For each subject, the study will last a maximum of up to 40 weeks. This includes the following study period durations:

- Screening Period: up to 4 weeks
- Treatment Period: 28 weeks
- Safety Follow-Up Period: a SFU Visit is planned 20 weeks after the last dose of study medication

The end of the study is defined as the date of the last visit of the last subject in the study.

Additional analysis periods for classification of concomitant medications and AEs are provided in Section 6.5.4 and Section 11.2.1 respectively.

3.3 Definition of Baseline values

Baseline will be the last available value prior to the first injection of IMP. Scheduled or unscheduled measurements can be used as the Baseline value. Measurement-specific Baseline timepoints (based on the planned timepoints in the protocol) are presented in Table 3–1.

Table 3–1: Definition of Baseline

Category	Measurement	Definition of Baseline
Efficacy	PASI IGA BSA HADS	Baseline Visit, or if missing the Screening results.
Pharmacodynamic	Mononuclear cell subtypes (flow cytometry)	Baseline Visit
Safety	Laboratory results (including hematology, biochemistry and urinalysis) Vital signs ECG Body weight C-SSRS	Baseline visit, or if missing the Screening results. For the C-SSRS the 'Baseline' version of the questionnaire will be completed at Screening and the 'Since Last Visit' version will be completed at all subsequent visits.
Immunological	ADA	Baseline Visit

ADA=anti-bimekizumab antibody; BSA=body surface area; C-SSRS=Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; HADS=Hospital Anxiety and Depression Scale; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index.

If a measurement is repeated at Baseline and is obtained prior to receiving the first dose of IMP, then the last available measurement will be used as the Baseline value.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK/PD outcomes

for an individual subject. The criteria for identifying such protocol deviations will be defined within the protocol deviation specifications document which is part of the data cleaning plan. Important protocol deviations will include the following categories:

- Inclusion/exclusion criteria deviations
- Administration of prohibited concomitant medications
- Deviations relating to withdrawal criteria
- Visit schedule deviations
- Study drug administration deviations (including incorrect treatment received)
- Missing data

Important protocol deviations will be reviewed as part of the ongoing data cleaning process and data evaluation.

After all data have been verified/coded/entered into the database, the final data evaluation meeting (DEM) will be performed. The purpose of this DEM will be to review all protocol deviations, define the analysis sets and check the quality of the data prior to unblinding. The review will also help decide how to manage problems in the subjects' data (eg, missing values and withdrawals).

After the pre-analysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent (ie, all screened subjects). This will therefore include screening failures.

3.5.2 Randomized Set

The Randomized Set (RS) will consist of all randomized subjects.

3.5.3 Safety Set

The Safety Set (SS) will consist of all subjects who received at least 1 dose of the study medication.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of the study medication and have a valid measurement of the primary efficacy variable at Baseline.

3.5.5 Per-Protocol Set

The Per-Protocol Set (PPS) will consist of all randomized subjects who received at least 1 dose of the study medication and have a valid measurement of the primary efficacy variable post-Baseline without important protocol deviations affecting the measurement.

The analyses of the efficacy variables will be repeated for the PPS where stated in the SAP. If the FAS and PPS are the same, any outputs based on the PPS will not be presented.

3.5.6 Pharmacokinetics Per-Protocol Set

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized subjects who received at least 1 dose of the study medication and provided at least 1 quantifiable plasma concentration post-dose.

3.5.7 Pharmacodynamics Per-Protocol Set

The Pharmacodynamics Per-Protocol Set (PD-PPS) will consist of all randomized subjects who received at least 1 dose of the study medication and provided at least 1 PD measurement post-dose without important protocol deviations affecting the measurement.

3.6 Treatment assignment and treatment groups

Treatment assignment for the SS, PK-PPS and PD-PPS will be according to the actual treatment received. Analyses of efficacy data (based on the FAS) will be conducted according to the randomized treatment.

Subjects receiving the incorrect treatment at a particular visit will be excluded from the PPS as this would be considered as an important protocol deviation. Subjects may be excluded from the analysis at a particular visit (or visits) only, following discussion at the DEM.

Listings and summaries will be presented by treatment group and overall where applicable (Table 14–1).

The following order will be used in the TFLs:

- Not randomized
- BKZ 320mg + PBO (Treatment arm A)
- BKZ 320mg (Treatment arm B)
- All subjects

In the case of dosing administration errors during the Treatment Period, all statistical analyses of safety, PK and PD data will be conducted according to the actual treatment received with the following rules:

- Subjects randomized to Treatment arm A who received bimekizumab at Week 16 will be summarized together with subjects in Treatment arm B
- Subjects randomized to Treatment arm B who received placebo at Week 16 will be summarized together with subjects in Treatment arm A

Any other dosing errors will be discussed at the DEM and the decision regarding the inclusion into the relevant analyses will be documented as part of the DEM minutes.

3.7 Center pooling strategy

The data from different sites will be pooled for all analyses. There will be no stratification by site or country performed.

3.8 Coding dictionaries

Adverse events and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 19.0.

Medications will be coded according to the World Health Organization Drug Dictionary (WHODD [September 2015]). Medical procedures will not be coded

3.9 Changes to protocol-defined analyses

In the clinical study protocol the definition of the FAS included all subjects with a valid measurement of the primary efficacy variable post-Baseline. However, this was adjusted to all subjects with a valid Baseline measurement for the primary efficacy variable in the SAP in order to comply with program standards and FDA requirements (ie, inclusion into the FAS is no longer dependent on availability of post-Baseline data).

According to the final clinical study protocol spaghetti plots of change from Baseline in PASI would be plotted for each subject over time. However as the PASI response is based on percentage change, it was deemed more appropriate to present the individual plots based on percentage change from Baseline.

The protocol stated that exposure at risk for defining treatment-emergence for treatment-emergent adverse events (TEAEs) would be cut off at the Week 16 visit (for subjects who complete through the Week 16 visit) or at 20 weeks (140 days) after the last administration of study treatment (for subjects that discontinue prior to the Week 16 visit). This was further stated to be done in order to provide a fair comparison across all subjects when comparing the incidence of TEAEs. In this SAP amendment it has been clarified that the definition of a TEAE is any AE with onset following the first administration of study medication until the final administration of study medication + 140 days (regardless of study discontinuation). In order to allow for direct comparison of the treatment groups with respect to incidence of TEAEs, prior to the point at which subjects are eligible to enter the extension study, it would be necessary to use a cut off at Week 20 (ie, the first point at which a subject may enter the extension study). This has also been clarified in the SAP amendment accordingly.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

There will be no adjustment for covariates.

4.2 Handling of dropouts or missing data

Missing data will be handled as described in the sections below for efficacy, safety and PK results. No other imputations will be performed.

4.2.1 Efficacy data

4.2.1.1 Psoriasis Area and Severity Index

Missing data for the individual items of the PASI score will be imputed as described in Section 8.1.1 in order to calculate the PASI score at each visit.

The primary efficacy variable is change from Baseline in PASI at Week 28. Missing data at this visit may be attributable to either premature discontinuation or subjects entering the extension study at Week 20 or Week 24. In both scenarios, missing data will be imputed using last observation carried forward (LOCF) where the last observed overall PASI score will be used to impute the missing data for all visits after the point of withdrawal or transition to the extension study. Missing data at other visits will also be imputed using LOCF (ie, if a subject has missing

at Week 12, for example, this will be imputed with the PASI score obtained at Week 8). In addition, PASI summaries will also be presented using observed cases.

There will be no imputation of missing individual item scores for the PASI; the LOCF imputation will apply to the overall PASI score only.

For the binary response variables (PASI25, PASI50, PASI75, PASI90 and PASI100), missing data will be imputed using nonresponder imputation (NRI), ie, subjects with missing data at a specific visit will be considered as nonresponders for the analysis. This will include visits after the point of withdrawal or after the point of transition to the extension study, if applicable. This will also be presented using observed cases.

4.2.1.2 Body surface area

For missing BSA, the missing data will be imputed using LOCF as described in Section 4.2.1.1 for the PASI score. This will also be presented using observed cases.

4.2.1.3 Investigator's Global Assessment

There will be no imputation of missing individual data for the IGA score. For the responder analysis, missing data will be imputed using NRI, ie, subjects with missing data at a specific visit will be considered as nonresponders for the analysis. This will include visits after the point of withdrawal or after the point of transition to the extension study, if applicable. In addition, IGA summaries will also be presented using observed cases.

4.2.1.4 Hospital Anxiety and Depression Scale

Missing data for the individual items of the HADS will be imputed as described in Section 14.2 in order to calculate the HADS-A and HADS-D scores at each visit. No other imputation will be performed.

4.2.2 Safety laboratory data

Measurements below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the purpose of calculating change from Baseline and for descriptive statistics. Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper quantification limit.

These rules will be applied to all numeric safety laboratory data including clinical chemistry, hematology and urinalysis variables.

4.2.3 Bimekizumab concentration data

Measurements that are BLQ will be imputed with LLOQ/2 for the purpose of calculating the geometric mean and its 95% CI, the geoCV, the arithmetic mean, and SD for summaries and figures.

For the individual figures, any concentrations that are BLQ will be imputed with LLOQ/2, with the exception of predose BLQ measurements on Day 1 (Baseline Visit), which will be imputed with zero for linear scale plots.

Additional rules for PK data summaries are provided in Section 9.1.

4.2.4 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as past, prior or concomitant

Imputed dates will not be shown in the listings; all dates will be displayed as reported in the database.

The following rules will be applied for partial start dates:

- If only the month and year are specified and the month and year of first dosing is not the same as the month and year of the start date then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00 h;
- If only the month and year are specified and the month and year of first dosing is the same as the month and year of the start date, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use the 1st of the month, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of first dosing then time will be imputed with the time of the first injection (ie, event will be regarded as treatment-emergent);
- If only the year is specified, and the year of dosing is not the same as the year of the start date then use January 01 of the year of the start date. If time is missing this will be imputed as 00:00 h;
- If only the year is specified, and the year of dosing is the same as the year of the start date, then use the date of first dosing in the given year. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of start date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of first dosing then time will be imputed with the time of the first injection (ie, event will be regarded as treatment-emergent);
- If the start date is completely unknown, then use the date of first dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of first dosing then time will be imputed as the start time of the first injection (ie, event will be regarded as treatment-emergent).

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month;
- If only the year is specified, then use December 31 of the known year;
- If the stop date is completely unknown, do not impute the stop date

Missing or partially missing date and/or times will be imputed as described in Table 4–1 for the calculation of duration of each AE. Adverse event duration is computed in and reported in day and time format: xx d hh:mm.

Table 4–1: Calculation rules for duration of adverse events

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h. Duration = <[(D2 – D1)*24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	--/--	D2/T2	Duration = <[(D2 – D0)*24 + (T2 – T0)]/24 d For a subject in the SS, D0 and T0 are the date and time of first administration of IMP and for screen failures, D0 is the date of the screening visit and T0 = 00:00h
End day and time missing	D1/T1	--/--	If the stop date is missing, duration will not be calculated.
Start and end date missing	--/--	--/--	If the stop date is missing, duration will not be calculated.

IMP=investigational medicinal product; SS=Safety Set.

4.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings, where applicable. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated or unscheduled measurements obtained prior to the first dose of IMP, the latest value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics at each visit (ie, Screening and/or Baseline);
- For repeated or unscheduled measurements obtained at the designated Baseline visit, the latest value (which may be scheduled or unscheduled) will be defined as the Baseline provided that this occurred prior to the first dose of IMP;
- For repeated or unscheduled measurements obtained at any timepoint after the first dose of IMP, the first value will be used in the calculation of changes from Baseline and for the descriptive statistics (ie, in summaries by timepoint). Unscheduled and repeated measurements will not be included in the summaries by timepoint, for all timepoints after the first dose of IMP;
- Data from unscheduled visits may be used for tables that present abnormalities (where stated in the SAP amendment).

4.4 Handling of measurements obtained at the early withdrawal visit

Subjects who withdraw from the study prematurely will be encouraged to return for the EWD and the SFU Visit, the latter at 20 weeks following the final dose of IMP. The following rules will apply with regard to the inclusion of the results obtained at the EWD in the descriptive summaries:

- Any efficacy, PK, PD, immunological and safety measurements conducted at the EWD should be included in the summaries for the respective scheduled visit, if the EWD occurs at the time of the next scheduled visit (within the tolerance window specified in the protocol). For example, if the EWD occurs on Day 28, the results would be summarized together with the Week 4 results.
- If the EWD does not correspond to the day of a scheduled visit, the efficacy, safety and other relevant assessments of the EWD should be mapped to the nearest scheduled visit, relative to the Baseline visit date, following the last scheduled visit where assessments are available.
- If the date of the EWD is equidistant between 2 scheduled visits at which no scheduled assessments were performed, the assessments from the EWD will be mapped to the earliest of these visits.

For example, vital sign assessments are performed at Baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28 and 36. If a subject discontinues on Day 37, and the previous vital sign assessment was done at Week 4 (Day 28), the nearest scheduled assessment (following the last visit at which assessments were available) would be Week 8 (Day 56). Therefore, the EWD assessment should be re-assigned to the Week 8 visit.

However, if a subject discontinues at Day 37, and the previous vital sign assessment was done at Week 2 (Day 14), the EWD assessments would be re-assigned to the Week 4 (Day 28) visit, which would be the nearest scheduled visit relative to the Baseline visit date.

Different domains (eg, vital signs, ECG, safety laboratory tests, PASI, IGA) from the same EWD may be re-assigned to different study visits depending on the study schedule of assessments, ie, measurements obtained at the EWD can only be mapped to a scheduled visit at which the respective assessment was intended to be measured. Assessments from the EWD that are mapped to scheduled visits will be flagged in the data listings.

4.5 Interim analyses and data monitoring

4.5.1 Data monitoring committee

An independent data monitoring committee (DMC) will be convened to periodically review and monitor safety data and to advise UCB accordingly. A separate cardiovascular adjudication committee and neuropsychiatric adjudication committee will also review the relevant data for assessment of cardiovascular and potential suicide events respectively, and will provide additional advice to UCB.

The detailed role, scope, responsibilities and complete procedures as well as the identity of the DMC members will be described in a separate DMC Charter. The DMC procedures will ensure that data remain blind to the study team and Investigators at all times during the conduct of the

study. The details regarding the outputs to be produced and the analyses to be performed for the DMC review will be provided in a separate DMC SAP.

A separate Charter will be written for each of the cardiovascular and neuropsychiatric adjudication committees.

4.5.2 Interim analysis

No formal interim analysis will be performed; however interim data cuts will be performed and evaluated. Please refer to the interim SAP for details on the timings and deliverables of these data cuts.

4.6 Multicenter studies

Individual center results will not be displayed.

4.7 Multiple comparisons/multiplicity

Not applicable.

4.8 Use of an efficacy subset of subjects

Not applicable.

4.9 Active-control studies intended to show equivalence

Not applicable.

4.10 Examination of subgroups

Not applicable.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number and percentage of subjects who were randomized into the study, subjects who completed (which includes those who entered the extension study at Week 36) or prematurely discontinued the study, as well as the reason for discontinuation will be presented by treatment group and for all subjects, based on the RS. The tabulation will also include the number and percentage of subjects who achieved a PASI25 response (for at least one post-Baseline visit), the number and percentage of subjects who relapsed, and the number and percentage of subjects entering the extension study prior to Week 36.

The number and percentage of subjects who discontinued due to AEs will be separately summarized by treatment group and for all subjects, based on the RS.

The number and percentage of subjects included into each of the analysis sets will be summarized by treatment group and for all subjects based on all subjects screened. Percentages will be based on the RS for the purpose of this summary.

Finally, screen failure reasons will be summarized, based on all subjects screened. A listing of subjects who did not meet study eligibility criteria (including glossary) will also be presented.

A subject who completed the study is defined as follows:

- All subjects not enrolling in the extension study will be regarded as completers if they continue in the current study (PS0016) until Week 28 (ie, and completed the Week 28 visit).
- From Week 20 through Week 28, subjects who were previously PASI25 responders but subsequently relapse will undergo the study assessments for that visit (ie, Week 20, Week 24 or Week 28) before receiving the first dose of IMP in the extension study. Subjects may also enter the extension study after the SFU Visit at Week 36. All subjects eligible for the extension study must have the assessment for SFU conducted prior to entering the extension study.

  Thus, a subject entering the extension study is regarded as completing PS0016 if they have completed the last visit (ie, Week 20, Week 24 or Week 28) up to the point of entering the extension study.

In addition, the following listings will be presented by treatment group:

- Subject disposition (all subjects screened [ES])
- Study discontinuation (RS)
- Visit dates (SS)
- Subject analysis sets (all subjects screened [ES])

The listing of subject disposition will include the date of informed consent, date of randomization, date and time of first and last dose of IMP (in PS0016), date of premature termination (and primary reason) and date of final contact. The listing will also flag any subjects who entered the extension study, including the visit at which this occurred (ie, Week 20, Week 24, Week 28 or Week 36). If applicable, the date and reason for premature unblinding will also be included.

The listing of study discontinuation will include the reason for discontinuation and the total days on IMP.

The number of days on IMP will be calculated as follows:

$$No.\,days\ on\ IMP = (Date\ of\ Last\ Dose\ Received - Date\ of\ First\ Dose\ Received) + 1 \quad [4]$$

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types listed in the protocol deviation specification document. A listing of all important protocol deviations will be presented for all subjects in the RS and will include the deviation type and description. The number and percentage of subjects with important protocol deviations will be summarized by treatment group and for all subjects for each deviation type, based on the RS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Derivation of variables

6.1.1 Calculation of body mass index

The BMI in kg/m^2 is calculated based on the height (in m) and the weight (in kg) using the following formula:

$$BMI = Weight/(Height)^2 \quad [5]$$

The BMI will be reported to 1 decimal place.

6.1.2 Classification of age categories

Age will be classified into categories based on requirements for European Union Drug Regulating Authorities Clinical Trials (EudraCT) and clinicaltrials.gov reporting.

For the EudraCT reporting, the categories will include:

- 18 to <65 years
- 65 to <85 years
- ≥85 years

For the clinicaltrials.gov reporting, the categories will include:

- ≤18 years
- 19 to <65 years
- ≥65 years

6.1.3 Duration of disease

The duration of disease will be calculated as follows and will be presented in years to 1 decimal place:

$$Duration = [(Date\ of\ Screening - Date\ of\ Diagnosis)/365.25] \quad [6]$$

In the event that the date of diagnosis is incomplete, it will be imputed to the most recent feasible date:

- If only the day is missing, it will be imputed to the last day of the known month
- If the day and month are missing, it will be imputed to December 31 in the known year
- If the date of diagnosis is completely missing, the duration of disease will not be calculated

6.2 Demographics

A by-subject listing of Baseline demographic characteristics will be presented by treatment group. This will include the year of birth (if available), age (in years), sex, race, ethnicity, height (in cm), weight at Screening (in kg) and BMI for all subjects screened. The age will be directly entered into the study database and will not be re-calculated for the statistical analysis.

All Baseline demographic characteristics (with the exception of year of birth) will be summarized by treatment group and for all subjects based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for EudraCT and clinicaltrials.gov reporting.

The tabulation will be repeated for the FAS, only if the SS differs from the FAS.

Childbearing potential will be listed for the SS.

6.3 Other Baseline characteristics

The following Baseline characteristics will be presented in a by-subject listing for the SS:

- *Duration of disease (including date of diagnosis)
- *Percentage BSA involvement
- *PASI total score
- IGA score
- *HADS-A and HADS-D scores
- Previous use (ie, those therapies classified as past medications) of biologic therapy (Yes/No)

Baseline for each variable (where applicable) is defined in Table 3–1.

The Baseline characteristics listed above will be summarized using descriptive statistics (for continuous variables only*). The IGA score will be summarized including the number and percentage of subjects with each specific IGA score. The previous use of biologic therapy (Yes/No) will be summarized using number and percentage of subjects. Previous use of biologic therapies will be listed as part of the past medications for psoriasis (Section 6.5.1) and will be confirmed at the DEM.

The tabulation will be presented by treatment group and for all subjects based on the FAS.

6.4 Medical history and concomitant diseases

Medical history will be listed for the RS and summarized for the SS by treatment group and overall, MedDRA system organ class (SOC) and preferred term (PT). The reported term will be included in the listing. The summary will include the number and percentage of subjects, and will be sorted alphabetically by SOC and by descending incidence of PT within each SOC, based on the 'All Subjects' column. A glossary of all medical history conditions will be presented for the RS including the SOC, PT and reported term.

Procedure history will be listed separately by treatment group for the procedure reported term based on the RS.

Concomitant medical procedures performed during the study will be listed for the RS.

6.5 Past, prior, and concomitant medications

Past, prior and concomitant medications will be listed for the RS by treatment group and subject and summarized for the SS by WHODD Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3) and PT. Tabulations will be presented by treatment group and for all subjects, with separate tabulations for prior (excluding past psoriasis medications) and concomitant categories. Concomitant medications will further be classified into 'Treatment Period' and 'Post-Treatment Period' medications as described in Section 6.5.4.

Past medications for the treatment of psoriasis (based on the information recorded on the psoriasis treatment history page of the case report form [CRF]) will be listed and tabulated separately. The listing will include the treatment name, treatment type (non-biologic systemic agent, biologic agent, phototherapy or photochemotherapy, topical prescription or non-prescription therapy, other) and reason for discontinuation. All other past medications will be summarized together with the prior medications.

All tabulations (excluding past psoriasis medications) will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All Subjects' column. For past psoriasis medications the tabulations will be presented by treatment type as these medications will not be coded.

A glossary of all past, prior and concomitant medications will be presented for the RS including the Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3), PT and reported term.

6.5.1 Past medication definition

Past medications will include any medications that started and stopped prior to the first administration of IMP. Past medications are therefore a subset of prior medications and include any prior medication with a stop date prior to the date of first administration of IMP. Any medications recorded on the psoriasis treatment history page of the CRF will be considered as past medications.

6.5.2 Prior medication definition

Prior medications include any medications that started prior to the date of administration of the first dose of IMP. This includes medications that started prior to dosing and continued after.

6.5.3 Concomitant medication definition

Concomitant medications are medications taken at least 1 day in common with the study Treatment Period.

Any medication that started prior to dosing and continued after dosing will therefore be classified as both prior and concomitant. Such medications will therefore be counted in tabulations for both prior and concomitant categories.

Any medications with missing dates and/or times will be handled as described in Section 4.2.4 in order to classify them as prior or concomitant.

6.5.4 Classification of concomitant medications

In order to allow for a comparative period across all subjects for incidence of concomitant medication usage, prior to the point at which subjects are eligible to enter the extension study, concomitant medications will be classified as follows:

- **Treatment Period medications:** all concomitant medications taken at least once from the time of the first administration of IMP up until the Week 20 visit. Any medications taken on the date of the Week 20 visit will be included (ie, the cut off will be assumed to be at 23:59 hours on the date of Week 20). Such medications will be designated as 'Treatment Period' medications in the tabulations. This will include medications that start prior to the Week 20 visit and are ongoing. Any subjects that withdraw prior to Week 20 will have Treatment Period medications cut off at 140 days relative to the first dose (ie, equivalent to 20 weeks).
- **Post-Treatment Period medications:** all concomitant medications with a start date/time after the Week 20 visit will be designated as 'Post-Treatment Period' medications in the tabulations. Thus, Post-Treatment Period medications will include only those medications for subjects not entering the extension study at all or those medications for subjects who enter the extension study at a later visit. For subjects that withdraw prior to Week 20, Post-Treatment Period medications are classified as those starting after 140 days relative to the first dose (ie, equivalent to 20 weeks).

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Overall compliance will be examined in terms of completed injections, where 1 dose consists of 2 sc injections.

This will be calculated as follows and will be presented to 1 decimal place in the listings:

$$Overall\ compliance\ (\%) = [100x(Total\ number\ of\ completed\ injections/Total\ number\ of\ expected\ injections)] \quad [7]$$

The total number of expected injections will be derived relative to the date of premature discontinuation for subjects who do not complete the treatment period. For a subject completing the treatment as per protocol, the total number of expected injections is 6 (ie, 2 injections at each of Baseline, Week 4 and Week 16).

The calculated overall compliance will be listed by treatment group and subject, and summarized by treatment group, based on the SS. The summary will include both descriptive statistics for overall compliance (n, mean, SD, median, minimum and maximum) and the number and percentage of subjects based on the following classifications:

- Compliance ≤75.0%
- Compliance >75.0%

All data regarding IMP administration will be listed as described in Section 11.1.

8 EFFICACY ANALYSES

8.1 Statistical analysis of the primary efficacy variable

The primary efficacy variable is the change from Baseline in PASI at Week 28.

8.1.1 Derivations of primary efficacy variable

The PASI is the most commonly used assessment for grading the severity of psoriasis in clinical studies and quantifies the severity and extent of the disease and weighs these with the percentage of BSA involvement. The body is divided into four regions comprising the head (h), upper extremities (ue), trunk (t), and lower extremities (le). In each of these regions, the total surface area-of-involvement (A) is graded on a scale of 0 to 6 (0 for no involvement up to 6 for 90% - 100% involvement). The body regions and associated BSA are presented in Table 8–1.

Table 8–1: Body regions for calculation of percent BSA for PASI

Body region	Details of region	BSA	Area-of-involvement of body region (A) [a]
Head (h)	Face, back of head	10%	0 to 6
Upper limbs (ue)	Left, right, upper lower, flexor surface, extensor surface	20%	0 to 6
Trunk (t)	Front, back, groin	30%	0 to 6
Lower limbs (le)	Left, right, upper lower, flexor surface, extensor surface, including buttocks	40%	0 to 6
Total		100%	

A=area-of-involvement score; BSA=body surface area; PASI=Psoriasis Area and Severity Index

[a] Where 0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected.

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Scoring of psoriatic plaques for the PASI is based on 3 criteria: redness (R), thickness (T), and scaliness (S). Severity is rated for each index (R, T, S) on a scale of 0 to 4 (0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked).

The various body regions are weighted to reflect their respective proportion of BSA. The composite PASI score is then calculated by multiplying the sum of the individual severity scores (R, T and S) for each region by the weighted area-of-involvement score (A) for that respective region, and then summing the 4 resulting quantities as follows:

$$\text{PASI} = 0.1x[(Rh + Th + Sh)xAh] + 0.2x[(Rue + Tue + Sue)xAue] + 0.3x[(Rt + Tt + St)xAt] + 0.4x[(Rle + Tle + Sle)xAle] \quad [8]$$

The following rules will be applied in the calculation of the PASI score in case of missing data:

- If 1 or 2 severity measurements are missing for a certain region (eg, head), the average of the remaining measurements within that region will be utilized to substitute the missing values
- If the area of affected skin and/or all severity measurements for 1 or 2 regions are missing, then the missing (R+T+S)×A for a region will be substituted by the average of the available (R+T+S)×A across the remaining regions
- If the PASI assessment has more missing data than indicated above, at a given visit, then the PASI will be set to missing for that visit

The highest potential PASI score is 72 for severe disease; the lowest score is 0 which indicates no psoriatic lesions are present. The PASI scores are considered as a continuous variable and will be calculated and presented to 1 decimal place in the listings. The percentage improvement in PASI score from Baseline will be calculated as follows:

Percentage improvement from Baseline $= 100x[(Baseline\ PASI - PostBaseline\ PASI)/Baseline\ PASI]$ [9]

Thus, for subjects with an improvement in the PASI score, the percentage will be positive. For subjects with a worsening in the PASI score, the percentage will be negative.

8.1.2 Primary analysis of the primary efficacy variable

The individual scores for the PASI for each body region (redness, thickness and scaliness severity scores and area-of-involvement score [A]), and the derived total PASI score (from 0 to 72) will be listed for each subject and visit. The listing will include the change from Baseline and percentage change from Baseline for the total score only.

Descriptive statistics (including 95% CI) will be presented by treatment group and visit for absolute values, changes from Baseline and percentage change from Baseline (based on the total PASI score only). For the purpose of the tabulations the lower and upper 95% confidence limits will be truncated as follows:

- For the absolute values the lower 95% confidence limit will be truncated at 0 and the upper 95% confidence limit will be truncated at 72
- For the changes from Baseline the lower 95% confidence limit will be truncated at -72 and the upper 95% confidence limit will be truncated at +72
- For the percentage change from Baseline the upper 95% confidence limit will be truncated at +100%, there will be no truncation of the lower 95% confidence limit

The following figures will be presented:

- Combined individual (spaghetti) plots displaying percentage change from Baseline in PASI score versus time (visit) by treatment group (all subjects will be overlaid on the same plot with separate plots for each treatment group)
- Mean (with 95% CI) percentage change from Baseline in PASI score versus time (visit) by treatment group (both treatment groups will be overlaid on the same plot)

All tabulations and both individual and mean figures will be presented using the FAS and repeated for the PPS (if it differs from the FAS). All listings will be presented using the SS.

For subjects that discontinue the study or those that enter the extension study, missing data will be imputed using LOCF as described in Section 4.2.1.1 for the tabulations and mean figures. Separate tables and mean figures will also be created based on the observed cases only. Missing data will not be imputed for the listings or the individual figures.

8.2 Statistical analysis of the secondary efficacy variables

The secondary efficacy variables are:

- PASI75, PASI90 and PASI100 response at Week 16

- IGA response (Clear or Almost Clear with at least a 2 category improvement from Baseline) at Week 16

The analysis of the secondary efficacy variables will be based on the FAS for all tabulations and figures. Listings will be based on the SS.

8.2.1 Psoriasis Area and Severity Index response variables at Week 16

The PASI75, PASI90, and PASI100 responses are based on at least 75%, 90%, and 100% improvement from Baseline in the PASI score. Thus, the following will apply:

- If the percentage improvement is ≥75% then the subject is a PASI75 responder
- If the percentage improvement is ≥90% then the subject is a PASI90 responder (and is a PASI75 responder also)
- If the percentage improvement is 100% then the subject is a PASI100 responder (and is a PASI75 and PASI90 responder also)

The number and percentage of subjects achieving a PASI75, PASI90, and PASI100 response at Week 16 will be tabulated by treatment group. The 95% CI for the percentage of responders will be calculated using a Wilson approximation and included in the tabulation. For the purpose of the tabulation the lower and upper 95% confidence limits for the percentage of responders will be truncated at 0 and 100% respectively.

Missing data will be imputed using NRI as described in Section 4.2.1.1. Subjects with missing data at Week 16 will be regarded as nonresponders for the PASI75, PASI90, and PASI100 variables. This will also be presented using observed cases. Missing data will not be imputed for the listing.

The individual PASI scores will be listed as described in Section 8.1.2. Subjects achieving a PASI75, PASI90 and PASI100 response at each visit will be flagged in the listing.

8.2.2 Investigator's Global Assessment Response at Week 16

A static IGA for psoriasis will be used to assess disease severity in all subjects during the study. The Investigator will assess the severity of psoriasis using a 5-point scale (Table 8–2).

Table 8–2: Investigator's Global Assessment

Score	Short Descriptor	Detailed Descriptor
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

A clinical response with regard to the IGA is defined as clear (0) or almost clear (1) with at least a 2-category improvement from Baseline.

The results of the IGA will be listed by subject and visit. Subjects achieving a clinical response at Week 16 will be flagged in the listing.

The number and percentage of subjects achieving an IGA response at Week 16 will be summarized by treatment group. The 95% CI for the percentage of responders will be included, calculated using a Wilson approximation. For the purpose of the tabulation the lower and upper 95% confidence limits for the percentage of responders will be truncated at 0 and 100% respectively.

Missing data will be imputed using NRI as described in Section 4.2.1.3. Subjects with missing data at Week 16 will be regarded as nonresponders for the analysis. Missing data will not be imputed for the listing.

8.3 Analysis of other efficacy variables

- Absolute and percentage change from Baseline in PASI with time (Week 2 to Week 36)
- PASI75, PASI90 and PASI100 response at Weeks 2, 4, 8, 12, 20, 24, 28 and 36
- PASI25 and PASI50 response (Week 2 to Week 36)
- IGA response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Weeks 2, 4, 8, 12, 20, 24, 28 and 36
- Change from Baseline in IGA score with time (Week 2 to Week 36)
- Change from Baseline in the BSA affected by psoriasis with time (Week 2 to Week 36)
- Change from Baseline in HADS-A and HADS-D scores with time (Week 4 to Week 36)
- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores) at each post-Baseline visit (Week 4 to Week 36)

Tabulations and figures will be based on the FAS and listings will be based on the SS.

8.3.1 Psoriasis Area and Severity Index

The absolute values and percentage change (improvement) from Baseline in the PASI score will be summarized as described in Section 8.1.2.

The PASI25 and PASI50 responses are based on at least 25% and 50% improvement from Baseline in the PASI score. Thus, the following will apply:

- If the percentage improvement is ≥25% then the subject is a PASI25 responder
- If the percentage improvement is ≥50% then the subject is a PASI50 responder (and is a PASI25 responder also)

The definitions of PASI75, PASI90 and PASI100 response are provided in Section 8.2.1. Subjects meeting the definition for PASI75, PASI90 and PASI100 response are also considered as PASI25 and PASI50 responders at the respective visit.

The number and percentage of subjects achieving a PASI25, PASI50, PASI75, PASI90 and PASI100 response will be tabulated by treatment group and visit. The 95% CI for the percentage of responders will be calculated using a Wilson approximation and included in the tabulation. In addition, the percentage of responders (including 95% CI) will be plotted at each post-Baseline visit for each response variable. Separate plots will be presented for each of PASI25, PASI50, PASI75, PASI90 and PASI100 with both treatment groups overlaid on the same plot

Missing data will be imputed using NRI as described in Section 4.2.1.1. Subjects with missing data will be regarded as nonresponders for each of the response variables. Missing data will not be imputed for the listing.

The tables and figures for PASI response variables will also be repeated using observed cases and will include a category for missing data; subjects who enroll in the extension study or those who discontinue will be counted in the missing category for this tabulation where applicable. For this tabulation based on observed cases the denominator for the percentage of responders and nonresponders will be the number of subjects with nonmissing data at the visit.

The individual PASI scores will be listed as described in Section 8.1.2. Subjects achieving a PASI25 and PASI50 response at each visit will be flagged in the listing.

8.3.2 Investigator's Global Assessment

The IGA results will be listed by subject and visit as described in Section 8.2.2. Subjects achieving a clinical response (clear [0] or almost clear [1] with at least a 2-category improvement from Baseline) at each visit (Weeks 2, 4, 8, 12, 20, 24, 28 and 36) will be flagged in the listing as responders.

The number and percentage of responders at each post-Baseline visit (Weeks 2, 4, 8, 12, 20, 24, 28 and 36) will be summarized by treatment group as described in Section 8.2.2. The 95% CI for the percentage of responders will be included, calculated using a Wilson approximation. The percentage of responders (with 95% CI) will also be plotted over time.

Missing data for the IGA response at a specific visit will be imputed using NRI as described in Section 4.2.1.3. Subjects with missing data will be regarded as nonresponders for the analysis. Missing data will not be imputed for the listing. The table and figure will also be repeated using observed cases and will include a category for missing data; subjects who enroll in the extension

study or those who discontinue will be counted in the missing category for this tabulation where applicable. For this tabulation based on observed cases the denominator for the percentage of responders and nonresponders will be the number of subjects with nonmissing data at the visit.

In addition to the IGA responder tabulations, shift tables will be presented including the change in IGA individual scores at Week 8, Week 16 and Week 24, compared to the Baseline score. In addition, a frequency table will be presented showing the number and percentage of subjects with each specific IGA score at each visit. Both tabulations will include a category for missing data. The denominator for the percentages will be the number of subjects in the FAS, for each treatment group.

8.3.3 Body surface area

The percentage BSA (0 to 100%) affected by psoriasis will be listed by subject and visit including the percentage change from Baseline. Descriptive statistics will be presented by treatment group and visit for both absolute values and percentage changes from Baseline.

For subjects that discontinue the study or those that enter the extension study, missing data will be imputed using LOCF for the tabulations as described in Section 4.2.1.2. Missing data will not be imputed for the listing.

Tabulations (absolute values and percentage change from Baseline) will also be repeated using observed cases.

8.3.4 Hospital Anxiety and Depression Scale

The HADS scores for anxiety (HADS-A) and depression (HADS-D) each range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal whereas a score of 15 and above is considered severe (Snaith and Zigmond, 1994). The individual items, associated item scores and calculation rules for the anxiety and depression domains are provided in Section 14.2.

The results of the HADS will be listed by subject and visit including the individual item responses and the derived domain scores for anxiety (HADS-A) and depression (HADS-D). Changes from Baseline will be calculated based on the domain scores only, and will be included in the listing.

Descriptive statistics will be presented by treatment group and visit for both absolute values and changes from Baseline, separately for each domain (HADS-A and HADS-D). The number and percentage of subjects with scores <8 for the HADS-A and HADS-D will be summarized by treatment group at each visit. The percentages will be based on the number of available observations at each visit; the number of subjects with missing data (including subjects who enroll in the extension study) will be included in the tabulation.

There will be no imputation of missing data for the HADS scores, either for the descriptive statistics or frequency tables.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

There will be no calculation of PK parameters for this study. The analysis of PK data for this study will focus on the concentrations of bimekizumab only.

The actual blood sampling times for bimekizumab concentrations will be obtained relative to the start time of the first injection and will be reported in weeks to 1 decimal place. Individual blood sampling times and concentrations of bimekizumab will be listed by treatment group for the SS and will include the actual sampling time in weeks relative to the first dose.

Individual concentrations will be summarized by treatment group at each scheduled visit based on the PK-PPS, using n, mean, median, SD, minimum, maximum, geometric mean, 95% CI for the geometric mean and geoCV (assuming log-normally distributed data).

Individual concentration versus time (week) profiles will be presented graphically in linear and semi-logarithmic scale with all subjects overlaid on the same plot (spaghetti plots) and separate plots for each treatment group. Geometric mean profiles of bimekizumab will also be presented on both linear and semi-logarithmic scale respectively with and without the corresponding lower and upper limit of the 95% CI for linear and semi-logarithmic plots respectively. Both treatment groups will be overlaid on the same plot. All figures will include the LLOQ on the semi-logarithmic plots.

The following rules will apply for PK data listings and summaries:

- Values below the LLOQ will be reported as BLQ
- Descriptive statistics of concentrations will be calculated if at most ⅓ of the individual data points are missing or are not quantifiable (<LLOQ). Values that are BLQ will be replaced by the numerical values of the LLOQ/2 in this instance. However, if n≤3 or more than ⅓ of the individual data points are missing or are not quantifiable, then only n, minimum and maximum will be presented. The other descriptive statistics will be left blank.
- The 95% CI for the geometric mean should be left blank if the SD (or equivalently, the geoCV) is 0
- The geoCV will be calculated using the following formula where SD is the standard deviation from the log-transformed data

$$geoCV = [100x\sqrt{(e^{SD^2} - 1)}] \quad [10]$$

Additional rules for handling values that are BLQ are described in Section 4.2.3.

9.2 Pharmacodynamics

The results of the PD assessments (flow cytometry variables) will be listed by treatment group and subject (based on the SS) including changes from Baseline.

Absolute values and changes from Baseline will be summarized (including 95% CI) by treatment group based on the PD-PPS.

Figures of mean and mean changes from Baseline (including 95% CI) will be presented with separate plots for each variable and both treatment groups overlaid on the same plot.

The list of flow cytometry variables to be measured is provided in Section 14.3.

9.3 Pharmacokinetic/pharmacodynamic analyses

A pooled PKPD analysis will be performed by combining the data from this study (PS0016) with the data from PS0010. The methodology for the PK/PD analysis will be described in a separate

data analysis plan (DAP). The results of the analysis will be reported in a separate PK/PD report and added as an appendix to the CSR.

10 IMMUNOLOGICAL ANALYSES

The results for the ADA measurements will be listed by treatment group and timepoint based on the SS, including the Screening assay, confirmatory assay and titre (if applicable).

A cut point will be determined by the bioanalytical laboratory that will be used to determine the status of ADA as above the cut point (ACP) or below the cut point (BCP). For any ADA levels that are ACP, a further confirmatory assay will be performed, the results of which will be determined as either 'confirmed positive' (CP) or 'not confirmed positive' (NCP). For samples that are CP, a further titre assay will be performed and the ADA titre will be reported.

The following definitions will be applied:

- An ADA status of positive will be concluded for any subject with an ADA level that is ACP and CP at any timepoint
- An ADA status of negative will be concluded for any subject with an ADA level that is either BCP or ACP and NCP at any timepoint
- A subject will be classified as having ADA positivity at Baseline if the Day 1, predose result is ACP and CP
- A subject will be classified as having treatment-induced ADA positivity when meeting one of the following criteria:
  - The Baseline result is either BCP or ACP and NCP, and at least one post-Baseline timepoint is ACP and CP
  - The Baseline result is positive (ACP and CP) and at least one post-Baseline measurement shows a pre-defined fold increase in titre from the Baseline value (the fold increase from Baseline required to meet this criteria will be defined with the development of the assay and will be included in the TFLs)
- A subject will be classified as overall positive if at least one post-Baseline measurement is ACP and CP (this includes subject who have negative results at Baseline)
- A subject will be classified as overall negative if at all post-Baseline visits the ADA status is negative (this includes subjects who have positive [ACP and CP] results at Baseline)

The ADA status (positive/negative) will be summarized as a categorical endpoint (number and percentage of subjects) by treatment group for all timepoints and overall, based on the SS.

In addition, the first occurrence of treatment-induced ADA positivity (based on the definitions above) will be summarized (number and percentage of subjects) by treatment group at each post-Baseline visit, based on the SS. This tabulation will count the number of subjects at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-induced positivity; subjects will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, subjects will be counted in the denominator (assuming a measurement is available). For all tabulations, percentages will be based on the number of observations at each visit.

A separate listing will be presented (based on the SS) showing the bimekizumab concentrations and ADA measurements in the same output in adjacent columns. The listing will include the bimekizumab concentration, ADA status (ACP or BCP) and confirmatory assay results if applicable (NCP or CP), together with the titre for results that are CP. In addition, the time since the previous administration of IMP will be reported (in days).

Finally, individual subject plots will be presented displaying the PASI total score, ADA titre and bimekizumab concentrations overlaid on the same figure. The figure will also show the timing and dose of each administration of bimekizumab (or placebo) received during the study. The ADA data will be plotted using a semi-logarithmic scale.

The rules for handling values that are BLQ in the bimekizumab concentration data are described in Section 4.2.3. For the ADA data, any negative results for which there are no titres available at a specific visit will be substituted with 0.001 for the purpose of the figure.

11 SAFETY ANALYSES

All analysis of safety variables will be performed using the SS, unless otherwise stated.

11.1 Extent of exposure

11.1.1 Drug administration

All drug administration details (including date, time of injection, location, side of body and volume delivered) will be listed. The IMP will be given as 2 sc injections at each planned dosing visit (Baseline, Week 4 and Week 16).

11.1.2 Number of injections received

The number of injections received will be summarized by treatment group using descriptive statistics, based on the SS. There are anticipated to be 2 injections per dosing visit, ie, a total of 6 injections for subjects that completed the treatment as planned.

11.1.3 Subject time at risk

The subject time at risk represents the time a subject was at risk for having an AE and will be used to calculate the exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER) as described in Section 11.2.

The subject time at risk (days) will be calculated as follows:

$$Time\ at\ risk = (Date\ of\ Last\ Dose - Date\ of\ First\ Dose) + 140 \quad [11]$$

In cases where the last clinical contact or last visit occurs prior to completion of the SFU period, the subject time at risk is calculated as follows:

$$Time\ at\ risk = (Date\ of\ Last\ Contact - Date\ of\ First\ Dose) + 1 \quad [12]$$

This will apply for the following:

- For subjects entering the extension study the date of last contact (in PS0016) refers to the date of the visit at which they enter the extension study (ie, Week 20, 24, 28 or 36)
- For subjects that discontinue prematurely (ie, and no SFU data are available), the date of final contact refers to the date of the latest contact with the subject during the study after

which no further information or data are available. This will be reported on the study termination page of the CRF.

- For subjects that have died during the study the date of last contact refers to the date of death

Subject-years at risk is defined as the subject time at risk divided by 365.25. The days at risk and subject-years at risk will be listed together with the drug administration information (Section 11.1.1).

11.2 Adverse events

11.2.1 Definitions and classification of adverse events

All AEs will be recorded in the CRF from informed consent until study completion or termination.

Adverse events with start date prior to the first administration of IMP are defined as pre-treatment AEs. A TEAE is defined as any AE with a start date/time at the time of or after the first administration of IMP up until the last received dose of IMP + 140 days (which covers the 20 week SFU Period). Adverse events occurring after this date will not be classified as TEAEs and will therefore be excluded from the summary tables.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to dosing. Handling of missing dates/times for classification of AEs as TEAEs is described in Section 4.2.4.

In order to allow for a comparative period across all subjects, prior to the point at which subjects are eligible to enter the extension study, TEAEs will be classified as follows:

- **Treatment Period TEAEs:** all TEAEs with onset at the time of or after the first administration of IMP up until the Week 20 visit. Any TEAEs that occur on the date of the Week 20 visit will be included (ie, the cut off will be assumed to be at 23:59 hours on the date of Week 20). Such TEAEs will be designated as 'Treatment Period' TEAEs in the tabulations. Any subjects that withdraw prior to Week 20 will have Treatment Period TEAEs cut off at 140 days relative to the first dose (ie, equivalent to 20 weeks).
- **Post-Treatment Period TEAEs:** all TEAEs with onset after the Week 20 visit up until the last dose of IMP + 140 days will be designated as 'Post-Treatment' TEAEs in the tabulations. Thus, any tabulation including Post-Treatment TEAEs will include only those TEAEs for subjects not entering the extension study at all or those TEAEs for subjects who enter the extension study at a later visit. For subjects that withdraw prior to Week 20, Post-Treatment Period TEAEs are classified as those starting after 140 days relative to the first dose (ie, equivalent to 20 weeks).

For the EAIR and EAER tabulations the above classifications will not be applicable, as these summaries are, by definition, adjusted for the individual exposure at risk for each subject.

All AEs will be coded and categorized by intensity (mild/moderate/severe) and relationship to IMP (related/not related).

11.2.2 Calculation of exposure adjusted incidence and event rates

The EAIR is defined as the number of subjects (n) with a specific TEAE adjusted for the exposure and will be scaled to 100 subject-years:

$$EAIR = 100 \times \frac{n}{\sum_{i=1}^{N} T_{Exp,i}} \quad [13]$$

In the above equation, N is the total number of subjects at risk (in each treatment group) and $T_{Exp,i}$ is the time at risk for subject i, expressed in years. Subject time at risk represents the time a subject was at risk for having a TEAE calculated as follows:

- For subjects experiencing the specific TEAE the time at risk ($T_{Exp,i}$) is calculated from the time of the first dose to the onset of the TEAE. If a subject has multiple events, the time at risk is calculated relative to the first occurrence of the TEAE being considered.
- For subjects who do not experience the specific TEAE the total time at risk ($T_{Exp,i}$) is calculated as described in Section 11.1.3.

Exact Poisson 95% CIs (lower confidence limit [LCL], upper confidence limit [UCL]) for the EAIR will be calculated using the relationship between the Poisson and the chi-square distribution (Fay and Feuer, 1997):

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2}, \quad UCL = \frac{\chi^2_{2(n+1),1-\frac{\alpha}{2}}}{2} \quad [14]$$

where n is the number of subjects with the specific TEAE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile. The LCL and UCL calculated above will be scaled to the number of subject-years by dividing these by the total exposure at risk for each treatment group ($\sum_{i=1}^{N} T_{Exp,i}$).

The EAER is defined as the total number of TEAEs (including repeat occurrences in individual subjects) divided by the total time at risk scaled to 100 subject-years:

$$EAER = 100 \times \frac{n_{AE}}{\sum_{i=1}^{N} T_{Risk,i}} \quad [15]$$

where n_{AE} is the total number of TEAEs and $T_{Risk,i}$ is the time at risk for subject i, expressed in years (calculated as described in Section 11.1.3).
No confidence intervals will be computed for EAER.

11.2.3 Presentation of adverse events

An overview of the number and percentage of subjects who experience TEAEs will be presented by treatment group (including All Subjects), based on the SS. This tabulation will include the number and percentage of subjects with any TEAEs, serious TEAEs, related TEAEs, discontinuation due to TEAEs, severe TEAEs, AEs leading to death and TEAEs leading to death; event counts will also be included. The tabulation will be repeated for Treatment Period TEAEs and Overall TEAEs.

In addition, the following summaries will be presented by treatment group (including All Subjects), SOC, high level term (HLT) and PT, based on the SS:

- Incidence of TEAEs during Treatment Period
- Incidence of TEAEs Overall
- Incidence of serious TEAEs during Treatment Period
- Incidence of serious TEAEs Overall

- Incidence of non-serious TEAEs during Treatment Period
- Incidence of non-serious TEAEs Overall
- Incidence of TEAEs during Treatment Period by relationship
- Incidence of TEAEs Overall by relationship
- Incidence of TEAEs during Treatment Period by maximum relationship
- Incidence of TEAEs Overall by maximum relationship
- Incidence of TEAEs during Treatment Period by maximum intensity
- Incidence of TEAEs Overall by maximum intensity
- Incidence of fatal TEAEs during Treatment Period by relationship
- Incidence of fatal TEAEs Overall by relationship
- Incidence of non-serious TEAEs during Treatment Period by relationship
- Incidence of non-serious TEAEs Overall by relationship
- Incidence of serious TEAEs during Treatment Period by relationship
- Incidence of serious TEAEs Overall by relationship
- Incidence of non-serious TEAEs during Treatment Period above threshold of 5% of subjects
- Incidence of non-serious TEAEs Overall above threshold of 5% of subjects
- Incidence of non-serious TEAEs during Treatment Period above threshold of 5% of subjects by relationship
- Incidence of non-serious TEAEs Overall above threshold of 5% of subjects by relationship
- Incidence of TEAEs during Treatment Period by SOC and PT (including the number and percentage of subjects and individual subject numbers/reported terms for each PT stratified by intensity, relationship and seriousness)
- Incidence of TEAEs (including all TEAEs during Treatment and Post-Treatment Periods) by SOC, HLT and PT and including the EAIR and EAER calculated as described in Section 11.2.2
- Incidence of TEAEs (including all TEAEs during Treatment and Post-Treatment Periods) by SOC, HLT and PT and including the EAIR and EAER, stratified by overall ADA status (positive/negative)

In addition, separate AE summaries by treatment group, SOC, HLT and PT (including all TEAEs during Treatment and Post-Treatment Periods combined) will be included for the following AEs of special monitoring (AESM):

- Major cardiovascular events
- Serious infections, including opportunistic infections and tuberculosis (TB)
- Malignancies including lymphoma

- Cytopenias
- Neuropsychiatric events (in particular, depression and suicide)
- Inflammatory bowel disease
- Anaphylactic reaction (hypersensitivity and anaphylactic reactions)
- Hepatic events and drug-induced liver injury

All summary tables (including those for AESM) will contain the number and percentage of subjects and the number of events where applicable. A subject who has multiple events in the same SOC, HLT and PT will be counted only once in the subject counts but all events will be included. In addition, for all tabulations of AESM, the EAER and EAIR will be reported.

The criteria for identifying AESM and additional criteria for reporting AESM are provided in Section 14.6.

In summaries including relationship to IMP, the following relationship categories will be included:

- Related
- Not related

Subjects who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing relationship will be considered as 'Related' for summary purposes but shown as missing in the data listings.

In summaries including intensity, the following categories will be summarized:

- Mild
- Moderate
- Severe

Subjects who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as severe for summary purposes. All data will be presented as recorded in the database for the listings.

Adverse event summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing frequency of PT in the 'BKZ 320mg' (Treatment arm B) column for tables including event counts. For tables including only number and percentage of subjects, summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing incidence of PT within HLT and SOC in the 'BKZ 320mg' (Treatment arm B) column.

Listings will be presented by treatment group and subject for all AEs, serious adverse events (SAEs), AEs leading to death and AEs leading to discontinuation. Listings will include the onset date/time and outcome date/time of the event (including relative days), the AE duration (derived), days since first dose of IMP, days since most recent dose of IMP, pattern of event, intensity, relationship, action taken and outcome. In addition the listing will flag AEs that led to discontinuation, TEAEs (including classification as 'Treatment Period' and 'Post Treatment' TEAEs), AESM, AEs of special interest (as reported on the CRF) and SAEs.

All AE listings will be based on all subjects screened (ES). A glossary of all TEAE terms will be provided including the SOC, HLT, PT and reported term.

11.3 Clinical laboratory evaluations

Laboratory data (clinical chemistry, hematology, and urinalysis) and changes from Baseline (if applicable) for numeric variables will be listed by treatment group and visit. Any laboratory variables with values that are BLQ or ALQ will be handled as described in Section 4.2.2 for calculation of changes from Baseline and for summary tables. Values outside the reference range for the numeric variables will be flagged in the listings and in addition, will be listed separately. The reference ranges will also be reported in the listings.

Clinical chemistry and hematology variables will be summarized by treatment group (including All Subjects) at each visit, for both absolute values and changes from Baseline.

Laboratory variables will be grouped according to the laboratory function panel and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory. For selected variables that are identified in Table 11-1, the change in category from Baseline will be presented in shift tables at all post-Baseline visits.

The number and percentage of subjects with treatment-emergent markedly abnormal (TEMA) laboratory results (to match the TEAE definition stated in Section 11.1.3) will be tabulated by treatment group and visit. Markedly abnormal laboratory values will be defined as those categorized as Grade 3 and above based on the ranges defined as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (2016). These are provided in Table 14–4. The tabulation will include a category for the incidence of TEMA results over all visits which will also count unscheduled measurements.

In addition, for absolute neutrophil count (ANC), all grade 2 CTCAE abnormalities (<1.5 – 1.0 $x10^9$/L) will be listed separately, with results from all visits for any subject that has any grade 2 abnormality.

Laboratory measurements meeting the criteria for TEMA will be listed separately for hematology and chemistry. The listings will include all measurements for any variable with at least one TEMA result for each subject.

Any additional laboratory variables not included in the outputs described previously will be listed separately. These will include the following:

- Serology
- Pregnancy tests (serum and urine)
- Follicle stimulating hormone (FSH) (only for postmenopausal women)

The results of the Quantiferon TB Gold test will be listed separately.

Subjects with treatment-emergent liver function test abnormalities at any post-Baseline visit will be summarized (number and percentage of subjects) by treatment group. The criteria for this tabulation are presented in Section 14.5.

Table 11–1: Clinical laboratory measurements

Category	Panel	Variable
Serology	Serology	HIV1-Ab, HIV2-Ab, HBsAg, anti-HBc, anti-HBs, anti-HCV-Ab, TB
Hematology	Red blood cell	RBC count[a], hemoglobin, hematocrit
	Red blood cell indices	MCH, MCHC, MCV
	Platelet	Platelets
	White blood cell	WBC count[a]
	White blood cell differential	Absolute counts: ANC[a], basophils, eosinophils, ALC, monocytes, atypical lymphocytes (if indicated) Percentages: neutrophils/leukocytes, basophils/leukocytes, eosinophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes.
Chemistry	Electrolytes	Sodium, chloride, potassium, calcium, magnesium
	Kidney function	BUN, creatinine
	Liver function	AST[a], ALT[a], GGT[a], ALP[a], LDH[a], total bilirubin (direct bilirubin, indirect bilirubin, if indicated)
	Lipids	Total cholesterol[a]
	Metabolic function	Glucose
	Hormones	FSH[b]
	Fertility	Pregnancy test[c]
	Other	CRP
Urinalysis	Dipstick	pH, protein, blood, leukocyte esterase, nitrite, glucose

Table 11–1: Clinical laboratory measurements

Category	Panel	Variable
	Urine sediment (if indicated)	WBC, RBC, epithelial cells (squamous, transitional and renal tubular), hyaline casts, WBC casts, RBC casts, waxy casts, granular casts, calcium oxalate crystals, uric acid crystals, triphosphate crystals, yeast, bacteria, amorphous urates, amorphous phosphates

ALC=absolute lymphocyte count; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; FSH=follicle stimulating hormone; GGT=gamma glutamyltransferase; anti-HBc= hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; HbsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV1-Ab=human immunodeficiency virus 1 antibody; HIV2-Ab= human immunodeficiency virus 1 antibody; LDH=lactate dehydrogenase; MCH=mean cell hemoglobin; MCHC=mean cell hemoglobin concentration; MCV=mean cell volume; RBC=red blood cell; TB=tuberculosis; WBC=white blood cell.

[a] Shift tables will be presented for these variables.

[b] FSH performed on postmenopausal females who have been postmenopausal for >=1year and last menstrual cycle occurred <2 years ago.

[c] Pregnancy testing will consist of serum testing at the Screening and SFU visits. The pregnancy test will be urine at all other visits and will be performed locally. If the subject is entering the extension study, a urine pregnancy test will be performed at SFU.

11.4 Vital signs, physical findings, and other observations related to safety

11.4.1 Vital signs

The following vital signs measurements will be obtained:

- Pulse rate
- Systolic and diastolic blood pressure
- Temperature (oral or otic)

A by-subject listing of all vital sign measurements and changes from Baseline will be presented by treatment group and visit. The listing will include a flag for measurements identified as TEMA/potentially clinically significant (PCS) as calculated by the criteria outlined in Table 14–6.

Descriptive statistics will be reported for all vital sign measurements. Measured values and changes from Baseline will be summarized by vital signs variable and visit for each treatment group.

The number and percentage of subjects with TEMA/PCS vital sign values (to match the TEAE definition stated in Section 11.1.3) will be summarized by treatment group (including All Subjects) and variable at each visit and overall (ie, across all post-Baseline visits).

11.4.2 Body weight

A by-subject listing of body weight will be presented, including changes from Baseline. No summary tabulations will be provided for this variable.

11.4.3 Electrocardiograms

Standard 12-lead ECG recordings will be obtained after 10 minutes of rest in the supine or semirecumbent position. The following ECG variables will be reported together with the Investigator's interpretation of the ECG profile:

- PR interval
- QRS interval
- QT interval
- Heart rate
- QT corrected for heart rate using Fridericia's formula (QTcF)

The results of all ECG variables will be reported in the by-subject listings. The listing will also include the change from Baseline and will be presented by treatment group and visit.

Measured values and changes from Baseline will be summarized for each variable by treatment group and visit.

The following cut-points in QTcF (raw data and change from Baseline) will be summarized categorically by treatment group (number and percentage of subjects) and visit. The denominator for the percentages will be the number of subjects with a non-missing measurement for the variable at the specific visit.

Raw QTcF data:

- <450msec
- ≥450 msec to <480msec
- ≥480msec to <500msec
- ≥500msec

Change from Baseline QTcF:

- <30msec
- ≥30msec to <60msec
- ≥60msec

Electrocardiogram findings will be listed separately.

11.4.4 Other safety variables

11.4.4.1 Physical examination

Subjects with abnormalities in the physical examination will be listed including details of the abnormality.

11.4.4.2 Chest x-ray and TB questionnaire

The results of the chest x-ray and the TB questionnaire will be listed for each subject. For the former listing, the date of the procedure will be included together with the evaluation (normal, abnormal not clinically significant or abnormal clinically significant).

11.4.4.3 C-SSRS

The results of the C-SSRS will be listed for each subject and visit.

12 OTHER ANALYSES

A listing of comments will be presented, if applicable.

13 REFERENCES

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. National Institutes of Health, National Cancer Institute, Division of Cancer Treatment and Diagnosis. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Updated 03 Mar 2016.

Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the gamma distribution. Statistics in Medicine 1997; Vol 16: 791-801.

Snaith RP, Zigmond AS. The hospital anxiety and depression scale, with the irritability-depression-anxiety scale and the Leeds situational anxiety scale manual 1994.

14 APPENDICES

14.1 Treatment group assignment for the TFLs

The treatment group labels and tabulation requirements for each data type are displayed in Table 14–1.

Table 14–1: Treatment group assignment for the TFLs

TFL group	BKZ 320mg + PBO	BKZ 320mg	All Subjects
Subject disposition	X	X	X
Protocol deviations	X	X	X
Demographics	X	X	X
Psoriasis history and Baseline characteristics	X	X	X
Medical history	X	X	X
Prior/concomitant medications	X	X	X
AEs	X	X	X
Safety data (including vital signs, ECGs and laboratory tests)	X	X	
Pharmacodynamic data	X	X	
Efficacy data	X	X	
Pharmacokinetic data	X	X	
ADA	X	X	

ADA=anti-bimekizumab antibody; AE=adverse event; BKZ=bimekizumab; ECG=electrocardiogram; PBO=placebo.

14.2 Hospital Anxiety and Depression Scale

The individual items and associated domains are indicated in Table 14–2.

Table 14–2: Hospital Anxiety and Depression Scale

Anxiety (HADS-A)	Depression (HADS-D)
I feel tense or wound up	I still enjoy the things I used to enjoy
I get a sort of frightened feeling as if something awful is about to happen	I can laugh and see the funny side of things
Worrying thoughts go through my mind	I feel cheerful
I can sit at ease and feel relaxed	I feel as if I am slowed down
I get a sort of frightened feeling like butterflies in the stomach	I have lost interest in my appearance
I feel restless as if I have to be on the move	I look forward with enjoyment to things
I get sudden feelings of panic	I can enjoy a good book or radio or television program

The scores for each item range from 0 to 3, with higher scores indicating more severe anxiety or depression. The total score for each domain ranges from 0 to 21. A score of <8 for a given domain is considered as normal.

In case of missing data, the following rules will be applied:

- If a maximum of 1 item is missing in a given domain, the missing item will be imputed with the mean score from the remaining completed items within the same domain
- If more than 1 item is missing in a given domain, the domain subscore will not be calculated

14.3 Flow cytometry variables

The individual variables to be reported are presented in Table 14–3.

Table 14–3: Flow cytometry variables

Cell Subset/Population	Phenotype	Reportable Units
TBNK Panel		
Lymphocytes	CD45+	% of singlets
Total T Cells	CD3+	% of Lymphocytes
T helper Cells	CD3+ CD4+	% of Lymphocytes
Cytotoxic T cells	CD3+ CD4+	% of Lymphocytes
B lymphocytes	CD3- CD19+	% of Lymphocytes
DC,Monocytes and NK cells	CD3- CD19-	% of Lymphocytes
NK cells	CD3- CD16+ CD56+	% of Lymphocytes
Activated T cells	CD69+	% of T cells
Activated Th	CD69+	% of T helper cells
Activated Tc	CD69+	% of Cytotoxic T cells
Activated B cells	CD69+	% of B cells
Activated NK cells	CD69+	% ok NK cells
Th Subset Panel		
Lymphocytes	CD45+	% of singlets
Total T Cells	CD3+	% of Lymphocytes
T helper Cells	CD3+ CD4+	% of Lymphocytes
Th1	CXCR3+	% of T helper Cells
Th2	CCR6-CCR4+	% of T helper Cells
Th17/22	CCR6+ CCR4+	% of T helper Cells
Th17	CCR6+CCR4+CCR10-	% of T helper Cells
Th22	CCR6+CCR4+CCR10+	% of T helper Cells
Activated Th1	CD69+	% of Th1
Activated Th2	CD69+	% of Th2
Activated Th17	CD69+	% of Th17

CCR=chemokine receptor; CD=cluster of differentiation; CXCR=CXC chemokine receptor; DC=dendritic cell; NK=natural killer; TBNK=T cell, B cell and NK cell assay ;Tc=T cytotoxic ;Th=T helper.

14.4 Classification of markedly abnormal laboratory values based on CTCAE grades

The criteria for assessing laboratory values as markedly abnormal are presented in Table 14–4.

Table 14–4: Criteria for markedly abnormal laboratory tests

Category	Panel	Variable	Criteria (CTCAE Grade 3 and above)
Hematology	Red blood cell	Hemoglobin (Decrease)	<80 g/L
		Hemoglobin (Increase)	>4 g/dL (>40 g/L) above ULN OR >4 g/dL (>40 g/L) above baseline if baseline is >ULN
	White blood cell	WBC count (Decrease)	<2.0 x 10^9/L
		WBC count (Increase)	>100 x 10^9/L
	White blood cell differential	ALC (Decrease)	<0.5 x 10^9/L
		ALC (Increase)	>20 x 10^9/L
		ANC	<1.0 x 10^9/L
	Platelet	Platelet	<50 x 10^9/L
Chemistry	Liver function	ALT	>5.0 x ULN
		ALP	>5.0 x ULN
		AST	>5.0 x ULN
		Total bilirubin	>3.0 x ULN
		GGT	>5.0 x ULN
	Kidney function	Creatinine	>3.0 x baseline value OR >3.0 x ULN
	Electrolytes	Calcium (Decrease)	<1.75 mmol/L
		Calcium (Increase)	>3.1 mmol/L
		Magnesium (Decrease)	<0.4 mmol/L
		Magnesium (Increase)	>1.23 mmol/L
		Potassium (Decrease)	<3.0 mmol/L
		Potassium (Increase)	>6.0 mmol/L
		Sodium (Decrease)	<130 mmol/L
		Sodium (Increase)	>155 mmol/L

Category	Panel	Variable	Criteria (CTCAE Grade 3 and above)
	Lipids	Total cholesterol	>10.34 mmol/L

ULN=upper limit of normal.

14.5 Treatment-emergent abnormal liver values

The criteria for identifying treatment-emergent liver function abnormalities are presented in Table 14–5. Subjects will be counted in all applicable categories for the tabulations ie, a subject with ≥5 x ULN in AST will also be counted in the ≥3 x ULN in AST category, the ≥3 x ULN in AST or ALT category and the ≥5x ULN in AST or ALT category.

Table 14–5: Definition of treatment-emergent liver function values

Criterion
≥3 x ULN increase for AST
≥5 x ULN increase for AST
≥10 x ULN increase for AST
≥20 x ULN increase for AST
≥3 x ULN increase for ALT
≥5 x ULN increase for ALT
≥10 x ULN increase for ALT
≥20 x ULN increase for ALT
≥3 x ULN increase for AST or ALT
≥5 x ULN increase for AST or ALT
≥10 x ULN increase for AST or ALT
≥20 x ULN increase for AST or ALT
≥1 x ULN increase for bilirubin
≥1.5 x ULN increase for bilirubin
≥1.5 x ULN increase for ALP
≥1 x ULN increase for bilirubin and 3 x ULN increase of either AST or ALT (at the same visit)
≥2 x ULN increase for bilirubin and 3 x ULN increase of either AST or ALT (at the same visit)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ULN=upper limit of normal.

14.6 Adverse events of special monitoring

The following AESM are defined for bimekizumab and will be summarized separately as described in Section 11.2:

- Major cardiovascular events
- Serious infections, including opportunistic infections and TB

- Malignancies including lymphoma
- Cytopenias
- Neuropsychiatric events (in particular, depression and suicide)
- Inflammatory bowel disease
- Anaphylactic reaction (hypersensitivity and anaphylactic reactions)
- Hepatic events and drug-induced liver injury

All AESM tabulations will be presented by treatment group, SOC, HLT and PT, based on the SS, and will include the EAIR and EAER.

14.6.1 Major cardiovascular events

Major adverse cardiovascular events (MACE) will be tabulated separately and will be identified using the following UCB-defined search criteria:

- All serious TEAEs which code to a PT included in the search=Broad scope of the following standardized MedDRA queries (SMQ):
  - Haemorrhagic central nervous system vascular disorders
  - Ischaemic central nervous system vascular disorders
- All serious TEAEs which code to a PT included in the HLT = 'Ischaemic coronary artery disorders' except events coding to PT = 'Chest pain' or PT = 'Chest discomfort'
- All serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders" as the Primary SOC

14.6.2 Serious infections, including opportunistic infections and tuberculosis

14.6.2.1 Serious infections

Serious infections are based on MedDRA classification using the SOC = 'Infections and Infestations'. Such events will be included in the tabulations of SAEs and no separate summary tabulations will be presented.

14.6.2.2 Fungal infections

Fungal infections will be summarized separately based on all TEAEs coding to the high level group term (HLGT) = 'Fungal infectious disorders'.

14.6.2.3 Opportunistic infections

Opportunistic infections (including TB) will be summarized in a separate table including all TEAEs identified using search criteria defined by UCB.

Opportunistic infections are identified in 2 steps:

- Step 1: Refer to column B of the spreadsheet which identifies the PTs to be classified as opportunistic infections using either a single 'x' or a double 'xx'.

- All TEAEs which code to a PT flagged with a single 'x' need to also be serious in order to be considered an opportunistic infection.
- All TEAEs which code to a PT flagged with a double 'xx' are considered to be an opportunistic infection, regardless of seriousness.

All serious TEAEs in the study database which code to a PT flagged with a single 'x' and all TEAEs in the study database which code to a PT flagged with a double 'xx' will be summarized as an opportunistic infection in the stand-alone table.

- Step 2: Refer to column C of the spreadsheet which identifies the PTs that need to be evaluated on a case-by-case basis by the study physician in order to determine whether it is a true opportunistic infection or not. The process for physician review is as follows:
  - Study programming team creates a spreadsheet which lists all of the subjects with a TEAE present in the database which codes to a PT identified as needing case-by-case review. Information from the AE dataset to be included in the spreadsheet: Subject ID, AE verbatim term, SOC, HLT, Lower Level Term (LLT), PT, AE start date, AE end date, seriousness, severity, relationship to study medication, action taken. Additionally, a column will be included where the study physician can document their decision on the case.
  - Study physician reviews the cases in the spreadsheet and indicates in the additional column which AEs are confirmed to be opportunistic infections via a single 'x'.
  - Study programming team incorporates these decisions into the analysis data adverse events (ADAE) dataset by merging the study physician decisions for individual subjects / PTs and flagging the confirmed opportunistic infections as such in the dataset.

All subjects with an AE reported that has been confirmed by the study physician to be an opportunistic infection (based on case-by-case review) will be summarized as such in the stand-alone table, together with all of the events identified in Step 1 of this process.

The timing and frequency of Step 2 should be outlined and agreed to by the study team at the beginning of the study.

Following the initial physician review of case-by-case events, subsequent reviews will be based on the cumulative set of case-by-case events present in the database at each timepoint of spreadsheet creation. Physician decisions from previous runs should be retained in each subsequent run. The final run of the spreadsheet, with all study physician decisions on the full set of case-by-case events, will be archived at the conclusion of the study.

14.6.3 Malignancies including lymphoma

Malignancies will be presented in 2 separate tables based on the following SMQs:

- Malignant or unspecified tumours
- Malignant tumours

Events included in the 'Malignant tumours' tabulation will be a subset of the events in the 'Malignant or unspecified tumours' tabulation. The SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each SMQ.

The output tables will include 2 different overall incidence rows:

- The first overall incidence row will summarize 'Any malignancies (including unspecified)' or 'Any malignancies' (depending on the table) and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the HLT it codes to.
- The second overall incidence row will summarize 'Any malignancy (including unspecified, excluding non-melanomic skin cancers)' or 'Any malignancy (excluding non-melanomic skin cancers)' (depending on the table) and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of 'skin neoplasms malignant and unspecified (excl melanoma)'.

14.6.4 Cytopenias

Cytopenias will be tabulated separately based on the SMQ = 'Haematopoietic cytopenias'. The SMQ search should include all TEAEs that code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

14.6.5 Neuropsychiatric events

Neuropsychiatric events (in particular depression, anxiety and suicide ideation or behavior) will be tabulated separately based on the SMQ = 'Depression and suicide/self-injury'. The SMQ search should include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

14.6.6 Inflammatory bowel disease

Inflammatory bowel disease events will be tabulated separately, based on the HLT = 'Colitis excl infective'.

14.6.7 Anaphylactic reaction

Anaphylactic reactions will be summarized together in a stand-alone table with the following incidence rows:

- The first row within the body of the table will be labeled 'Any hypersensitivity/anaphylactic reaction' and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction or at least one anaphylactic reaction.
- The second row within the body of the table will be labeled 'Any hypersensitivity reaction' and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction.
- The third row within the body of the table will be labeled 'Any anaphylactic reaction' and will represent the overall incidence of subjects who reported at least one anaphylactic reaction.

Following these three overall incidence rows, all TEAEs that have been identified as either a hypersensitivity reaction or an anaphylactic reaction will be summarized by SOC, HLT and PT (these will not be presented by subcategory).

Hypersensitivity reactions and anaphylactic reactions will be identified as follows:

- **Hypersensitivity reactions:** all TEAEs with onset (start date/time) within 24 hours after any administration of IMP, which code to a PT which contains the term 'hypersensitivity' will be considered to be a hypersensitivity reaction and included in the summary table
- **Anaphylactic reactions:** An algorithmic approach will be used to identify TEAEs that are considered to be anaphylactic reactions. Preferred terms are separated into 4 distinct categories (A, B, C, D) prior to the algorithmic approach being applied.

  All TEAEs with onset (start date/time) within 24 hours after any administration of IMP, and which fulfill any of the 3 criteria described in Section 14.6.7.1 will be included in the summary table.

Any TEAEs with missing start time will be assumed to have occurred at the time of or after dosing for this purpose, if the event date is on the same day as a dosing date.

14.6.7.1 Anaphylactic reaction algorithm

The SMQ = 'anaphylactic reaction' consists of 3 parts:

- A **narrow search** containing PTs that represent core anaphylactic reaction terms. If a subject reports any TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction and summarized as such in the table.
  - **Category A**
    1. Anaphylactic reaction
    2. Anaphylactic shock
    3. Anaphylactic transfusion reaction
    4. Anaphylactoid reaction
    5. Anaphylactoid shock
    6. Circulatory collapse
    7. Dialysis membrane reaction
    8. Kounis syndrome
    9. Shock
    10. Shock symptom
    11. Type I hypersensitivity
- A **broad search:** If a subject reports any TEAE which codes to a PT included in Category B **AND** reports any TEAE which codes to a PT included in Category C, **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions and summarized as such in the table.
  - **Category B**
    1. Acute respiratory failure
    2. Asthma
    3. Bronchial oedema

4. Bronchospasm
5. Cardio-respiratory distress
6. Chest discomfort
7. Choking
8. Choking sensation
9. Circumoral oedema
10. Cough
11. Cyanosis
12. Dyspnoea
13. Hyperventilation
14. Irregular breathing
15. Laryngeal dyspnoea
16. Laryngeal oedema
17. Laryngospasm
18. Laryngotracheal oedema
19. Mouth swelling
20. Nasal obstruction
21. Oedema mouth
22. Oropharyngeal spasm
23. Oropharyngeal swelling
24. Respiratory arrest
25. Respiratory distress
26. Respiratory dyskinesia
27. Respiratory failure
28. Reversible airways obstruction
29. Sensation of foreign body
30. Sneezing
31. Stridor
32. Swollen tongue
33. Tachypnoea
34. Throat tightness
35. Tongue oedema
36. Tracheal obstruction

37. Tracheal oedema
38. Upper airway obstruction
39. Wheezing

- **Category C**
  1. Allergic oedema
  2. Angioedema
  3. Erythema
  4. Eye oedema
  5. Eye pruritis
  6. Eye swelling
  7. Eyelid oedema
  8. Face oedema
  9. Flushing
  10. Generalised erythema
  11. Injection site urticaria
  12. Lip oedema
  13. Lip swelling
  14. Nodular rash
  15. Ocular hyperaemia
  16. Oedema
  17. Periorbital oedema
  18. Pruritis
  19. Pruritis allergic
  20. Pruritis generalised
  21. Rash
  22. Rash erythematous
  23. Rash generalized
  24. Rash pruritic
  25. Skin swelling
  26. Swelling
  27. Swelling face
  28. Urticaria

29. Urticaria papular

– **Category D**

1. Blood pressure decreased
2. Blood pressure diastolic decreased
3. Blood pressure systolic decreased
4. Cardiac arrest
5. Cardio-respiratory arrest
6. Cardiovascular insufficiency
7. Diastolic hypertension
8. Hypotension

- An **algorithmic approach:** If a subject reports any TEAE which codes to a PT included in Category D **AND** reports (either a TEAE which codes to a PT included in Category B **OR** a TEAE which codes to a PT included in Category C), **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions and summarized as such in the table.

14.6.8 Hepatic events and drug-induced liver injury

Hepatic events will include:

- Events based on the SMQ = 'Drug related hepatic disorders – comprehensive search' (excluding sub-SMQs = 'Liver neoplasms, benign [incl cysts and polyps]' and 'Liver neoplasms, malignant and unspecified'). All AEs should be included in the tabulation (included those considered both related and not related to the IMP) which code to a PT included in the Scope=Narrow group within each SMQ.
- Hy's Law cases will also be summarized separately in a table of liver function abnormalities as described in Section 11.3 (with adjudication for potential drug-induced liver injury cases).

14.7 Treatment-emergent markedly abnormal vital signs values

The criteria for identifying TEMA/PCS vital signs values are provided in Table 14–6.

Table 14–6: TEMA/PCS criteria for vital signs

Variable	Unit	Low[a]	High[a]
Systolic blood pressure	mmHg	Value ≤90 and ≥20 decrease from Baseline	Value ≥180 and ≥20 increase from Baseline
Diastolic blood pressure	mmHg	Value ≤50 and ≥15 decrease from Baseline	Value ≥105 and ≥15 increase from Baseline

Note: the change in measurement (increase or decrease) will be calculated relative to the value obtained at Baseline.
[a] Both conditions must be satisfied for a measurement to be considered TEMA/PCS.

15 AMENDMENTS TO THE SAP

15.1 Rationale for the amendment

Amendment 1 for this SAP was primarily created to add the extra tables and figures that were generated for Interim Analysis 3. In addition, the SAP focuses on the percentage change in PASI score from Baseline rather than the percentage improvement, to recognize the possibility that the change may be worsening.

15.2 List of changes

Change #1: Introduction, 2nd paragraph

This SAP Amendment 1 is based on, and assumes familiarity, with the following documents:

- Final protocol, dated 06 June 2016
- Protocol amendment 1, dated 04 August 2016
- Protocol amendment 2, dated 06 September 2016
- Protocol amendment 3, dated 23 September 2016

The following bullet has been added:

- Statistical analysis plan, dated 23 February 2017

Change #2: Section 4.3

The following bullet has been added:-

- Data from unscheduled visits may be used for tables that present abnormalities (where stated in the SAP amendment).

Change #3: Section 4.5.2

No formal interim analysis will be performed; however data cuts will be performed and evaluated.

Has been changed to:-

No formal interim analysis will be performed; however interim data cuts will be performed and evaluated.

Change #4: Section 8.1.1

Improvement from Baseline $= 100x[(Baseline\ PASI - PostBaseline\ PASI)/Baseline\ PASI]$ [9]

Has been changed to:-

Percentage improvement from Baseline $= 100x[(PostBaseline\ PASI - Baseline\ PASI)/Baseline\ PASI]$ [9]

Change #5: Section 8.1.2, 4th paragraph

All tabulations and both individual and mean figures will be presented using the FAS and repeated for the PPS.

Has been changed to:-

All tabulations and both individual and mean figures will be presented using the FAS and repeated for the PPS (only if the PPS differs from the FAS).

Change #6: Section 8.1.2, final paragraph

Tabulations (absolute values and percentage improvement from Baseline) will also be repeated using observed cases, based on the FAS only.

Has been changed to:-

Separate tables and mean figures will also be created based on the observed cases only.

Change #7: Section 8.2.1, 3rd paragraph

Missing data will be imputed using NRI as described in Section 4.2.1.1. Subjects with missing data at Week 16 will be regarded as nonresponders for the PASI75, PASI90, and PASI100 variables. Missing data will not be imputed for the listing.

Has been changed to:-

Missing data will be imputed using NRI as described in Section 4.2.1.1. Subjects with missing data at Week 16 will be regarded as nonresponders for the PASI75, PASI90, and PASI100 variables. This will also be presented using observed cases. Missing data will not be imputed for the listing.

Change #8: Section 8.3.1, 6th paragraph deleted

The tabulation will also be repeated using observed cases and will include a category for missing data;

Change #9: Section 8.3.1, 5th paragraph:

Has been added

The tables and figures for PASI response variables will also be repeated using observed cases and will include a category for missing data;

Change #10: Section 8.3.2, 2nd paragraph

This sentence has been added:-

The percentage of responders (with 95% CI) will also be plotted over time.

Change #11: Section 8.3.2, 3rd paragraph

The tabulation will also be repeated using observed cases

Has been changed to:-

The table and figure will also be repeated using observed cases

Change #12: Section 11.2.3

In addition, the following summaries will be presented by treatment group, SOC, high level term (HLT) and PT, based on the SS:

- Incidence of TEAEs during Treatment Period
- Incidence of TEAEs during Post-Treatment Period
- Incidence of serious TEAEs during Treatment Period
- Incidence of serious TEAEs during Post-Treatment Period
- Incidence of non-serious TEAEs during Treatment Period
- Incidence of TEAEs during Treatment Period by relationship
- Incidence of TEAEs during Treatment Period by maximum relationship
- Incidence of TEAEs during Treatment Period by maximum intensity
- Incidence of fatal TEAEs during Treatment Period by relationship
- Incidence of non-serious TEAEs during Treatment Period by relationship
- Incidence of serious TEAEs during Treatment Period by relationship
- Incidence of non-serious TEAEs during Treatment Period above threshold of 5% of subjects
- Incidence of non-serious TEAEs during Treatment Period above threshold of 5% of subjects by relationship
- Incidence of TEAEs during Treatment Period by SOC and PT (including the number and percentage of subjects and individual subject numbers/reported terms for each PT stratified by intensity, relationship and seriousness)
- Incidence of TEAEs (including all TEAEs during Treatment and Post-Treatment Periods) by SOC, HLT and PT and including the EAIR and EAER calculated as described in Section 11.2.2
- Incidence of TEAEs (including all TEAEs during Treatment and Post-Treatment Periods) by SOC, HLT and PT and including the EAIR and EAER, stratified by overall ADA status (positive/negative)

Has been changed to:-

In addition, the following summaries will be presented by treatment group (including All Subjects), SOC, high level term (HLT) and PT, based on the SS:

- Incidence of TEAEs during Treatment Period
- Incidence of TEAEs Overall

- Incidence of serious TEAEs during Treatment Period
- Incidence of serious TEAEs Overall
- Incidence of non-serious TEAEs during Treatment Period
- Incidence of non-serious TEAEs Overall
- Incidence of TEAEs during Treatment Period by relationship
- Incidence of TEAEs Overall by relationship
- Incidence of TEAEs during Treatment Period by maximum relationship
- Incidence of TEAEs Overall by maximum relationship
- Incidence of TEAEs during Treatment Period by maximum intensity
- Incidence of TEAEs Overall by maximum intensity
- Incidence of fatal TEAEs during Treatment Period by relationship
- Incidence of fatal TEAEs Overall by relationship
- Incidence of non-serious TEAEs during Treatment Period by relationship
- Incidence of non-serious TEAEs Overall by relationship
- Incidence of serious TEAEs during Treatment Period by relationship
- Incidence of serious TEAEs Overall by relationship
- Incidence of non-serious TEAEs during Treatment Period above threshold of 5% of subjects
- Incidence of non-serious TEAEs Overall above threshold of 5% of subjects
- Incidence of non-serious TEAEs during Treatment Period above threshold of 5% of subjects by relationship
- Incidence of non-serious TEAEs Overall above threshold of 5% of subjects by relationship
- Incidence of TEAEs during Treatment Period by SOC and PT (including the number and percentage of subjects and individual subject numbers/reported terms for each PT stratified by intensity, relationship and seriousness)
- Incidence of TEAEs (including all TEAEs during Treatment and Post-Treatment Periods) by SOC, HLT and PT and including the EAIR and EAER calculated as described in Section 11.2.2

Change #13: Section 14.6.1

- All serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups of the following standardized MedDRA queries (SMQ):

Has been changed to:-

- All serious TEAEs which code to a PT included in the search=Broad scope of the following standardized MedDRA queries (SMQ):

Change #14: Section 14.6.1

- All serious TEAEs which code to a PT = 'Cardiac failure congestive'

Has been changed to:-

- All serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders" as the Primary SOC

Change #15: Section 14.6.4

Cytopenias will be tabulated separately based on the SMQ = 'Haematopoietic cytopenias'. Only serious TEAEs will be included in the tabulation. The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Has been changed to:-

Cytopenias will be tabulated separately based on the SMQ = 'Haematopoietic cytopenias'. The SMQ search should include all TEAEs that code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Change #16: Section 14.6.6

Inflammatory bowel disease events will be tabulated separately, based on the HLGT = 'Colitis excl infective'.

Has been changed to:-

Inflammatory bowel disease events will be tabulated separately, based on the HLT = 'Colitis excl infective'.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the SAP or amended SAP is released for execution.

PS0016 Statistical Analysis Plan Amendment 1

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
PPD	Subject Matter Expert Approval	30-Nov-2017 10:40 GMT+0
PPD	Clinical Approval	18-Dec-2017 12:14 GMT+01