STATISTICAL ANALYSIS PLAN

Study: PS0011

Product: BIMEKIZUMAB

A MULTICENTER, 48-WEEK, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

SAP/Amendment Number	Date
Final SAP	31 March 2017
SAP Amendment 1	7 June 2018

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LIST OF ABBREVIATIONS

AE	adverse event
AESM	adverse events of special monitoring
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BKZ	Bimekizumab
BLQ	below level of quantification
BMI	Body Mass Index
BSA	body surface area
CV	coefficient of variation
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
ES	Enrolled Set
FAS	Full Analysis Set
GGT	gamma glutamyltransferase
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depression
HLGT	high level group term
HLT	high level term
IGA	Investigator's Global Assessment
LLQ	lower level of quantification
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov-Chain Monte Carlo
MCS	Mental Component Score
MI	multiple imputation
mNAPSI	modified Nail Psoriasis Severity Index
NRI	non-responder imputation
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Score
PGADA	Patient's Global Assessment of Disease Activity
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PSSI	Psoriasis Scalp Severity Index
PT	preferred term
Q4W	every four weeks
SAP	Statistical Analysis Plan
SD	standard deviation
SF-36	Short Form 36 item Health Survey
SFU	Safety Follow-Up
SMQ	standard MedDRA query

SOC	system organ class
SOP	standard operating procedure
SS	Safety Set
TEAE	treatment-emergent adverse event
VAS	visual analog scale
WBC	white blood cell
WHO	World Health Organization

1 INTRODUCTION

This statistical analysis plan (SAP) defines the summary tables, figures, and listings to be generated for the clinical study report and is based on the protocol amendment 1 (12 Aug 2016).

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objective

The primary objective of the study is to assess the long-term safety and tolerability of bimekizumab.

2.1.2 Secondary objective

The secondary objective of the study is to assess the efficacy of bimekizumab administered every four weeks (Q4W) over 48 weeks.

2.1.3 Other objectives

The other objectives of the study are to:

- Assess the pharmacokinetics (PKs) of bimekizumab
- Assess the immunogenicity of bimekizumab.

2.2 Study variable(s)

2.2.1 Safety variables

2.2.1.1 Primary safety variable

The primary safety variable is the incidence of treatment-emergent adverse events (TEAEs) adjusted by duration of subject exposure to treatment.

2.2.1.2 Other safety variables

Change from Baseline variables will be defined relative to the Baseline measurements from PS0011.

The other safety variables are:

- Change from Baseline in clinical laboratory values (chemistry, hematology, and urinalysis)
- Change from Baseline in vital signs
- Change from Baseline in physical examination
- Change from Baseline in 12-lead Electrocardiogram (ECG) results.

2.2.2 Pharmacokinetic variable

The PK variable is plasma concentrations of bimekizumab.

2.2.3 Immunological variable

The immunological variable is anti-bimekizumab antibody levels prior to and following study treatment.

2.2.4 Efficacy variables

Change from Baseline and responder variables will be defined relative to the PS0010 Baseline for subjects who are PS0010 Week 12 PASI90 responders and relative to both the PS0010 and PS0011 Baselines for subjects who are PS0010 Week 12 PASI90 non-responders).

2.2.4.1 Secondary efficacy variables

The secondary efficacy variables are:

- Psoriasis Area and Severity Index (PASI)90 response (defined as a subject that achieves 90% reduction in the PASI score from the Baseline of PS0010) over time
- Investigator's Global Assessment (IGA) response (Clear or Almost Clear with at least a 2 category improvement from Baseline on a 5-point scale) over time.

2.2.4.2 Other efficacy variables

The efficacy variables detailed below will be evaluated at all scheduled visits in accordance with the Schedule of Assessment (see study protocol Table 5-1):

- PASI75 and PASI100 response
- Absolute and percent change from Baseline in PASI score
- Shift from PS0011 Baseline in IGA score
- Change from Baseline in Dermatology Life Quality Index (DLQI)
- Percent of subjects achieving a DLQI score of 0 or 1
- Absolute and percent change from Baseline in the body surface area (BSA) affected by psoriasis
- Change from Baseline in modified Nail Psoriasis Severity Index (mNAPSI) score (in the subgroup of subjects with psoriatic nail disease at Baseline)
- Change from Baseline in the Psoriasis Scalp Severity Index (PSSI) (in the subgroup of subjects with scalp psoriasis at Baseline)
- Change from Baseline in the Patient's Global Assessment of Disease Activity (PGADA) for the arthritis visual analog scale (VAS)
- Change from Baseline in Short Form 36 item Health Survey (SF-36) Physical Component Summary (PCS) score, Mental Component Summary (MCS) score, and individual domains
- Change from Baseline in the Hospital Anxiety and Depression Scale Anxiety (HADS-A) and Depression (HADS-D) scores
- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores).

2.3 Study design and conduct

2.3.1 Study description

This is a Phase 2b, multicenter, 48-week, double-blind, placebo-controlled, parallel-group extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab administered subcutaneously in eligible adult subjects with moderate to severe chronic psoriasis who complete PS0010.

2.3.2 Study periods

This study will include two periods:

- Treatment Period (48 weeks)
- Safety Follow-Up (SFU) Period (20 weeks after the last dose of study medication).

Treatment Period

To be eligible to participate in this study:

- Subjects in PS0010 who received placebo or bimekizumab 64mg, 160mg, or 320mg loading dose + 160mg Q4W must achieve PASI90 response at Week 12 before entering PS0011 extension study on the same treatment dose
- Subjects who do not achieve PASI90 response at Week 12 in PS0010 while receiving placebo or bimekizumab 64mg Q4W will be assigned to receive bimekizumab 160mg on entering PS0011
- Subjects who do not achieve PASI90 response at Week 12 in PS0010 while receiving bimekizumab 160mg or 320mg loading dose + 160mg Q4W will be assigned to receive bimekizumab 320mg Q4W on entering PS0011
- Subjects who receive bimekizumab 320mg or 480mg Q4W in PS0010 will be assigned to receive bimekizumab 320mg Q4W on entering PS0011, regardless of their PASI90 response at Week 12 in PS0010.

Up to 240 subjects are anticipated to enroll in the study and the study medication will be administered in the clinic Q4W.

Subjects withdrawing early from the study will undergo the Early Withdrawal visit assessments and will enter the SFU Period.

Safety Follow-Up Period

Following completion or early withdrawal from the 48-week Treatment Period, subjects will return for a SFU visit 20 weeks after their last dose of study medication.

2.3.3 Study duration per subject

For each subject, the study is expected to last for a maximum of 64 weeks. This includes the following study period durations:

- Double-blind, placebo-controlled Treatment Period: up to 48 weeks
- SFU Period: 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.

2.4 Determination of sample size

Up to 240 subjects are anticipated to enroll in PS0011. This number is based on the 240 subjects that are planned to be randomized in the feeder study, PS0010. The calculations to reach this sample size are outlined in the PS0010 protocol and SAP. As the primary objective of this study is to assess the long-term safety and tolerability of bimekizumab, the number of subjects anticipated is based on the number of subjects completing PS0010 and meeting eligibility requirements for PS0011.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.3 or higher. All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of subjects in each category will be presented. Unless otherwise noted, all percentages will be displayed to one decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. For continuous variables, descriptive statistics will include number of subjects with available measurements (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. For bimekizumab PK concentrations, summary statistics will include geometric mean, geometric coefficient of variation (CV), 95% confidence interval for the geometric mean, median, minimum, and maximum. All summaries of PK variables will be based on the observed values. No imputation will be used.

Decimal places for descriptive statistics will always apply the following rules:

- "n" will be an integer
- Mean, SD, and median will use one additional decimal place compared to the original data
- CV[%] will be presented with one decimal place
- Minimum and maximum will have the same number of decimal places as the original value.

A complete set of data listings containing all documented data as well as calculated data (eg, change from Baseline) will be generated and will be presented by PS0010/PS0011 treatment group.

3.2 Definition of Baseline values

Two separate baseline values are defined for use in this study:

PS0010 Baseline

The last valid measurement before study medication administration in the double-blind period of PS0010 will be used as the PS0010 Baseline value. If a Baseline visit measurement is missing, and a PS0010 Screening visit measurement is available, the Screening value will be utilized as Baseline. If a scheduled Baseline assessment is taken on the same day as first administration of

PS0010 study medication, it will be assumed to have been taken prior to PS0010 study medication.

PS0011 Baseline

The last valid measurement before study medication administration in the double-blind period of PS0011 will be used as the PS0011 Baseline value. If a Baseline visit measurement is missing, the most recent PS0010 assessment value will be utilized as Baseline. If a scheduled Baseline assessment is taken on the same day as first administration of PS0011 study medication, it will be assumed to have been taken prior to PS0011 study medication.

3.3 Mapping of assessments performed at early study withdrawal visit

Study assessments at an early withdrawal visit where the early withdrawal visit date matches the visit date of a scheduled visit will be summarized at the scheduled visit with the same visit date. Premature withdrawal visit assessments that do not have a scheduled visit with a matching date will be assigned to the next scheduled site visit following the last visit where assessments were available. The only exception to this rule is for anti-Bimekizumab (BKZ) antibody assessments, where all premature withdrawal visit assessments will be assigned to the next scheduled visit at which anti-BKZ antibodies are assessed.

All by-visit summaries will contain nominal visits only. Unscheduled visits will not be mapped to scheduled visits.

3.4 Protocol deviations

Important protocol deviations are defined as those deviations from the protocol likely to have a meaningful impact on the efficacy, safety, or PK outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. All protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented in a separate protocol deviation tracker prior to unblinding to confirm any exclusions from the Pharmacokinetics Per Protocol Set (PK-PPS).

3.5 Analysis sets

All safety variables will be summarized using the Safety Set (SS). All efficacy analyses will be based on the Full Analysis Set (FAS).

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent for PS0011.

3.5.2 Safety Set

The SS will consist of all subjects who receive at least one dose of the study medication in PS0011.

3.5.3 Full Analysis Set

The FAS will consist of all enrolled subjects who receive at least one dose of the study medication in PS0011 and have a valid efficacy measurement for PASI at Baseline of PS0011.

3.5.4 Other analysis sets

3.5.4.1 Pharmacokinetics Per Protocol Set

The PK-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations affecting the pharmacokinetic variables, as confirmed during ongoing data cleaning meetings prior to database lock.

3.6 Treatment assignment and treatment groups

At Baseline, eligible subjects will be assigned as described in Section 2.3.2. Summaries using the FAS will be based on treatments according to the assignment and not actual treatment received.

It is expected that subjects will receive treatment as assigned. Hence, safety analyses should be based on assigned treatment for the SS. However, if it is determined after unblinding that subjects assigned to placebo received bimekizumab at any time, then these subjects will be reallocated to the appropriate bimekizumab group and will be summarized accordingly from the time point at which the misallocation occurred. If a subject receives different doses of bimekizumab at different time points, then the subject will be allocated to the highest dose received. If the highest dose was received earlier than the other(s), then all safety data will be summarized under that dose. If the highest dose was received later than the other(s), then safety data will be summarized under that dose starting from the time point at which it was first received. Since the period of exposure at risk includes an additional 140 days following the last dose of study medication, no consideration is given to the time at which exposure to misallocated doses can be considered complete.

Subjects assigned to a bimekizumab group will only be reallocated to the placebo treatment group if they never received bimekizumab.

Because subjects entering PS0011 may or may not be continuing on the same dose as that received in PS0010, there are various combinations of treatment that could be received when considering both PS0010 and PS0011 together. For describing the summaries to be produced, treatment groups will be categorized as either the PS0011 treatment groups or PS0010/PS0011 treatment groups. The categorizations are outlined below.

PS0011 treatment groups

This refers to the study treatment assigned to the subject at the beginning of PS0011 and does not account for the treatment received in PS0010. The PS0011 treatment groups are as follows:

- Placebo
- Bimekizumab 64mg Q4W
- Bimekizumab 160mg Q4W
- Bimekizumab 320mg Q4W
- All Bimekizumab (optional – to be used only if specified)

PS0010/PS0011 treatment groups

This refers to the combination of the randomized treatment in PS0010 and the treatment assigned at the beginning of PS0011. Some groups have been combined where it is considered appropriate to do so. The PS0010/PS0011 treatment groups are as follows:

- Placebo to Placebo
- Placebo to Bimekizumab 160mg Q4W
- Bimekizumab 64mg Q4W to Bimekizumab 64mg Q4W
- Bimekizumab 64mg Q4W to Bimekizumab 160mg Q4W
- Bimekizumab 160mg Q4W to Bimekizumab 160mg Q4W – note that the PS0010 160mg Q4W groups with and without the loading dose are both included here
- Bimekizumab 160mg Q4W to Bimekizumab 320mg Q4W – note that the PS0010 160mg Q4W groups with and without the loading dose are both included here
- Bimekizumab 320mg Q4W to Bimekizumab 320mg Q4W
- Bimekizumab 480mg Q4W to Bimekizumab 320mg Q4W

The treatment groups to be used in the presentations of safety and efficacy will depend on the objective of the summaries and will be specified accordingly.

3.7 Center pooling strategy

Centers will be pooled into regions for analysis purposes. Centers will be grouped in the following regions: North America, Europe and Asia. These regions include the following countries:

- North America: Canada, USA
- Europe and Asia: Czech Republic, Hungary, Poland, Japan

3.8 Coding dictionaries

All prior and concomitant medications other than study drug will be classified by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC Level 3), and preferred term, using version SEP/2015 of the WHO Drug Dictionary, according to UCB standard operating procedures (SOPs).

All adverse events (AEs) will be classified by primary system organ class (SOC), high level term (HLT) and preferred term (PT) using version 19.0 of the Medical Dictionary for Regulatory Activities (MedDRA®) according to UCB SOPs. Previous and ongoing medical history will be classified by MedDRA® SOC and PT.

3.9 Analysis time points

3.9.1 Double-blind treatment period

The double-blind treatment period begins at the Baseline visit (Week 0) at the time of first study medication administration (inclusive) and ends at the Week 48/withdrawal visit.

Subjects will be classified as completing the study if they complete the Week 48 visit without withdrawal from the study. This is regardless of whether they attend the SFU visit.

3.9.2 Follow-up period

The SFU visit will take place 20 weeks after the last dose of study medication.

3.10 Relative day

The relative day will be included in different listings and will be calculated as follows:

- If the start (stop) date occurred on or after the first dose, but prior to the double-blind drug stop date, relative day is calculated as start (stop) date minus first dose + 1
- If the start (stop) date occurred after the last dose of double-blind drug, the relative day to the most recent dose is calculated as start (stop) date minus most recent dose date. The relative day in this situation should be preceded by a '+'
- If the start (stop) occurred before the first dose, the relative day is calculated as start (stop) date minus first dose date. The relative day in this situation should be preceded by a '-'.

3.11 Changes to protocol-defined analyses

There have been no changes to the protocol-defined analyses.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

Not applicable.

4.2 Handling of dropouts or missing data

4.2.1 Handling missing data for the safety analyses

For analyses of AEs and concomitant medication usage, a complete date must be established in order to correctly identify the AE or medication as occurring during treatment or not. For purposes of imputing missing components of partially-reported start and stop dates for AEs and for medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listings).

Partial AE and concomitant medication start dates will be imputed as follows:

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of start date, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose
- If only the year is specified, and the year of first dose is not the same as the year of the start date, then use the 1st of January of the year of the start date
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.

Imputation of 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 31st of that year
- If the stop date is completely unknown, do not impute the stop date.

In the event of ambiguity or incomplete data which makes it impossible to determine whether a medication was concomitant or an adverse event was treatment emergent, the medication will be considered as concomitant or the adverse event will be considered treatment emergent.

4.2.2 Handling missing data for the efficacy analyses

For the planned efficacy analysis, missing responder data will be imputed using non-responder imputation (NRI). That is, subjects that discontinue study medication early or who have missing data at a given time point will be counted as non-responders. Summaries based on observed case data will also be prepared.

Continuous efficacy variables will be imputed using multiple imputation (MI) via the Markov-Chain Monte Carlo (MCMC) method. Summaries based on observed case data will also be prepared.

The MI procedure for continuous efficacy variables (based on MCMC) will be applied as follows:

1. Create a dataset, one for each treatment group, of subjects with observed values and those needing estimation by multiple imputation. The missing values in each dataset will be filled in using the MCMC method with a total of 100 sets of imputations being performed. Values at Baseline and at each post-Baseline visit will be included in the imputation model in chronological order with prior biologic exposure and region as factors. The resulting datasets for each treatment arm will be combined into one complete dataset based on each of the 100 imputations.

   Note: The imputation model based on the MCMC method will only allow continuous variables in the imputation model. Therefore, prior biologic exposure and region will be re-coded as indicator variables (with values of 0 or 1 for each level of the variable). In order to achieve model convergence, prior biological exposure may be dropped from the model, if convergence is still not obtained then region may also be dropped from the model.

2. The relevant change from Baseline (or percent change from Baseline) values will then be derived based on the imputed datasets and will be summarized by imputation.

3. The summary statistics from each of the 100 imputed datasets will be combined for the calculation of means and standard deviations using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). This will be done using SAS PROC MIANALYZE. For calculation of other descriptive statistics such as the median, min and max, Rubin's rules do not apply. Multiple imputation estimates will be computed by simply averaging the estimates from the $m = 1, \ldots, M$ independent repetitions of the imputation algorithm:

$$\bar{\theta} = \frac{1}{M} \sum_{m=1}^{M} \hat{\theta}_m$$

where $\hat{\theta}_m$= estimate of θ from the completed dataset $m = 1, \ldots, M$.

There may be cases where the multiple imputation model fails to converge (eg, sparse subgroups). In such situation, the LOCF approach will instead be used to impute missing data. If LOCF is used instead of multiple imputation for this reason, this will be clearly specified in the corresponding table summary. Should there be no missing data for a study variable then only observed case data will be produced.

4.3 Interim analyses and data monitoring

When PS0010 is unblinded, Sponsor study team members from PS0011 with access to the PS0010 data will be unblinded. However, subjects and investigators will remain blinded. This operational unblinding to PS0011 treatment assignment will pertain to selected clinical PS0010 study team members (some of whom may be involved in PS0011). PS0010 and PS0011 will have the same blinded programming teams for reporting and will remain blinded to PS0010 and PS0011 treatment assignment. An independent programming team will be used for the final unblinding for PS0010 reporting.

A Data Monitoring Committee (DMC) will review the safety data on a recurring basis as outlined in the DMC charter. The outputs reviewed by the DMC will include the accrued data from both PS0010 and PS0011, allowing for summaries of the combined data across the studies. The details of the outputs to be prepared are described in a separate DMC SAP.

An interim analysis focusing on PS0011 only will take place once all subjects have completed the Week 48 visit, but not including the SFU visit. The Clinical Study Report will be updated at a later date in order to incorporate the SFU data once available.

4.4 Multicenter studies

This is a multicenter study with sites in Europe, Canada, Japan and USA.

4.5 Multiple comparisons/multiplicity

Not applicable.

4.6 Active-control studies intended to show equivalence

Not applicable.

4.7 Examination of subgroups

Subgroup analyses will be performed on the secondary efficacy variables.

The following subgroup analyses will be performed:

- Age (<65 years, ≥65 years)
- Gender (male, female)
- Duration of disease at PS0010 Baseline (<median, ≥median)
- Region (North America [Canada, USA], Europe and Asia [Czech Republic, Hungary, Poland, Japan])
- Body weight at PS0010 Baseline (<100 kg, ≥100 kg)
- Body Mass Index (BMI) at PS0010 Baseline (<25 kg/m², 25 to <30 kg/m², ≥30 kg/m²)
- Prior biologic systemic therapy at PS0010 Baseline (yes, no)

- Prior anti-TNF therapy at PS0010 Baseline (yes, no)
- Any prior systemic therapy at PS0010 Baseline (yes, no)
- Anti-bimekizumab antibody positivity at any time on treatment during PS0010 or PS0011 (yes, no)
- PASI score at PS0010 baseline (<20, ≥20)
- Psoriasis BSA at PS0010 baseline (<20%, ≥20%).

These summaries, using the FAS, will be based on imputed data (NRI) and will include descriptive statistics only. If there are less than 2 subjects in any subgroup category/treatment group, then that subgroup category will not be summarized. If it is possible to collapse subgroups with more than 2 categories, then collapsing may be done to get categories with no less than 2 subjects per subgroup category/treatment group.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Summaries of the disposition of subjects (for all subjects enrolled in PS0011) as well as the subjects who discontinued due to AEs (for the FAS) will be produced based on the PS0011 treatment group. The disposition of subjects for all subjects enrolled will include the number of subjects included in each analysis set (FAS, SS and PK-PPS) overall and by site.

In addition, the number and percentage of subjects who discontinued the study, including a breakdown of the main reasons for discontinuation, will be presented for subjects in the FAS.

5.2 Protocol deviations

A summary, using the ES, of the number and percentage of subjects with an important protocol deviation (including a summary of subjects excluded from the PK-PPS due to important protocol deviations) by PS0011 treatment group, overall and by type of deviation will be provided.

If the dosing for a visit is +/- 7 days out of window, then the plasma concentration from that visit and all subsequent visits will be excluded from the PK summary. The number and percentage of subjects with at least one measurement excluded from the PK analysis will be summarized by PS0010/PS0011 treatment group.

A by-subject listing of important protocol deviations will be provided.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Unless specified otherwise, all summaries detailed in this section will be performed on the SS, where Baseline is defined relative to PS0010.

6.1 Demographics

Demographic variables will be summarized by PS0011 treatment group and overall.

The following continuous variables will be summarized using descriptive statistics (number of subjects, mean, SD, median, minimum and maximum):

- Age at the time of study entry (years)

- Weight (kg)
- Height (cm)
- BMI (kg/m²)

BMI (kg/m²) will be calculated as:

$$\text{BMI} = \frac{\text{Weight}}{\text{Height}^2} \quad (1)$$

where weight is given in kg and height is given in m.

The following categorical variables will be summarized using frequency counts and percentages:

- Age group (≤18 years, 19 to <65 years, ≥65 years)
- Age group (18 to <65 years, 65 to <85 years, ≥85 years)
- Age group (<40 years, 40 to <65 years, ≥65 years)
- Gender
- Race
- Ethnicity
- Weight (<100 kg, ≥100 kg)
- BMI (<25 kg/m², 25 to <30 kg/m², ≥30 kg/m²).

By-subject listings of demographics will be provided.

6.2 Other Baseline characteristics

Baseline characteristics (including Baseline clinical measurements) will be summarized by PS0011 treatment group and overall.

The following continuous variables will be summarized using descriptive statistics (number of subjects, mean, SD, minimum, median and maximum):

- Psoriasis BSA (%)
- Duration of disease (years)
- PASI score
- DLQI total score.

Duration of disease (years) will be calculated as:

$$\text{Duration of disease} = \frac{(\text{Date of informed consent} - \text{Date of onset of plaque psoriasis}^{1})}{365.25} \quad (2)$$

[1]If the date of onset of plaque psoriasis is partial, it should be imputed to the most feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing).

The following categorical variables will be summarized using frequency counts and percentages:

- Duration of disease (<median, ≥median)
- Region (North America [Canada, USA], Europe and Asia [Czech Republic, Hungary, Poland, Japan])
- Country
- Prior systemic phototherapy or chemophototherapy (yes, no)
- Prior nonbiologic systemic therapy (yes, no)
- Prior biologic systemic therapy (yes, no)
- Prior anti-TNF therapy (yes, no)
- Any prior systemic therapy (yes, no)
- PASI score (<20, ≥20)
- Psoriasis BSA (<20%, ≥20%)
- IGA score (0, 1, 2, 3, 4).

6.3 Medical history and concomitant diseases

All medical history will be listed and the number and percentage of subjects with any medical history will be summarized by PS0011 treatment group, SOC and PT.

6.4 Prior and concomitant medications

Medication start and stop dates will be compared to the date of first dose of both PS0010 and PS0011 treatments to allow medications to be classified as either Prior or Concomitant.

Prior medications include any medications that started prior to the start date of study medication. Concomitant medications are medications taken at least one day in common with the study medication dosing period.

Details of imputation methods for missing or partial dates are described in Section 4.2.1.

The number and percentage of subjects taking Prior medications (excluding past psoriasis medications) will be summarized by PS0011 treatment group, overall and by ATC class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC Level 3), and preferred term.

The number and percentage of subjects taking Concomitant medications will be summarized similarly.

A by-subject listing of all Prior and Concomitant medications will be provided.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

All summaries detailed in this section will be performed on the SS.

Due to the method of administration of the treatments, compliance will be examined in terms of completed injections, where two injections will be considered as one complete treatment administration (ie, one dose).

Treatment compliance will be calculated as:

$$\text{Treatment compliance} = \frac{\text{total number of completed injections}}{\text{total number of expected injections}} \times 100 \quad (3)$$

where the total number of expected injections is derived relative to when the subject finishes treatment. If a subject completes treatment, 24 injections are expected (two at each Q4W). If a subject discontinues early, then the number of expected injections is based on the time of early discontinuation relative to the dosing visits.

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by PS0011 treatment group.

A by-subject listing of treatment compliance will be provided.

8 SAFETY ANALYSES

All safety summaries and listings will be performed using all subjects in the SS.

8.1 Statistical analysis of the primary safety variable

8.1.1 Derivation of TEAEs

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

TEAEs are defined as those AEs that have a start date on or following the first administration of study treatment in PS0011 through the final administration of study treatment + 140 days (covering the 20-week SFU period). If it is not possible (due to partial dates) to determine whether or not an AE is treatment-emergent then it will be assumed to be a TEAE. TEAEs will be categorized to the treatment group based on the dose being received at the time of onset of the event.

8.1.2 Derivation of Duration of Exposure

The duration of exposure (in days) will be calculated as:

$$\text{Duration of exposure} = \text{Date of last dose in PS0011} - \text{Date of first dose in PS0011} + 28 \quad (4)$$

Should the date of the last dose plus 28 days equate to a date that is beyond the Week 48 visit date then the exposure will be calculated as:

$$\text{Duration of exposure} = \text{Week 48 visit date} - \text{Date of first dose in PS0011} \quad (5)$$

For subjects who have died and the date of last dose plus 28 days extends beyond the date of death, the exposure will be as follows:

$$\text{Duration of exposure} = \text{Date of death} - \text{Date of first dose in PS0011} + 1 \quad (6)$$

8.1.3 Derivation of exposure at risk

Throughout this section, date of last clinical contact for each subject is defined as the maximum of [last visit date including SFU visits, last imputed AE start date, date of study termination or completion, last date of study drug administration].

In general, exposure days at risk will be calculated as:

$$\text{Exposure days at risk} = \text{Date of last dose in PS0011} - \text{Date of first dose in PS0011} + 140 \quad (7)$$

Alternatively, for subjects who die or are lost to follow-up prior to the Week 48 visit, total exposure days at risk will be calculated as:

$$\text{Exposure days at risk} = \text{Date of last clinical contact in PS0011} - \text{Date of first dose in PS0011} + 1 \quad (8)$$

For the analysis based on data through to the last Week 48 visit (see Section 4.3), there may be subjects who are still ongoing in the SFU period at the time of data cut-off. For such subjects, exposure days at risk will be calculated as follows:

$$\text{Exposure days at risk} = \text{Data cutoff date} - \text{Date of first dose in PS0011} + 1 \quad (9)$$

8.1.4 Derivation of EAIR

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

$$\text{EAIR} = 100n \Big/ \sum_{i=1}^{N} T_{Exp(i)} \quad (10)$$

where the numerator is the total number of subjects experiencing the AE and the denominator is the total time at risk scaled to 100 subject-years; that is, the total summation of individual subject-years at risk up to the first occurrence of the AE for subjects with that AE, and the total subject-years at risk for those subjects not experiencing that AE, divided by 100.

If a subject has multiple events, the time of exposure is calculated to the first occurrence of the AE being considered. If a subject has no events, the total time at risk is used as defined in Section 8.1.3.

Exact Poisson 95% confidence intervals for incidence rates are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 1990):

$$\text{LCL} = {\chi^2}_{2n,\alpha/2}/2 \quad (11)$$

$$\text{UCL} = {\chi^2}_{2(n+1),1-\alpha/2}/2 \quad (12)$$

where n is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of degrees of freedom for the chi-square quantile for the upper tail probability χ^2.

8.1.5 Derivation of EAER

The exposure adjusted event rate (EAER) will be the number of AEs including repeat occurrences in individual subjects divided by the total time at risk scaled to 100 subject-years and calculated using:

$$\text{EAER} = 100N_{AE} \Big/ \sum_{i=1}^{N} T_{Risk,i} \quad (13)$$

where N_{AE} is the total number of AEs.

No confidence interval will be computed for EAER.

8.1.6 Analysis of the primary safety variable

All TEAEs will be summarized descriptively by PS0011 treatment group, primary SOC, HLT, and PT. This summary will include the number and percentage of subjects experiencing the event, the number of events, EAIR with associated 95% confidence interval based upon the Chi-Square distribution (Ulm, 1990), and the EAER.

8.2 Other safety analysis

8.2.1 TEAEs

The following summaries will be provided by PS0011 treatment group and for the "All bimekizumab" group. In addition, all summaries of TEAEs "per 100 subject years" will display EAIR and EAER:

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 subject years by SOC, HLT and PT
- Incidence of TEAEs per 100 subject years by SOC, HLT, PT and by Timing of Onset Relative to Anti-bimekizumab Antibody Status
- Incidence of TEAEs by Decreasing Frequency of PT
- Incidence of TEAEs by Maximum Severity, SOC, HLT and PT
- Incidence of Non-Serious TEAEs by SOC, HLT and PT
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by SOC and PT

The incidence of TEAEs per 100 subject years will also be summarized for PS0010 and PS0011 combined, where treatment emergence and exposure at risk are relative to the first dose of study drug in PS0010. In the case of a subject that switches study treatment when starting PS0011, exposure at risk to PS0010 treatment will end the day prior to the first PS0011 dose. Adverse events that occur on the PS0011 baseline visit date will be attributed to the PS0010 treatment. The only exception to this definition is for the following types of events:

- Those that code to a High Level Term (HLT) of "Injection Site Reactions"
- Those which have been designated as an Injection Reaction on the AE CRF and do not code to a System Organ Class (SOC) of "Investigations"
- Those which have been identified as a hypersensitivity reaction or an anaphylactic reaction

When any of these events occur on the date of treatment switch at PS0011 Baseline, the AE will be attributed to the treatment initiated in PS0011.

All AE summaries will be ordered alphabetically by SOC and HLT within SOC and in terms of decreasing frequency for PT within HLT in the "All bimekizumab" treatment group.

For each subject and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, the worst case will be assumed.

If the intensity of an AE is unknown, it will be considered as severe. If the relationship to study drug is missing, it will be considered as related.

Additional tables will summarize TEAEs by relationship to study medication, TEAEs leading to withdrawal from the study, treatment-emergent SAEs, and deaths:

- Incidence of TEAEs by Relationship, SOC, HLT and PT
- Incidence of Non-Serious TEAEs by Relationship, SOC, HLT and PT
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by Relationship, SOC and PT
- Incidence of Serious TEAEs per 100 subject years by SOC, HLT and PT
- Incidence of Serious TEAEs by Relationship, SOC, HLT and PT
- Incidence of TEAEs Leading to Discontinuation by SOC, HLT and PT
- Incidence of TEAEs Leading to Death by SOC, HLT and PT
- Incidence of TEAEs Leading to Death by Relationship, SOC, HLT and PT

The incidence of serious TEAEs per 100 subject years will also be summarized for PS0010 and PS0011 combined, where treatment emergence and exposure at risk are relative to the first dose of study drug in PS0010. In the case of a subject that switches study treatment when starting PS0011, exposure at risk to PS0010 treatment will end the day prior to the first PS0011 dose. Adverse events that occur on the PS0011 baseline visit date will be attributed to the PS0010 treatment. The only exception to this definition is for the following types of events:

- Those that code to a High Level Term (HLT) of "Injection Site Reactions"
- Those which have been designated as an Injection Reaction on the AE CRF and do not code to a System Organ Class (SOC) of "Investigations"
- Those which have been identified as a hypersensitivity reaction or an anaphylactic reaction

When any of these events occur on the date of treatment switch at PS0011 Baseline, the AE will be attributed to the treatment initiated in PS0011.

The following by-subject listings will be provided:

- All serious TEAEs
- All TEAEs leading to discontinuation of study treatment

- All death data
- All TEAEs and all non-TEAEs
- All treatment-emergent adverse drug reactions
- All AEs of special monitoring (AESM).

The following are AESM that require special statistical analyses:

1. Serious infections, opportunistic infections including TB and fungal infections

Serious infections will be identified based on MedDRA classification (SOC "Infections and infestations") using the "Any SAE" table. A separate table does not need to be produced to summarize these events.

Fungal infections will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs which code into the high level group term (HLGT) of "Fungal infectious disorders".

The number and percentage of subjects experiencing fungal infections will be summarized by region and country by PS0011 treatment group. This summary will also include the number and percentage of subjects experiencing the PT "Oral Candidiasis" by region and country.

Opportunistic infections (including tuberculosis) will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs identified using UCB-defined search criteria as described in Section 12.2.

2. Malignancies, including lymphomas

These events will be presented in two stand-alone tables which include EAIR and EAER:

- One table will be based on the criteria standard MedDRA query (SMQ) = "Malignant or unspecified tumours (SMQ)"
- One table will be based on the criteria SMQ = "Malignant tumours (SMQ)".

Note that the events included in the "Malignant tumours" table will be a subset of the events included in the "Malignant or unspecified tumours" table. 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 two 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)"

3. Major cardiovascular events

Major cardiovascular events will be presented in a stand-alone table which includes EAIR and EAER. The table will include TEAEs that are identified using the following UCB-defined search criteria:

- All serious TEAEs which code to a PT included in the Scope = Broad and/or Scope = Narrow groups of the following SMQs:
  - Haemorrhagic central nervous system vascular conditions (SMQ)
  - Ischaemic central nervous system vascular conditions (SMQ).
  - All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to a PT "Chest pain" or "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 Primary SOC.

4. Cytopenias

These events will be presented in a stand-alone table that is based on the SMQ = "Haematopoietic cytopenias". 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.

5. Neuropsychiatric events (in particular depression and suicide)

These events will be presented in a stand-alone table including EAIR and EAER. The table will be based on the SMQ = "Depression and suicide/self-injury (SMQ)". The SMQ search will include all TEAEs which code to a PT included in the Scope = Broad and/or Scope = Narrow groups within the SMQ.

6. Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLGT of "Colitis (excl infective)".

7. Anaphylactic reaction

Anaphylactic reactions will be summarized together in a stand-alone table.

The first row within the body of the table will be labeled "Any hypersensitivity reaction/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 (together – not broken out by type) by SOC, HLT and PT.

Hypersensitivity reactions and anaphylactic reactions will be identified as follows:

a) Hypersensitivity reactions

All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, which code to a PT which contains the term "hypersensitivity" will be considered to be a hypersensitivity reaction and included in the summary table as such.

b) Anaphylactic reactions

An algorithmic approach will be used to identify TEAEs that are considered to be anaphylactic reactions. PTs are separated into the four distinct categories (A, B, C, D) prior to the algorithmic approach being applied.

All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, and which fulfill any of the three criteria described in Section 12.3 will be included in the summary table.

8. Hepatic events and DILI

Although not officially considered to be AEs of special monitoring, hepatic events are nonetheless considered to be interesting enough to be summarized in stand-alone tables.

Hepatic events will be summarized in a stand-alone table that includes all TEAEs in the SMQ "Drug related hepatic disorders – comprehensive search (SMQ)". Note that the following two sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps)" and "Liver neoplasms, malignant and unspecified (SMQ)".

The SMQ search should include all TEAEs (regardless of whether they have been judged as related to study medication or not) which code to a PT included in the Scope = Narrow group within each SMQ.

Hy's Law cases are to be reported separately in the liver function test summary table (with adjudication for "Potential drug-induced liver injury" cases).

Additional tables will summarize TEAEs by responder status (defined as PS0010 Week 12 PASI90 response):

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 subject years by SOC, HLT and PT
- Incidence of Serious TEAEs per 100 subject years by SOC, HLT and PT
- Incidence of Fungal Infectious Disorders per 100 subject years by SOC, HLT and PT

8.2.2 Clinical laboratory evaluations

All laboratory data recorded in the electronic case report form (eCRF) will be summarized. If any additional analytes to those in Table 8-1 are also recorded then these will be listed only.

Table 8-1: Laboratory measurements

Hematology	Chemistry	Urinalysis
Basophils	Calcium	Albumin

Hematology	Chemistry	Urinalysis
Eosinophils	Chloride	Bacteria
Lymphocytes	C-reactive protein	Crystals
Monocytes	Magnesium	Glucose
Neutrophils	Potassium	pH
Hematocrit	Sodium	Red blood cell
Hemoglobin	Glucose	White blood cell (WBC)
Mean corpuscular hemoglobin	Blood urea nitrogen	Urine dipstick for pregnancy testing[a]
Mean corpuscular hemoglobin concentration	Creatinine	
Mean corpuscular volume	Alkaline phosphatase	
Platelet count	Aspartate aminotransferase (AST)	
Red blood cell count	Alanine aminotransferase (ALT)	
White blood cell count	Gamma glutamyltransferase (GGT)	
	Total bilirubin	
	Lactate dehydrogenase	
	Total cholesterol	
	Serum pregnancy testing[a]	

[a] Pregnancy testing will be done in all women of childbearing potential and will consist of serum testing at the Safety Follow-Up visit and urine testing at all other visits.

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. For tables where multiple measurements over a period of time are considered (as in shift tables), unscheduled and repeat visits will be considered as long as they were collected during the treatment period. All summaries will be presented in International System of units and will be based on observed case values. In the case where laboratory values are below the lower limit of quantification, then these will be set to the midpoint between zero and the lower limit of quantification for the purpose of summarizing the data.

The change from Baseline tables will be presented using descriptive statistics by PS0011 treatment group. The table presentations will display descriptive statistics for the PS0011 Baseline followed by descriptive statistics for the change from PS0011 Baseline results by scheduled visit for PS0011.

The following summaries will be provided:

- The observed and change from Baseline values in each laboratory variable by PS0011 treatment group and visit

- The number and percentage of subjects experiencing markedly abnormal values by laboratory variable, PS0011 treatment group and visit
- A shift table of the number and percentage of subjects experiencing low, normal or high values at Baseline to maximum post-Baseline value (ie, low, normal, high), by laboratory variable and PS0011 treatment group
- A shift table of the number and percentage of subjects experiencing low, normal or high values at Baseline to minimum post-Baseline value (ie, low, normal, high), by laboratory variable and PS0011 treatment group
- A shift table of the number and percentage of subjects experiencing low, normal or high values at Baseline to the End of Treatment[1] value (ie, low, normal, high), by laboratory variable and PS0011 treatment group.

[1]The End of Treatment value refers to the value from the last observed non-missing post baseline visit prior to the end of treatment.

A by-subject listing of all laboratory data will be provided. This listing will be presented by PS0011 treatment group and will include: center, subject identifier, age, gender, race, weight, visit, laboratory variable, result (with abnormal values flagged as "L" or "H" accordingly) and unit.

A summary table highlighting the potential cases of Hy's Law within each PS0011 treatment group will be presented. Hy's Law is defined as:

- AST > 3xULN or ALT >3xULN and
- Total Bilirubin ≥2xULN.

Markedly abnormal values are defined as those with a severity of Grade 3 and above based on the common terminology criteria for adverse events criteria (U.S. Department of Health and Human Services 2010). The markedly abnormal laboratory data will be summarized by visit and for any visit while on treatment. Definitions of markedly abnormal values using the Grade 3 cutpoints are given in the tables below for age ranges of ≥ 17 years (Table 8-2 for markedly abnormal liver function test values, Table 8-3 for markedly abnormal hematology values and Table 8-4 for markedly abnormal biochemistry values). The laboratory results classified as Grade 3 or 4 will be listed separately.

Table 8–2: Definitions of Marked Abnormal Liver Function Tests

Parameter name	Conventional		Standard		
	Unit	Criteria	Unit	Criteria	Abnormal Designation
Alkaline Phosphatase		≥5.0 x ULN		≥5.0 x ULN	AH
ALT	U/L	≥5.0 x ULN	U/L	≥5.0 x ULN	AH
AST	U/L	≥5.0 x ULN	U/L	≥5.0 x ULN	AH
Total Bilirubin	mg/dL	≥3.0 x ULN	umol/L	≥3.0 x ULN	AH
GGT	U/L	≥5.0 x ULN	U/L	≥5.0 x ULN	AH

Table 8–3: Definitions of Marked Abnormal Clinical Chemistry Values

Parameter name	Conventional		Standard		
	Unit	Criteria	Unit	Criteria	Abnormal Designation
Albumin	g/dL	<2.0	g/L	<20	AL
Creatinine	mg/dL	>3.0 x ULN	umol/L	>3.0 x ULN	AH
Glucose	mg/dL	<30 >250	umol/L	<1.7 >13.9	AL AH
Calcium	mg/dL	<7.0 >12.5	umol/L	<1.75 >12.5	AL AH
Magnesium	mg/dL	<0.9 >3.0	umol/L	<0.4 >1.23	AL AH
Potassium	umol/L	<3.0 >6.0	umol/L	<3.0 >6.0	AL AH
Sodium	umol/L	<130 >155	umol/L	<130 >155	AL AH
Total Cholesterol	mg/dL	>400	umol/L	>10.34	AH

Table 8–4: Definitions of Marked Abnormal Hematology Values

Parameter name	Conventional		Standard		
	Unit	Criteria	Unit	Criteria	Abnormal Designation
Hemoglobin	g/dL	<8.0 >4.0 above ULN	g/L	<80 >40 above ULN	AL AH
Lymphocytes Absolute	10^9/L	<0.5 >20.0	10^9/L	<0.5 >20.0	AL AH
Neutrophils Absolute	10^9/L	<1.0	10^9/L	<1.0	AL
Platelets	10^9/L	<50	10^9/L	<50	AL
WBC/Leukocytes	10^9/L	<2.0 >100	10^9/L	<2.0 >100	AL AH

8.2.3 Vital signs

The following vital signs variables will be summarized: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C) and pulse rate (beats/min).

The change from Baseline table will be presented using descriptive statistics by PS0011 treatment group. The table presentations will display descriptive statistics for the PS0011

Baseline followed by descriptive statistics for the change from PS0011 Baseline results by scheduled visit for PS0011.

The following summaries will be provided:

- A summary of the absolute and change from PS0011 Baseline value for each vital sign variable by PS0011 treatment group and visit
- A summary of the number and percentage of subjects experiencing at least one markedly abnormal value for a vital sign variable as defined in Table 8-5, by PS0011 treatment group and visit.

Table 8–5: Definitions of markedly abnormal blood pressure values

Parameter (unit)	Markedly Abnormal Low	Markedly Abnormal High
Systolic blood pressure (mmHg)	<90 and a decrease from Baseline of ≥20	>180 and an increase from Baseline of ≥20
Diastolic blood pressure (mmHg)	<50 and a decrease from Baseline of ≥15	>105 and an increase from Baseline of ≥15

A by-subject listing of all vital signs data will be provided. This listing will be presented by PS0011 treatment group and will include: center, subject identifier, age, gender, race, weight, visit, vital sign variable and result (with abnormal values flagged as "L" or "H" accordingly).

8.2.4 Physical examination

A physical examination is conducted at PS0011 Baseline, Week 48 visit and SFU visit. Findings are collected as AEs and will be listed as such.

8.2.5 Electrocardiograms

A summary of the number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant ECG results at all applicable visits will be presented by PS0011 treatment group.

The change from Baseline tables will be presented using descriptive statistics by PS0011 treatment group. The table presentations will display descriptive statistics for the PS0011 Baseline followed by descriptive statistics for the observed and change from PS0011 Baseline results by scheduled visit for PS0011.

The following ECG variables will be summarized (observed values and change from PS0011 Baseline) by visit: QTcF, RR, PR, QRS, and QT.

QTc abnormalities are defined as QTcF values following dosing that are greater than 450 ms or are increases from PS0011 Baseline greater than 30 ms. QTcF outliers will be highlighted in the data listings and summarized using the following categories:

- Values >450 ms, >480 ms, >500 ms
- Increase from PS0011 Baseline of >30 ms, increase from PS0011 Baseline of >60 ms, increase from PS0011 Baseline of >90 ms
- Values >450 ms and increases from PS0011 Baseline of >30 ms, values >500 ms and increases from PS0011 Baseline of >60 ms.

The number and percentage of subjects who meet the ECG outlier criteria at any assessment post-date of first dose in PS0011 will be summarized by PS0011 treatment group.

A by-subject listing of all 12-Lead ECG data will be provided.

8.2.6 Exposure

The number of doses received will be summarized by PS0011 treatment group over the 48 week administration period. Each dose should consist of two injections.

Extent of exposure to study medication in PS0011 will be summarized using descriptive statistics by PS0011 treatment group.

Subject exposure at risk in days in PS0011 will also be summarized using descriptive statistics by PS0011 treatment group. Total subject exposure at risk in years for each PS0011 treatment group will also be provided.

8.2.7 Assessment and management of TB and TB risk factors

A by-subject listing of all the "Evaluation of signs and symptoms of tuberculosis" questionnaire data will be provided.

8.2.8 Electronic Columbia Suicide Severity Rating Scale

The results of the Columbia Suicide Severity Rating Scale (C-SSRS) will be summarized using number of subjects and percentages with (i) events in suicidal behavior, (ii) suicidal ideation, (iii) suicidal behavior and ideation, and (iv) self-injurious behavior without suicidal intent.

[redacted]

Self-injurious behaviour without suicidal intent is defined as an event in the category non-suicidal self-injurious behavior.

The incidence of subjects with suicidal behavior and self-injurious behavior will be summarized by PS0011 treatment group and visit. A by-subject listing of the electronic C-SSRS questionnaire data will be provided.

9 PHARMACOKINETICS

9.1 Pharmacokinetics

Descriptive statistics for the plasma concentrations at PS0011 Baseline will be presented followed by descriptive statistics for the observed and change from PS0011 Baseline results for scheduled visits in PS0011. For the descriptive statistics, geometric mean, geometric coefficient of variation, and 95% confidence interval for the geometric mean will be used instead of the arithmetic mean and standard deviation. The median, minimum, and maximum will also be displayed.

If bimekizumab plasma concentration measurements are deemed to be below the level of quantification (BLQ), then for calculation of the derived statistics this sample result will be set to half the lower level of quantification (LLQ). The subjects with at least one result that is defined as BLQ will also be listed within the respective analysis table. Descriptive statistics will be calculated if at least 2/3 of the values are above the LLQ. If this is not the case, only median, minimum, and maximum will be presented.

If the dosing for a visit is +/- 7 days out of window, then the plasma concentration from that visit and all subsequent visits will be excluded from the PK summary.

The bimekizumab concentrations, including the concentrations excluded from the summaries, will also be listed.

9.2 Immunogenicity

9.2.1 Anti-bimekizumab antibodies

Subjects with a positive on-treatment (i.e, excluding PS0010 Baseline) anti-BKZ antibody result in either PS0010 or PS0011 will be classified as anti-BKZ positive.

Anti-BKZ antibody status will be summarized for each PS0010/PS0011 treatment group at each scheduled PS0010 and PS0011 visit using the PK-PPS analysis set. The first occurrence of anti-BKZ antibody positivity will also be presented for each PS0010/PS0011 treatment group at each scheduled PS0010 and PS0011 visit.

The anti-BKZ antibody status will be determined for each visit where samples are taken for drug concentration means. The cut point for determining whether the anti-bimekizumab antibody level is sufficiently high to be considered anti-BKZ antibody positive is not yet known. However, this will be determined prior to the database lock of the PK and anti-BKZ antibody data.

A line plot of the percentage of anti-BKZ antibody positive subjects at each visit will be produced by PS0010/PS0011 treatment group. All individual subject-level anti-BKZ antibody results will be listed.

10 EFFICACY ANALYSES

10.1 Statistical analysis of the efficacy variables

Efficacy variables will be analyzed for all subjects in the FAS.

Also, summary tables of each endpoint by visit and treatment will be provided.

Unless otherwise specified, summary tables for efficacy endpoints by PS0010/PS0011 treatment group will present data separately by responder status (defined as PS0010 Week 12 PASI90 response).

Efficacy endpoints will also be listed.

10.1.1 PASI score and response

10.1.1.1 Derivation of PASI score and response

PASI scoring of psoriatic plaques is based on three criteria: redness (R), thickness (T), and scaliness (S). Severity is rated for each index (R, S, T) on a 0-4 scale (0 for no involvement, up to 4 for very marked involvement). The body is divided into four areas comprising the head (h), upper extremities (u), trunk (t), and lower extremities (l). In each of these areas, the fraction of total surface area affected is graded on a 0-6 scale (0 for no involvement, up to 6 for 90%-100% involvement).

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 for each area by the weighted area-of-involvement score for that respective area, and then summing the four resulting quantities. PASI is therefore calculated as (note that the R, T, and S scores are as follows: 0 = none, 1 = slight, 2 = moderate, 3 = marked, and 4 = very marked):

$$\begin{aligned}\text{PASI} = {} & (0.1 \times (R_h + T_h + S_h) \times A_h) + (0.2 \times (R_u + T_u + S_u) \times A_u) \\ & + (0.3 \times (R_t + T_t + S_t) \times A_t) \\ & + (0.4 \times (R_l + T_l + S_l) \times A_l)\end{aligned} \quad (14)$$

where

R_h, R_u, R_t, R_l = redness score of plaques on the head, upper extremities, trunk, and lower extremities, scored 0-4 respectively

T_h, T_u, T_t, T_l = thickness score of plaques on the head, upper extremities, trunk, and lower extremities, scored 0-4 respectively

S_h, S_u, S_t, S_l = scaliness score of plaques on the head, upper extremities, trunk, and lower extremities, scored 0-4 respectively

A_h, A_u, A_t, A_l = numerical value translation of % area of psoriatic involvement score for the head, upper extremities, trunk, and lower extremities respectively (where 0 = 0% [clear], 1 = >0% to <10%, 2 = 10% to <30%, 3 = 30% to <50%, 4 = 50% to <70%, 5 = 70% to <90%, and 6 = 90% to 100%).

The highest potential PASI score is 72 for severe disease and the lowest is 0 for no psoriasis lesions. PASI scores are treated as a continuous score, with 0.1 increments within these values. The percent improvement in PASI scores from Baseline will be computed as:

$$\text{Percent improvement in PASI} = 100 \times \frac{\text{Baseline PASI} - \text{Post–Baseline PASI}}{\text{Baseline PASI}} \quad (15)$$

If a subject has experienced an improvement, this measure will be positive. If a subject has experienced a worsening in their condition, this measure will be negative.

If a subject is missing one or two severity measurements for a certain region, the average of the remaining severity measurement(s) within that region will be utilized to substitute for the missing severity measurement(s) in that region. If the area of affected skin and/or all severity measurements for up to two regions are missing, then the missing (R + T + S) x A for a region will be substituted by the average of the available (R + T + S) x A. Otherwise, the PASI will be set to missing.

A categorical variable, PASI90 response, is defined to be equal to 1 if the percentage improvement from Baseline in the PASI scores is 90% or greater and 0 if the percentage improvement from Baseline is less than 90%. This definition is introduced for the purpose of identifying subjects who respond to the treatment (1 = responder, 0 = non-responder). Similarly, the categorical efficacy variables PASI75 and PASI100 response are equal to 1 for subjects with improvements of 75% or greater and 100% from Baseline in PASI score respectively, and equal to 0 otherwise.

10.1.1.2 Analysis of PASI score and response

Summaries of the PASI75, PASI90 and PASI100 response will be summarized descriptively using counts and percentages by PS0010/PS0011 treatment group and visit. In general, summaries of PASI score and response will include only PS0011 visits. PS0010 visits will be added for select summaries as specified.

The PASI responder variables will be derived relative to both the PS0010 Baseline and the PS0011 Baseline for subjects who are PS0010 Week 12PASI90 non-responders at PS0010 Week 12 in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480mg to BKZ 320mg. PASI response will be calculated relative to the original PS0010 Baseline only for subjects who are PS0010 Week 12 PASI90 responders in the following treatment groups: Placebo to Placebo, BKZ 64mg to BKZ 64mg, BKZ 160mg to BKZ 160mg, BKZ 320mg to BKZ 320mg, and BKZ 480mg to BKZ 320mg. Missing data will be imputed via NRI. Summaries for PASI90 and PASI100 response will include PS0010 visits.

In addition, PASI90 and PASI100 response relative to the PS0010 Baseline will also be summarized descriptively using counts and percentages by PS0011 treatment group and visit. Missing data will be imputed via NRI.

Change from Baseline in PASI score will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit separately by PS0010 Week 12 PASI90 response. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS0010 Week 12 PASI90 non-responders at PS0010 Week 12 in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480mg to BKZ 320mg. A similar summary will be presented for the percent change from Baseline in PASI score.

Missing data for the continuous change from Baseline and percent change from Baseline variables will be handled by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

In addition, the percent change from PS0010 Baseline in PASI score will also be presented using descriptive statistics by PS0011 treatment group and visit. Missing data will be handled using the same multiple imputation as described above.

A line plot of the mean percentage change from PS0010 Baseline in PASI score over time using MI via the MCMC method specified in Section 4.2.2, by PS0010/PS0011 treatment group will be produced.

The number and percentage of subjects who achieve an absolute PASI score ≤1, ≤2, ≤3, and ≤5 at each visit will be summarized by both PS0010/PS0011 treatment group and PS0011 treatment group. Missing data will be imputed using NRI. These summaries will include PS0010 visits.

10.1.2 IGA response

10.1.2.1 Derivation of IGA response

A static IGA for psoriasis will be used to assess disease severity in all subjects during the study.

The Investigator will assess the overall severity of psoriasis using the following five-point scale (see Table 10-1):

Table 10–1: Five-point 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

IGA response is defined as clear (0) or almost clear (1) with at least a two category improvement from Baseline.

10.1.2.2 Analysis of IGA response

The number and percentage of subjects achieving an IGA response (defined as clear (0) or almost clear (1) with at least two category improvement from Baseline) will be summarized descriptively using counts and percentages by PS0010/PS0011 treatment group and visit. In general, summaries of PASI score and response will include only PS0011 visits. PS0010 visits will be added for select summaries as specified.

The IGA response variables will be derived relative to both the PS0010 Baseline and the PS0011 Baseline for subjects who are PS0010 Week 12 PASI90 non-responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg. PASI response will be calculated relative to the original PS0010 Baseline only for subjects who are PS0010 Week 12 PASI90 responders in the following treatment groups: Placebo to Placebo, BKZ 64mg Q4W to

BKZ 64mg Q4W, BKZ 160mg Q4W to BKZ 160mg Q4W, BKZ 320mg Q4W to BKZ 320mg Q4W, and BKZ 480mg Q4W to BKZ 320mg Q4W. Missing data will be imputed via NRI. Summaries for IGA response will include PS0010 visits.

IGA response relative to the PS0010 Baseline will also be summarized descriptively using counts and percentages by PS0011 treatment group and visit. Missing data will be imputed via NRI.

In addition, a shift table of IGA response compared to PS0010 Baseline will be summarized by PS0010/PS0011 treatment group based on observed data.

10.1.3 Analysis of BSA

Change from Baseline in BSA affected by psoriasis will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit separately by PS0010 Week 12 PASI90 response. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS0010 Week 12 PASI90 non-responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480mg to BKZ 320mg. A similar summary will be presented for the percent change from Baseline in BSA.

Missing data for the continuous change from Baseline and percent change from Baseline variables will be handled by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

The percent change from PS0010 Baseline in BSA will also be presented using descriptive statistics by PS0011 treatment group and visit. Missing data will be handled using the same multiple imputation as described above.

The number and percentage of subjects who achieve BSA =0%, ≤1%, ≤3%, and ≤5% at each visit will be summarized by both PS0010/PS0011 treatment group and PS0011 treatment group. Missing data will be imputed using NRI. These summaries will include PS0010 visits.

10.1.4 DLQI

10.1.4.1 Derivation of DLQI

The DLQI questionnaire is used for patients with psoriasis and consists of 10 questions. Question 7 consists of a sub-question which is only to be answered following a “No” response to the main question. The questions are scored as shown below in Table 10-2, and the DLQI score is categorized as shown in Table 10-3.

Table 10–2: DLQI Scoring

Question Number	0 points	1 point	2 points	3 points
1, 2	Not at all	A little	A lot	Very much
3, 4, 5, 6, 8, 9, 10	Not at all/Not relevant	A little	A lot	Very much
7	No – Not at all/Not relevant	No – A little	No – A lot	Yes

Table 10–3: DLQI - Categorization

Category	Score Range
No Effect	0-1
Small Effect	2-5
Moderate Effect	6-10
Very Large Effect	11-20
Extremely Large Effect	21-30

In the case of one missing value the result imputed for that question will be 0 and the DLQI score created as normal. Should two or more questions be unanswered then the DLQI score will be set to missing. For question 7, if "Not relevant" is selected then the score for the question will be 0, if the question is answered "No" but the second half of the question is incomplete then the question will still be scaled as 0.

A DLQI absolute score of 0 or 1 indicates no or small impact of the disease on health related quality of life.

10.1.4.2 Analysis of DLQI

The number and percentage of subjects achieving a DLQI score of 0 or 1 at each visit will be summarized descriptively using counts and percentages by PS0010/PS0011 treatment group and visit. Missing data will be imputed via NRI.

The number and percentage of subjects achieving a DLQI score of 0 or 1 at each visit will also be summarized descriptively using counts and percentages by PS0011 treatment group and visit. Missing data will be imputed via NRI.

Change from Baseline in DLQI score will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS0010 Week 12 PASI90 non-responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg.

Missing data for the continuous change from Baseline variable will be handled by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

A line plot of the mean change from PS0010 Baseline in DLQI response over time using MI via the MCMC method specified in Section 4.2.2, by PS0010/PS0011 treatment group will be produced.

10.1.5 mNAPSI

10.1.5.1 Derivation of mNAPSI

Psoriatic nail disease will be evaluated at the Baseline visit using the mNAPSI. All affected nails will be scored (0 to 3) for onycholysis/oil drop dyschromia, nail plate crumbling, and pitting and

will be scored (0 for "no" or 1 for "yes") for leukonychia, nail bed hyperkeratosis, splinter haemorrhages and red spots in the lunula. The score for an individual nail ranges from 0 to 13 with higher scores indicative of more severe nail disease. The total mNAPSI score is the sum of the scores for each individual nail. If a nail is unaffected, it will be recorded as such and will not contribute to the total mNAPSI score. Subjects with nail disease at Baseline are defined as those with a mNAPSI score >0 at Baseline.

If 1 or 2 response items scored on the 0 to 1 scale are missing, the missing response(s) will be imputed by the average of the available responses. Otherwise, the total mNAPSI score will be set to missing.

10.1.5.2 Analysis of mNAPSI

Change from Baseline in mNAPSI scores for the subset of subjects with psoriatic nail disease at PS0010 Baseline will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS0010 Week 12 PASI90 non-responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg.

Missing data for the continuous change from Baseline variable will be handled by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

10.1.6 PGADA for the arthritis VAS

10.1.6.1 Derivation of PGADA for the arthritis VAS

The PGADA for the arthritis VAS will be used to provide an overall evaluation of arthritis disease symptoms. Subjects will respond to the question, "Considering all the ways your arthritis affect you, please mark a vertical line on the scale below to show how you are feeling today", using a VAS where 0 is "very good, no symptoms" and 100 is "very poor, severe symptoms".

10.1.6.2 Analysis of PGADA for the arthritis VAS

Change from Baseline in PGADA VAS scores will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS0010 Week 12 PASI90 non-responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg.

Missing data for the continuous change from Baseline variable will be handled by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

10.1.7 PSSI

10.1.7.1 Derivation of PSSI

The PSSI considers both the extent of the scalp area of involvement and the severity based on the scoring scales outlined in Table 10-4 and Table 10-5.

The assessment considers erythema, induration and desquamation on the scalp. For each of these three elements, the scores of the area and severity are multiplied. Then, the score from each element is totaled to obtain the PSSI score. As with the PASI, the PSSI score ranges from 0 to 72 with a higher score indicating increased scalp disease severity.

If a subject is missing one severity measurement, the average of the remaining severity measurements will be utilized to substitute for the missing severity measurement. If the area of affected skin is missing or if two or more severity measurements are missing, then the PSSI score will be set to missing.

Table 10–4: PSSI assessment of extent of scalp psoriasis

Score	Definition
1	<10%
2	10 – 29%
3	30 – 49%
4	50 – 69%
5	70 – 89%
6	90 – 100%

Table 10–5: PSSI assessment of clinical symptoms

Score	Definition
0	Absent
1	Slight
2	Moderate
3	Severe
4	Severest possible

10.1.7.2 Analysis of PSSI

Change from Baseline in PSSI for the subset of subjects with scalp psoriasis at PS0010 Baseline will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS00010 Week 12 PASI90 non-responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg. A similar summary will be presented for the percent change from Baseline.

Missing data for the continuous change from Baseline variable will be handled by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

A line plot of the mean percent change from PS0010 Baseline in PSSI over time using MI via the MCMC method (or LOCF if necessary, as determined in Section 4.2.2),, by PS0010/PS0011 treatment group will be produced.

The percent change from PS0010 Baseline in PSSI score will also be presented using descriptive statistics by PS0011 treatment group and visit. Missing data will be handled using the same multiple imputation as described above.

10.1.8 SF-36

10.1.8.1 Derivation of SF-36

The SF-36v2, standard recall, measures the following eight health domains as rated by the subjects over the past four weeks: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The classification of the questionnaire items to the health domains is shown in Section 12.1.

The SF-36 PCS and MCS scores are used to measure the two broad components, or aspects, of health-physical and mental. PCS and MCS are based on the aggregate of the eight health concepts described above and all of the eight health domain scales are used to score both components summary measures.

One additional item asks responders about health change over the past year.

The SF-36 will be used using QualityMetric's Health Outcomes™ Scoring Software. The software uses updated 2009 U.S. population norms and applies a Full Missing Score Estimation (Full MSE) method as follows:

- A health domain score (except the PF domain) will be estimated provided that at least one non-missing response is available within that domain
- For the PF domain item, response theory will be used to develop a model for estimates of the missing score
- Regression methods are then applied to estimate the PCS and the MCS on the basis of the available domains.

10.1.8.2 Analysis of SF-36

Change from Baseline in the SF-36 PCS and MCS scores as well as for the individual domain scores will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS0010 Week 12 PASI90 non-responders the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg.

Missing data for the continuous change from Baseline variable will be handed by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

10.1.9 HADS

10.1.9.1 Definition of HADS

The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with chronic plaque psoriasis (Snaith et al, 1994). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. The HADS scores and the severity based on the scoring scales are outlined in Table 10-6 (Langley et al, 2009).

Table 10–6: HADS Assessment of clinical symptoms

Score	Definition
<8	Normal
8 - 10	Mild
11 - 14	Moderate
≥15	Severe

10.1.9.2 Analysis of HADS

Change from Baseline in HADS-A and HADS-D will be summarized using descriptive statistics by PS0010/PS0011 treatment group and visit. The table will display descriptive statistics for the PS0010 Baseline, followed by descriptive statistics for the change from PS0010 Baseline for all treatment groups. The change from PS0011 Baseline will also be displayed for subjects who are PS0010 Week 12 PASI90 non-responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg.

Missing data for the continuous change from Baseline variable will be handed by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

In addition the percentage of subjects with scores below 8 in HADS-A and HADS-D will be summarized by visit and treatment group for imputed data (NRI) and observed cases.

11 REFERENCES

Langley, R. G., Feldman, S. R., Han, C., Schenkel, B., Szapary, P., Hsu, M. C., et al., Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-sever psoriasis: Results from a randomized, doubleblind, placebo controlled phase III trial. J Am Acad Dermatol., 2010; 63(3), 457-65.

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Snaith, R. P., & Zigmond, A. S., The hospital anxiety and depression scale, with the irritability-dpression-anxiety scale and the Leeds situational anxiety scale manual, 1994.

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12.2 AESM Opportunistic infections

Opportunistic infections are identified in two 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'.

- 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:

1. 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 case-by-case. Information from the AE dataset to be included in the spreadsheet: Subject ID, AE verbatim term, SOC, HLT, 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
2. 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'
3. Study programming team incorporates these decisions into the AE 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 a case-by-case PT reported that has been confirmed by the study physician to be an opportunistic infection will be summarized as such in the stand-alone table, along with all of the events identified in Step 1 of this process.

The timing and frequency of Step 2 should be outlines and agreed to by the study team at the beginning of the study. It is suggested that this process be executed multiple times throughout the course of the study, more frequently in the weeks leading up to database lock, and one final time immediately prior to database lock.

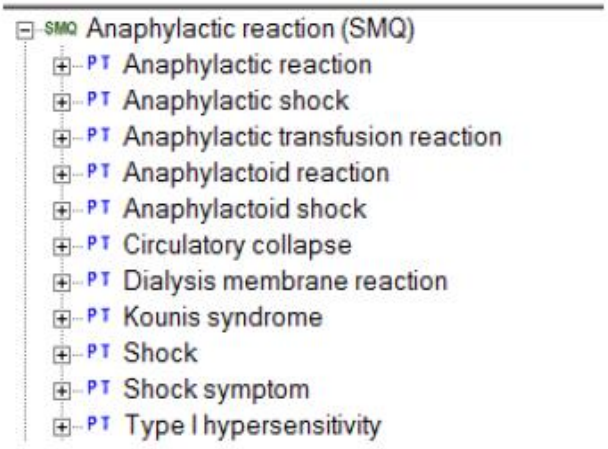
Following the initial physician review of case-by-case events, subsequent reviews will be based on the cumulative set of case-by-case events present in the database at each time point of spreadsheet creation. Physician decisions from previous runs should be retained in each subsequent run. The final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

12.3 MedDRA algorithmic approach to anaphylaxis

The SMQ *Anaphylactic reaction* consists of three parts:

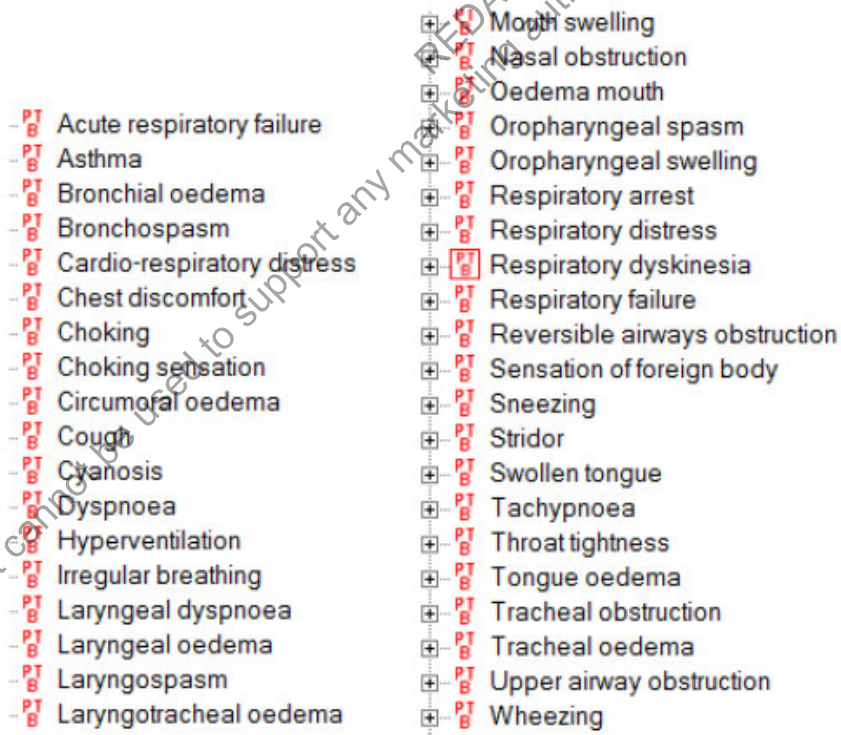
- A **narrow search**: If a subject reports any TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction and summarized as such in the table

- Category A



- 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



- Category C

- Allergic oedema
- Angioedema
- Erythema
- Eye oedema
- Eye pruritus
- Eye swelling
- Eyelid oedema
- Face oedema
- Flushing
- Generalised erythema
- Injection site urticaria
- Lip oedema
- Lip swelling
- Nodular rash
- Ocular hyperaemia
- Oedema
- Periorbital oedema
- Pruritus
- Pruritus allergic
- Pruritus generalised
- Rash
- Rash erythematous
- Rash generalised
- Rash pruritic
- Skin swelling
- Swelling
- Swelling face
- Urticaria
- Urticaria papular

- Category D

- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure systolic decreased
- Cardiac arrest
- Cardio-respiratory arrest
- Cardiovascular insufficiency
- Diastolic hypotension
- 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 an anaphylactic reactions and summarized as such in the table.

13 AMENDMENT TO THE STATISTICAL ANALYSIS PLAN

Rationale for the amendment

The purpose of this amendment is to apply modifications as a result of conclusions made at Data Evaluation Meetings 1/2 and 3.

Global changes

Various spelling and formatting amendments were made.

Due to the small population size in the Asia region, Asia was combined with Europe in all cases.

Efficacy analysis summaries were updated to group subjects by responder status (defined as PS0010 Week 12 PASI90 response) instead of by whether or not a subject switched treatment from PS0010 to PS0010.

Efficacy analysis summaries were added by PS0011 treatment groups for the following endpoints:

- PASI90 and PASI100 response
- IGA response (defined as clear (0) or almost clear (1) with at least two category improvement from Baseline)
- DLQI (0,1) response
- Percent change in PASI, BSA, PSSI

The MI procedure for continuous efficacy endpoints was clarified to refer to Section 4.2.2: Missing data for the continuous change from Baseline and percent change from Baseline variables will be handled by using MI via the MCMC method specified in Section 4.2.2

Specific changes

Change #1

Page 9 Section 2.2.4 Efficacy Variable, the following text was updated

From

Change from Baseline and responder variables will be defined relative to the PS0010 Baseline for subjects who do not change treatment between PS0010 and PS0011 (non-switchers) and relative to both the PS0010 and PS0011 Baselines for subjects who change treatments (switchers).

To

Change from Baseline and responder variables will be defined relative to the PS0010 Baseline for subjects who are PS0010 Week 12 PASI90 responders and relative to both the PS0010 and PS0011 Baselines for subjects who are PS0010 Week 12 PASI90 non-responders).

Change #2

Page 13 Section 3.6 Treatment assignment and treatment groups, updated the text for PS0010/PS0011 treatment groups

From

This refers to the combination of the randomized treatment in PS0010 and the treatment assigned at the beginning of PS0011. Some groups have been combined where it is considered appropriate to do so. The PS0010/PS0011 treatment groups are as follows:

- Placebo to Placebo
- Placebo to Bimekizumab 160mg Q4W
- Bimekizumab 64mg Q4W to Bimekizumab 64mg Q4W
- Bimekizumab 64mg Q4W to Bimekizumab 160mg Q4W
- Bimekizumab 160mg Q4W to Bimekizumab 160mg Q4W – note that the PS0010 160mg Q4W groups with and without the loading dose are both included here
- Bimekizumab 160mg Q4W to Bimekizumab 320mg Q4W – note that the PS0010 160mg Q4W groups with and without the loading dose are both included here
- Bimekizumab 320mg or greater to Bimekizumab 320mg Q4W - note that PS0010 320mg Q4W and 480mg Q4W are both included here.

To

This refers to the combination of the randomized treatment in PS0010 and the treatment assigned at the beginning of PS0011. Some groups have been combined where it is considered appropriate to do so. The PS0010/PS0011 treatment groups are as follows:

- Placebo to Placebo
- Placebo to Bimekizumab 160mg Q4W
- Bimekizumab 64mg Q4W to Bimekizumab 64mg Q4W
- Bimekizumab 64mg Q4W to Bimekizumab 160mg Q4W
- Bimekizumab 160mg Q4W to Bimekizumab 160mg Q4W – note that the PS0010 160mg Q4W groups with and without the loading dose are both included here
- Bimekizumab 160mg Q4W to Bimekizumab 320mg Q4W – note that the PS0010 160mg Q4W groups with and without the loading dose are both included here
- Bimekizumab 320mg Q4W to Bimekizumab 320mg Q4W
- Bimekizumab 480mg Q4W to Bimekizumab 320mg Q4W

Change #3

Page 15 Section 4.2.2 Handling of Missing Data for the Efficacy Analyses, the following paragraphs were added:

Note: The imputation model based on the MCMC method will only allow continuous variables in the imputation model. Therefore, prior biologic exposure and region will be re-coded as indicator variables (with values of 0 or 1 for each level of the variable). In order to achieve model convergence, prior biological exposure may be dropped from the model, if convergence is still not obtained then region may also be dropped from the model.

There may be cases where the multiple imputation model fails to converge (eg, sparse subgroups). In such situation, the LOCF approach will instead be used to impute missing data. If LOCF is used instead of multiple imputation for this reason, this will be clearly specified in the corresponding table summary. Should there be no missing data for a study variable then only observed case data will be produced.

Change #4

Page 17 Section 5.2 Protocol Deviations, the analysis set used to summarize protocol deviations was changed from FAS to ES. The following text was added.

If the dosing for a visit is +/- 7 days out of window, then the plasma concentration from that visit and all subsequent visits will be excluded from the PK summary. The number and percentage of subjects with at least one measurement excluded from the PK analysis will be summarized by PS0010/PS0011 treatment group.

Change #5

Page 19 Section 6.2 Other Baseline Characteristics, deleted the text "Prior biologic therapy (yes, no)

Change #6

Page 20 Section 8.1.2 Derivation of Duration of Exposure, added the text, "and the date of last dose plus 28 days extends beyond the date of death."

Change #7

Page 20 Section 8.1.3 Derivation of exposure at risk, added the text, "Throughout this section, date of last clinical contact for each subject is defined as the maximum of [last visit date including SFU visits, last imputed AE start date, date of study termination or completion, last date of study drug administration]."

Change #8

Page 232 Section 8.2.1 TEAEs, added the following text.

Adverse events that occur on the PS0011 baseline visit date will be attributed to the PS0010 treatment. The only exception to this definition is for the following types of events:

- Those that code to a High Level Term (HLT) of "Injection Site Reactions"
- Those which have been designated as an Injection Reaction on the AE CRF and do not code to a System Organ Class (SOC) of "Investigations"
- Those which have been identified as a hypersensitivity reaction or an anaphylactic reaction

When any of these events occur on the date of treatment switch at PS0011 Baseline, the AE will be attributed to the treatment initiated in PS0011.

Change #9

Page 24 Section 8.2.1 TEAEs, added the text, "The number and percentage of subjects experiencing fungal infections will be summarized by region and country by PS0011 treatment group. This summary will also include the number and percentage of subjects experiencing the PT "Oral Candidiasis" by region and country."

Change #10

Page 26 Section 8.2.1 TEAEs, added the text:

"Additional tables will summarize TEAEs by responder status (defined as PS0010 Week 12 PASI90 response):

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 subject years by SOC, HLT and PT
- Incidence of Serious TEAEs per 100 subject years by SOC, HLT and PT
- Incidence of Fungal Infectious Disorders per 100 subject years by SOC, HLT and PT"

Change #11

Page 26 Section 8.2.2 Clinical laboratory evaluations, removed "Atypical lymphocytes" from laboratory measurements in Table 8-1.

Change #12

Page 32 Section 9.1, Pharmacokinetics, the following text was added, "If the dosing for a visit is +/- 7 days out of window, then the plasma concentration from that visit and all subsequent visits will be excluded from the analysis."

Change #13

Page 32 Section 9.1, Pharmacokinetics, the following text was changed

From

The bimekizumab concentrations will also be listed.

To

The bimekizumab concentrations, including the concentrations excluded from the summaries, will also be listed.

Change #14

Pages 32-33 Section 9.2.1 Anti-bimekizumab antibodies, the following sentences were deleted.

"The impact of positive anti-BKZ antibody status on corresponding c_{trough} concentrations will be summarized for each PS0010/PS0011 treatment group and overall."

"Similar line plots will be produced showing the percentage of persistent and transient anti-BKZ positive antibody subjects."

Change #15

Page 33 Section 10.1 Statistical analysis of the efficacy variables, added the text "Unless otherwise specified, summary tables for efficacy endpoints by PS0010/PS0011 treatment group will present data separately by responder status (defined as PS0010 Week 12 PASI90 response)."

Change #16

Pages 34-35 Section 10.1.1.2 Analysis of PASI score and response, the following text was added:

"Summaries of PASI score and response will include PS0011 visits. PS0010 visits will be shown for select summaries as specified."

"Summaries for PASI90 and PASI100 response will include PS0010 visits."

"PASI90 and PASI100 response relative to the PS0010 Baseline will also be summarized descriptively using counts and percentages by PS0011 treatment group and visit. Missing data will be imputed via NRI."

"The percent change from PS0010 Baseline in PASI score will also be presented using descriptive statistics by PS0011 treatment group and visit. Missing data will be handled using the same multiple imputation as described above."

"The number and percentage of subjects who achieve an absolute PASI score ≤1, ≤2, ≤3, and ≤5 at each visit will be summarized by both PS0010/PS0011 treatment group and PS0011 treatment group. Missing data will be imputed using NRI. These summaries will include PS0010 visits."

Change #17

Page 36 Section 10.1.1.2 Analysis of PASI score and response, the following text was changed:

From

Missing data for the continuous change from Baseline and percent change from Baseline variables will be handled by using MI via the MCMC method. Details on how the descriptive statistics are to be derived are included in Section 4.2.2. Supportive summaries will be based on observed data.

To

Missing data for the continuous change from Baseline and percent change from Baseline variables will be handled by using MI via the MCMC method specified in Section 4.2.2. Supportive summaries will be based on observed data.

Change #18

Page 36 Section 10.1.2.2 Analysis of IGA response, the following text was changed

From

The number and percentage of subjects achieving an IGA response (defined as clear (0) or almost clear (1) with at least two category improvement from Baseline) will be summarized descriptively using counts and percentages by PS0010/PS0011 treatment group and visit. Missing data will be imputed via NRI.

To

The number and percentage of subjects achieving an IGA response (defined as clear (0) or almost clear (1) with at least two category improvement from Baseline) will be summarized descriptively using counts and percentages by PS0010/PS0011 treatment group and visit. Summaries of PASI score and response will include PS0011 visits. PS0010 visits will be shown for select summaries as specified.

The following text was added:

"The IGA response variables will be derived relative to both the PS0010 Baseline and the PS0011 Baseline for subjects who are not PS0010 Week 12 PASI90 responders in the following treatment groups: Placebo to BKZ 160mg, BKZ 64mg to BKZ 160mg, BKZ 160mg to BKZ 320mg, BKZ 320mg to BKZ 320mg, and BKZ 480 mg to BKZ 320mg. PASI response will be calculated relative to the original PS0010 Baseline only for subjects who are PS0010 Week 12 PASI90 responders in the following treatment groups: Placebo to Placebo, BKZ 64mg Q4W to BKZ 64mg Q4W, BKZ 160mg Q4W to BKZ 160mg Q4W, BKZ 320mg Q4W to BKZ 320mg Q4W, and BKZ 480mg Q4W to BKZ 320mg Q4W. Missing data will be imputed via NRI. Summaries for IGA response will include PS0010 visits.

IGA response relative to the PS0010 Baseline will also be summarized descriptively using counts and percentages by PS0011 treatment group and visit. Missing data will be imputed via NRI."

Change #18

Page 36 Section 10.1.3 Analysis of BSA, added the following text

"The percent change from PS0010 Baseline in BSA will also be presented using descriptive statistics by PS0011 treatment group and visit. Missing data will be handled using the same multiple imputation as described above."

"The number and percentage of subjects who achieve BSA =0%, ≤1%, ≤3%, and ≤5% at each visit will be summarized by both PS0010/PS0011 treatment group and PS0011 treatment group. Missing data will be imputed using NRI. These summaries will include PS0010 visits."

Change #19

Page 38 Section 10.1.4.2 Analysis of DLQI, added the text, "The number and percentage of subjects achieving a DLQI score of 0 or 1 at each visit will also be summarized descriptively using counts and percentages by PS0011 treatment group and visit. Missing data will be imputed via NRI."

Change #20

Page 40 Section 10.1.7.2 Analysis of PSSI, added the text, "The percent change from PS0010 Baseline in PSSI score will also be presented using descriptive statistics by PS0011 treatment group and visit. Missing data will be handled using the same multiple imputation as described above."

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 Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

Name: ps0011-sap-amendment 1

Version: 2.0

Document Number: CLIN-000119638

Title: PS0011 - Statistical Analysis Plan Amendment 1

Approved Date: 11 Jan 2019

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 10-Jan-2019 20:46:14 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 11-Jan-2019 10:38:27 GMT+0000