STATISTICAL ANALYSIS PLAN AMENDMENT 1

Study: PS0018

Product: Bimekizumab (UCB4940)

A MULTICENTER, 48-WEEK, OPEN-LABEL EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

PHASE 2

SAP/Amendment Number	Date
Final SAP	14 September 2017
SAP Amendment 1	29 October 2018

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LIST OF TABLES

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LIST OF ABBREVIATIONS

ACP	above cut point
ADA	anti-drug (bimekizumab) antibody
AE(s)	adverse event(s)
AESM	adverse events of special monitoring
ALC	absolute lymphocyte count
ALP	alkaline phosphatase
ALQ	above the limit of quantification
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BCP	below cut point
BKZ	bimekizumab
BLQ	below the limit of quantification
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CIs	confidence interval(s)
CP	confirmed positive
CRP	C-reactive protein
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DEM	data evaluation meeting
DMC	Data Monitoring Committee
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic Case Report Form
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set

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FSH	follicle stimulating hormone
geoCV	geometric CV
GGT	gamma glutamyltransferase
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale -Anxiety
HADS-D	Hospital Anxiety and Depression Scale -Depression
HLT	high level term
IGA	Investigator's Global Assessment
IMP	investigational medicinal product
LCL	lower confidence limit
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov Chain Monte Carlo
MCV	mean corpuscular volume
MedDRA®	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NCP	not confirmed positive
NRI	non responder imputation
PASI	Psoriasis Area and Severity Index
PBO	placebo
PCS	potentially clinically significant
PK	pharmacokinetics
PK-PPS	Pharmacokinetic Per-Protocol Set
PT	preferred term
Q4W	every four weeks
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE(s)	serious adverse event(s)
SAP	statistical analysis plan
sc	subcutaneous
SD	standard deviation

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SFU	Safety Follow-Up
SIB	suicidal ideation and behavior
SMQ	standard Medical Dictionary for Regulatory Activities query
SOC	system organ class
SS	Safety Set
TB	tuberculosis
TEAE(s)	treatment-emergent adverse event(s)
TEMA	treatment-emergent markedly abnormal
TFLs	tables, figures and listings
ULN	upper limit of normal
WBC	white blood cell
WD	withdrawal
WHODD	World Health Organization Drug Dictionary

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1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all information that is necessary to perform the required statistical analysis of study PS0018. It also defines the summary tables, figures and listings (TFLs) to be included in the final clinical study report (CSR) according to the protocol.

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

- Final protocol dated 01 August 2016
- Protocol amendment 1 dated 06 September 2016
- Protocol amendment 2 dated 23 September 2016
- Protocol amendment 3 dated 16 February 2018

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

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

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

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 objectives

Secondary objectives of the study are:

- To assess the safety and tolerability of increasing the dose of bimekizumab from 160mg every four weeks (Q4W) to 320mg Q4W for subjects with an inadequate response at Week 12
- To assess pharmacokinetics (PK) of bimekizumab
- To assess the immunogenicity of bimekizumab
- To assess the efficacy of open label bimekizumab 160mg Q4W administered over 48 weeks

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2.2 Study variables

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 Secondary safety variables

Change from Baseline variables will be defined relative to the Baseline measurement from PS0016.

The other safety variables are:

- Severity and frequency of TEAEs
- 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 variables

The PK variables are:

- Plasma concentrations of bimekizumab

2.2.3 Immunogenicity variable

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

2.2.4 Efficacy variable

Change from Baseline variables will be defined relative to the Baseline measurement from PS0016.

The efficacy variables are listed below and will be evaluated at all scheduled visits in accordance with the schedule of assessments in Table 5–1 of the clinical study protocol.

- Psoriasis Area and Severity Index (PASI)50, PASI75, PASI90, and PASI100 response
- Investigator's Global Assessment (IGA) response (Clear or Almost Clear with at least a 2 category improvement from Baseline on a 5-point scale)
- Absolute and percent change from Baseline in PASI score
- Shift from Baseline in IGA score
- Absolute and percent change from Baseline in the body surface area (BSA) affected by psoriasis
- Change from Baseline in the Hospital Anxiety and Depression Scale (HADS) Anxiety (HADS-A) and Depression (HADS-D) scores

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- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores)

2.3 Study design and conduct

PS0018 is a multicenter, 48-week, open-label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult subjects with moderate to severe chronic plaque psoriasis who participated in PS0016.

During the Open-Label Treatment Period, subjects will attend study visits at the site Q4W for study assessments and administration of bimekizumab by study site staff through Week 48. Following completion or Withdrawal (WD) from the 48-week Open-Label Treatment Period, subjects will return for a Safety Follow-Up (SFU) Visit 20 weeks after their last dose of bimekizumab. Subjects withdrawing early from the study will also undergo the WD assessments and will enter the SFU Visit.

Bimekizumab will initially be administered at a dose of 160mg Q4W subcutaneously (sc) during the 48 week Open-Label Treatment Period. There will be an option to increase the dose to 320mg Q4W at the discretion of the Investigator if the subject's PASI reduction is ≥50% to <75% from the PS0016 Baseline at Week 12 or later in the PS0018 study. If the subject's disease is adequately controlled on the 320mg Q4W dose, they may return to 160mg Q4W at the discretion of the Investigator. The decision to return to 160mg Q4W dosing should be based upon treatment response, tolerability, and Investigator discretion, with the aim to use the dosing regimen that achieves the optimal benefit-risk for each subject. If a subject does not achieve a PASI50 at Week 12 or later during the PS0018 study based on change from PS0016 Baseline then they will be withdrawn from the study.

2.4 Determination of sample size

Up to 45 subjects are anticipated to enroll in PS0018. This number is based on the fact that 45 subjects are planned to be randomized in the feeder study, PS0016. The calculations to reach that sample size are outlined in the PS0016 protocol. As the primary objective of the PS0018 study is to assess the long-term safety and tolerability of bimekizumab 160mg Q4W, the number of subjects anticipated is based on the number of subjects completing PS0016 and meeting eligibility requirements for PS0018.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

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

All analyses will be performed using SAS version 9.3 or higher (SAS Institute, Cary, North Carolina, United States).

Continuous variables will be summarized by PS0016 randomized treatment group, visit and timepoint (where applicable) including number of subjects (n), mean, standard deviation (SD), median, minimum, maximum and confidence intervals (CI) where stated in the SAP. Categorical variables will be summarized by PS0016 randomized treatment group, visit and timepoint (where applicable) with frequency counts and percentages. Coefficient of variation (CV), geometric mean and 95% CI for the geometric mean will also be presented in the descriptive statistics for

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the PK concentration data. In all outputs the confidence limits will be restricted to the possible values that the variable can take.

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

- For values where all subjects fulfill certain criteria, the percentage value will be displayed as 100
- For values where the absolute frequency is zero, there will be no percentage displayed at all
- All other percentage displays will use 1 decimal place
- Percentages displayed based on continuous data (eg percentage changes from baseline) will be displayed to 1 decimal place. Unless otherwise stated, the denominator for the percentages will be based on the number of subjects in the respective analysis.
- When reporting descriptive statistics, the following rules will apply in general (with the exception of PK concentration data, for which additional rules are stated below):
- n will be an integer
- Mean (arithmetic and geometric), SD and median will use 1 decimal place more than the original data
- CV will be reported as a percentage to 1 decimal place
- Minimum and maximum will be reported using the same number of decimal places as the original value
- If no subjects have data at a given timepoint, for example, then only n=0 will be presented. If n<3, then only the n, minimum and maximum will be presented. If n=3, then only n, median, minimum and maximum will be presented. The other descriptive statistics will be left blank

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

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

All tabulations will be presented by treatment group, visit and timepoint (where applicable). In the tabulations, the order the treatment groups will be displayed is detailed in Section 3.6.

Data listings containing all documented data and all derived data will be generated. Data listings will highlight the dose switching; all timepoints on or after the dose increases to 320mg Q4W will be flagged, up to the time point the dose switches back to 160mg Q4W.

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3.2 General study level definitions

3.2.1 Analysis time points

3.2.1.1 Relative day

Relative day for an event will be derived with the date of the first sc injection of investigational medicinal product (IMP) in PS0018 as reference.

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

$$Relative\ Day = Event\ Date - Date\ of\ First\ Injection\ in\ PS0018 \quad [1]$$

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

$$Relative\ Day = (Event\ Date - Date\ of First\ Injection\ in\ PS0018) + 1 \quad [2]$$

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

$$Relative\ Day = Event\ Date - Date\ of\ Last\ Injection\ in\ PS0018 \quad [3]$$

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

For AE listings only, relative day will, in addition, be calculated with respect to the first sc injection in PS0016.

3.2.1.2 Study periods

For each subject, the study duration is estimated to be up to a maximum of 64 weeks:

- Open-Label Treatment Period: 48 weeks
- SFU Visit: 20 weeks after the last dose of study medication scheduled at Week 44

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

3.2.2 Daylight saving dates

Daylight saving dates will be considered in the calculation of the absolute scheduled and actual times and in the duration when this is based on times. Therefore, if any daylight saving change occurs during the study development, this will impact the description of the blood sample collections, the calculation of the PK parameters, and any AE duration in case the time is included in the calculation of the duration.

3.3 Definition of Baseline values

Baseline is defined as the last available value prior to the first injection of study medication in the PS0016 study.

All changes from Baseline refer to changes from PS0016 Baseline, unless stated otherwise. Scheduled or unscheduled measurements can be used as the Baseline value in either case. Measurement specific Baseline timepoints are presented in Table 3–1.

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Table 3–1: Definition of Baseline

Category	Measurement or analysis	Definition of Baseline
Safety	Clinical laboratory values (chemistry, hematology, and urinalysis) Vital signs 12-lead ECG results	PS0016 Baseline Visit or if missing the PS0016 Screening results.
Safety	C-SSRS	The 'Baseline' version of the questionnaire will be completed at PS0016 Screening and the 'Since Last Visit' version will be completed at all subsequent visits.
Efficacy	PASI score IGA score BSA affected by psoriasis HADS	PS0016 Baseline Visit or if missing the PS0016 Screening results
Immunological	ADA	PS0016 Baseline

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

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

The rollover visit from PS0016 will be the entry visit into PS0018. The day of first dose will be labelled as PS0018 Week 0 in the tabulations, and will be included in any change from PS0016 Baseline summaries.

3.4 Protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct or on the key safety, efficacy or PK outcomes for an individual subject. The criteria for identifying such protocol deviations will be defined within the protocol deviation specifications document which is part of the data cleaning plan. Important protocol deviations will include the following categories:

- Inclusion criteria deviation
- Exclusion criteria deviation
- Withdrawal criteria deviation
- Prohibited concomitant medication use
- Incorrect treatment or dose
- Treatment non-compliance
- Procedural non-compliance

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

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

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

3.5 Analysis sets

3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent for PS0018. This is equivalent to All Subjects Screened.

3.5.2 Safety Set

The Safety Set (SS) will consist of all subjects who received at least 1 dose of the study medication in PS0018.

Safety variables will be summarized on the SS.

3.5.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all enrolled subjects who received at least 1 dose of the study medication and have a valid efficacy measurement for PASI at PS0018 Week 0.

Efficacy variables will be summarized based on the FAS.

3.5.4 Pharmacokinetic-Per Protocol Set

The Pharmacokinetic-Per Protocol Set (PK-PPS) will consist of all enrolled subjects who received at least one dose of the study medication, provide at least one quantifiable plasma concentration postdose in PS0018, and have no important protocol deviations that impact the pharmacokinetics.

Pharmacokinetic and immunology variables will be summarized on the PK-PPS.

3.6 Treatment assignment and treatment groups

Treatment assignment for the SS and PK-PPS will be according to the actual treatment received in PS0018, unless stated otherwise in Table 3–1. Analyses of efficacy data (based on the FAS) will be conducted according to the PS0016 randomized treatment group.

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

Listings will be presented by subjects as randomized in PS0016. Summaries will be presented by treatment group and overall where applicable. See Table 3–1 for the treatment assignment of the 3 different sets of treatment groups.

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In the TFLs the treatment groups based on the PS0016 randomized treatment group will be displayed as follows, where BKZ refers to bimekizumab and PBO refers to placebo:

- BKZ 320mg + PBO
- BKZ 320mg
- All Subjects

In the TFLs the treatment groups based on the actual PS0018 treatment received (ie PS0018 dose at onset of event or measurement) will be displayed as follows:

- BKZ 160mg Q4W
- BKZ 320mg Q4W
- All BKZ

Lastly there will be the grouping based on dose adjustment in PS0018 defined as follows:

- Nonadjusters – This group consists of subjects who do not experience a dose adjustment during the study.
- Single adjusters – This group consists of subjects who experience just one dose adjustment during the study. Per the protocol, if just a single adjustment occurs, then that adjustment must go from bimekizumab 160mg Q4W to 320mg Q4W.
- Multiple adjusters – This group consists of subjects who experience more than 1 dose adjustment during the study. This means that the subjects in this group dose adjust from bimekizumab 160mg Q4W to 320mg Q4W and then adjust back to 160mg Q4W (with further dose adjustments possible).

For summary purposes, the single and multiple adjuster groupings will be combined.

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The treatment group labels and tabulation requirements for each data type are displayed in Table 3–1 **Error! Reference source not found.**.

Table 3–1: Treatment group assignment for the TFLs

	PS0016 randomized treatment group			PS0018 dose at onset			Dose adjustment group	
TFL group	**BKZ 320mg + PBO**	**BKZ 320mg**	**All Subjects**	**BKZ 160mg Q4W**	**BKZ 320mg Q4W**	**All BKZ**	**Non-adjuster**	**Adjuster**
Subject disposition	X	X	X					
Protocol deviations	X	X	X					
Demographics	X	X	X					
Medical history	X	X	X					
Prior/concomitant medications	X	X	X					
Compliance	X	X	X					
Exposure				X	X	X		
AEs [a]	X	X	X	X	X	X	X	X
Safety data (including vital signs, ECGs and laboratory tests)	X	X						
Efficacy (except PASI)	X	X	X					
PASI	X	X	X				X	X
Pharmacokinetic data	X	X						
ADA	X	X						

ADA= anti-bimekizumab drug antibody; AE=adverse events; ECG= electrocardiogram; IMP= investigational medicinal product; Q4W= every four weeks; TFL= tables, figures, and listings.

[a] Select tables presenting TEAEs by PS0016 randomized treatment group and Dose adjustment group, as defined in Section 11.2.3.

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3.7 Center pooling strategy

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

3.8 Coding dictionaries

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

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

3.9 Changes to protocol-defined analyses

Change from Baseline in physical examination is listed as a secondary safety variable, in Section 2.2.1.2. Only whether the physical examination was performed and the date it was performed is recorded on the CRF. Thus no summaries for the change from Baseline in physical examination will be provided."

For the continuous efficacy variables based on the change from Baseline (PASI, BSA, and HADS), imputation for missing values in the protocol is based on multiple imputation (MI) via the Markov Chain Monte Carlo (MCMC) method. However, due to the smaller sample size in PS0018 this may cause problems in the algorithm. For this reason and for consistency with the PS0016 SAP, imputation in PS0018 will instead be based on last observation carried forward (LOCF).

For the dose adjustment groupings, the single and multiple dose adjuster groupings will be combined for summary purposes, unless stated otherwise.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

There will be no adjustments for covariates.

4.2 Handling of dropouts or missing data

If a subject does not achieve a PASI50 at Week 12 or later during the open-label treatment period then they will be withdrawn from the study, in order to provide the subjects with alternative therapy to treat the condition. Therefore, in many cases, missing data due to study treatment discontinuation will occur. For missing continuous data single imputation by means of LOCF will be applied.

Missing data for the binary response variables will be imputed using non responder imputation (NRI), ie subjects with a missing score at a specific visit will be considered as non-responders for the summaries. This will include visits after the point of withdrawal.

Supportive summaries will be based on observed case data and will be repeated for all analyses presented with imputation.

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

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4.2.1 Efficacy data

4.2.1.1 Psoriasis Area and Severity Index

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

For the summaries of the observed, change and percentage change from PS0016 Baseline in PASI score, LOCF will be applied to address the issue of missing scores as described in Section 4.2. There will be no imputation of missing individual item scores in the summaries for the PASI; LOCF will apply to the overall PASI score only.

Missing data for the binary response variables (PASI50, PASI75, PASI90 and PASI100) will be imputed using NRI for the summaries. This will include visits after the point of withdrawal.

4.2.1.2 Body surface area

Missing body surface area (BSA) data will be handled using LOCF as described in Section 4.2.

4.2.1.3 Investigator's Global Assessment

There will be no imputation of missing individual data for the IGA score. For the responder analysis, missing data will be imputed using NRI, ie subjects with missing data at a specific visit will be considered as non-responders for the analysis. This will include visits after the point of withdrawal if applicable.

4.2.1.4 Hospital Anxiety and Depression Scale

Missing data for the individual items of the HADS will be imputed as described in Section 8.1.3 in order to calculate the HADS-A and HADS-D scores at each visit. Missing HADS-A and HADS-D domain scores will be handled using LOCF as described in Section 4.2.

4.2.2 Safety laboratory data

Measurements below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the purpose of calculating change from PS0016 Baseline and for descriptive statistics. Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper quantification limit.

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

4.2.3 Bimekizumab concentration data

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

For the individual figures, any concentrations that are BLQ will be imputed with LLOQ/2.

Additional rules for PK data summaries are provided in Section 9.

4.2.4 Dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent

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- Classification of medications as prior or concomitant

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

The following rules will be applied for partial start dates with respect to the first dosing in PS0018:

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

The following rules will be applied for partial stop dates:

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

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

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

Data availability	Onset date/time	Outcome date/time	Calculation rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1)*24 + (T2 – T1)]/24 d

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

Data availability	Onset date/time	Outcome date/time	Calculation rules
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format) Duration = <[(D2 – D1)*24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by time 00:00h. Duration = <[(D2 – D1)*24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = <D2 – D1 + 1
Start day and time missing	--/--	D2/T2	Duration = <[(D2 – D0)*24 + (T2 – T0)]/24 d For a subject in the SS, D0 and T0 are the date and time of first administration of PS0018 study medication and for PS0018 screen failures, duration will not be calculated.
End day and time missing	D1/T1	--/--	If the stop date is missing, duration will not be calculated.
Start and end date missing	--/--	--/--	If the stop date is missing, duration will not be calculated.

IMP=investigational medicinal product; SS=Safety Set.

4.3 Handling of repeated and unscheduled measurements

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

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

4.4 Handling of measurements obtained at the withdrawal visit

Subjects who withdraw from the PS0018 study prematurely will be encouraged to return for the early WD visit and the SFU Visit, the latter at 20 weeks following the final dose of study medication.

The following rules will apply with regard to the inclusion of the results obtained at the early WD visit in the descriptive summaries:

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- Any efficacy, PK, immunological and safety measurements conducted at the early WD visit should be included in the summaries for the respective scheduled visit, if the early WD visit occurs at the time of the next scheduled visit (within the tolerance window specified in the protocol). For example, if the early WD visit occurs on Day 28, the results would be summarized together with the Week 4 results.
- If the early WD visit does not correspond to the day of a scheduled visit, all assessments of the early WD visit should be mapped to the nearest scheduled visit, relative to the PS0018 Week 0 visit date, following the last scheduled visit where assessments are available.
- If the date of the early WD visit is equidistant between 2 scheduled visits at which no scheduled assessments were performed, the assessments from the early WD visit will be mapped to the earlier of these visits.
- If an EW visit mapping results in data being mapped to a visit where the specific assessment is not actually collected per the protocol schedule of assessments, these data will not be included in the summary statistics and will be listed only.
- The only exception to the above rule is for ADA (for both BKZ and CZP) assessments, in which all early withdrawal visit assessments will be assigned to the next scheduled visit at which ADA are assessed. The rationale for this is that ADA positivity is summarized over a given study period. As part of that summary, a table indicating the first visit at which ADA positivity is observed will be presented. In order to match the number of subjects who were ADA positive at specific visits with the overall positivity for the period, it is necessary to ensure that ADA positivity is attributed to a visit where ADA antibody assessments were performed.

Assessments from the EW visit will be displayed as the mapped visit and will be flagged in the by-visit data listings.

For example, vital sign assessments are performed at PS0018 Weeks 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40 and 44. If a subject discontinues on Day 37, and the previous vital sign assessment was done at Week 4 (Day 28), the nearest scheduled assessment (following the last visit at which assessments were available) would be Week 8 (Day 56). Therefore, the early WD visit assessment should be re-assigned to the Week 8 visit.

However, if a subject discontinues at Day 37, and the previous vital sign assessment was done at PS0018 Week 0, the early WD visit assessments would be re-assigned to the Week 4 (Day 28) visit, which would be the nearest scheduled visit relative to the PS0018 Week 0 visit date.

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

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4.5 Interim analyses and data monitoring

There will be no interim analysis.

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

The detailed role, scope, responsibilities and complete procedures as well as the identity of the DMC members will be described in a separate DMC Charter. The details regarding the outputs to be produced and the analyses to be performed for the DMC review will be provided in a separate DMC SAP.

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

4.6 Multicenter studies

Individual center results will not be displayed.

4.7 Multiple comparisons/multiplicity

Not applicable.

4.8 Use of an efficacy subset of subjects

Not applicable.

4.9 Active-control studies intended to show equivalence

Not applicable.

4.10 Examination of subgroups

Not applicable.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

The number and percentage of subjects who were enrolled into the PS0018 study, subjects who completed or prematurely discontinued the PS0018 study, as well as the reason for discontinuation will be presented by PS0016 randomized treatment group and for all subjects, based on the SS. Subjects withdrawn from the study due to not achieving PASI50 at week 12 or later will be presented in the summary under primary reason for discontinuation in the category 'Lack of efficacy'.

The number and percentage of subjects who discontinued due to AEs will be separately summarized by PS0016 randomized treatment group for all subjects, based on the SS.

The number and percentage of subjects included into each of the analysis sets will be summarized by PS0016 randomized treatment group and for all subjects based on the ES (all subjects screened). Percentages will be based on the SS for the purpose of this summary.

Finally, screen failure reasons will be listed, including glossary and summarized, based on the ES.

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A subject who completed the study is defined as a subject having completed the 48 weeks of Open-Label Treatment Period.

In addition, the following listings will be presented by PS0016 randomized treatment group:

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

The listing of subject disposition will include the date of informed consent, date and time of first and last dose of study medication in PS0018, date of premature termination (and primary reason) and date of final contact.

The listing of study discontinuation will include the reason for discontinuation and the total days on study medication relative to first dose in PS0018.

A summary of the dose adjustment grouping (nonadjuster, single adjuster, and multiple adjuster) will be presented by the FAS and SS, respectively.

The number of days on PS0018 study medication will be calculated as follows:

$$Number\ of\ Days\ on\ Study\ Medication = (Date\ of\ Last\ Dose\ Received - Date\ of\ First\ Dose\ Received) + 1 \quad [4]$$

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types listed in the protocol deviation specification document. A listing of all important protocol deviations will be presented for all subjects by PS0016 randomized treatment group and will include the deviation type and description. The number and percentage of subjects with important protocol deviations will be summarized by PS0016 randomized treatment group and for all subjects for each deviation type, based on the SS.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Derivation of variables

Demographic and baseline characteristics are based on data recorded at the PS0016 Baseline visit.

6.1.1 Calculation of body mass index

The body mass index (BMI) in kg/m2 is calculated based on the height (in m) and the weight (in kg) using the following formula:

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

The BMI will be reported to 1 decimal place.

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6.1.2 Classification of age categories

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

For the EudraCT reporting, the categories will include:

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

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

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

6.2 Demographics

A by-subject listing of Baseline demographic characteristics will be presented by PS0016 randomized treatment group based on all subjects screened, ie ES. This will include the year of birth (if available), age (in years), sex, race, ethnicity, height (in cm), weight at PS0016 Screening (in kg) and BMI for all subjects enrolled into PS0018. The age will be directly entered into the study database and will not be re-calculated for the statistical analysis.

All Baseline demographic characteristics (with the exception of year of birth) will be summarized by PS0016 randomized treatment group and for all subjects based on the SS. The summary of age will include descriptive statistics and categorical summaries, the latter based on requirements for EudraCT and clinicaltrials.gov reporting.

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

6.3 Other Baseline characteristics

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

- *Percentage BSA involvement
- *PASI total score
- IGA score
- *HADS-A and HADS-D scores

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

The Baseline characteristics listed above will be summarized using descriptive statistics (for continuous variables only*). The IGA score will be summarized including the number and percentage of subjects with each specific IGA score.

The tabulation will be presented by PS0016 randomized treatment group and for all subjects based on the FAS.

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6.4 Medical history and concomitant diseases

Medical history not reported in PS0016 will be listed for the SS by PS0016 randomized treatment group. The reported term will be included in the listing as well as whether the condition is related to psoriasis (yes/no). A glossary of all medical history conditions will be presented for the SS including the system organ class (SOC), preferred term (PT) and reported term.

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

6.5 Prior and concomitant medications

Prior and concomitant medications will be listed for the SS by PS0016 randomized treatment group and subject and summarized for the SS by WHODD Anatomical Main Group (Level 1), Pharmacological Subgroup (Level 3) and PT. Tabulations will be presented by PS0016 randomized treatment group and for all subjects, with separate tabulations for prior (and concomitant categories.

All tabulations will be sorted alphabetically by Level 1 term, alphabetical Level 3 term within Level 1 and decreasing frequency of PT in the 'All Subjects' column.

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

6.5.1 Prior medication definition

Prior medications include any medications that started prior to the date of administration of the first dose of PS0018 study medication.

6.5.2 Concomitant medication definition

Concomitant medications are medications taken on or after the start of PS0018 study medication and up to and including 28 days after last dose, ie during the Open-Label Treatment Period.

Any medication that started prior to PS0018 dosing and continued after dosing will therefore be classified as both prior and concomitant. Such medications will therefore be counted in tabulations for both prior and concomitant categories.

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

7 MEASUREMENTS OF TREATMENT COMPLIANCE

During the Open-Label treatment period of this study, study medication will be administered in the clinic and compliance will be determined at the visit by study personnel.

Due to the method of administration of the treatments, compliance will be examined in terms of completed number of injections. One dose of 160 mg requires one injection, one dose adjustment of 320 mg requires two injections. A dose reduction from 320 mg back down to 160 mg is allowed.

Treatment compliance will be calculated as:

$$\textit{Overall compliance (\%)} = \frac{\textit{total number of completed injections}}{\textit{total number of expected injections}} \times 100 \quad [6]$$

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where the total number of expected injections is derived relative to when the subject finishes treatment. If a subject discontinues early, then the number of expected completed injections is based on the date of early discontinuation relative to the dosing visits. The planned dose recorded at a given visit will indicate if one injection for bimekizumab 160 mg Q4W, or two injections for bimekizumab 320mg Q4W are expected to be given. If a subject completes treatment with no dose adjustment, 12 injections are expected (one each at Weeks 0, 4, 8, 12, etc. through to Week 44).

The calculated overall compliance will be listed by PS0016 randomized treatment group and subject, and summarized by PS0016 randomized treatment group, based on the SS. The summary will include both descriptive statistics for overall compliance (n, mean, SD, median, minimum and maximum) and the number and percentage of subjects based on the following classifications:

- Compliance ≤80.0%
- Compliance >80.0%

8 EFFICACY ANALYSES

All efficacy listings will be based on the FAS and be summarized based on this population. Changes and improvements from Baseline are relative to PS0016 Baseline.

Supportive summaries based on observed case data will be included for all analysis based on imputations, see Section 4.2.

8.1 Derivations of efficacy variables

8.1.1 Psoriasis Area and Severity Index

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

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

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

A=area of involvement score; BSA=body surface area; PASI=Psoriasis Area and Severity Index
a Where 0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected.

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

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

$$\text{PASI} = 0.1 \times [(\text{Rh} + \text{Th} + \text{Sh}) \times \text{Ah}] + 0.2 \times [(\text{Rue} + \text{Tue} + \text{Sue}) \times \text{Aue}$$

$$+0.3[(\text{Rt} + \text{Tt} + \text{St}) \times \text{At}] + 0.4 \times [(\text{Rle} + \text{Tle} + \text{Sle}) \times \text{Ale}] \quad [7]$$

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

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

The highest potential PASI score is 72 for severe disease; the lowest score is 0 which indicates no psoriatic lesions are present. The PASI scores are considered as a continuous variable and will be calculated and presented to 1 decimal place in the listings. The percentage change in PASI score from PS0016 Baseline will be calculated as follows:

$$Percentage\ change\ from\ PS0016\ Baseline =$$

$$100 \times [(PS0018\ PASI - PS0016\ Baseline\ PASI)/PS0016\ Baseline\ PASI] \quad [8]$$

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

A categorical response variable, such as PASI90, is defined to be equal to 1 if the percentage improvement from PS0016 Baseline in the PASI scores is 90% or greater and 0 if the percentage improvement from PS0016 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 secondary efficacy variables PASI50, PASI75, and PASI100 response are equal to 1 for subjects with improvements of 50% or greater, 75% or greater and 100% from PS0016 Baseline in PASI score, respectively (and equal to 0 otherwise).

If a subject does not achieve PASI50 at Week 12 or reverts below PASI50 later during the PS0018 study based on a change from PS0016 Baseline then they will be withdrawn from the study.

8.1.2 Investigator's Global Assessment Response

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

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A clinical response with regard to the IGA is defined as Clear (0) or Almost Clear (1) with at least a 2 category improvement from PS0016 Baseline on a 5-point scale.

Table 8–2: Investigator's Global Assessment

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

For the handling of missing data see Section 4.2.1.3.

8.1.3 Hospital Anxiety and Depression Scale

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

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

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

[redacted]

For the handling of missing domain data see Section 4.2.1.4.

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8.2 Statistical analysis of the primary efficacy variables

In addition to the summaries described below, the impact of dose adjustment on efficacy will be considered. This will be done primarily by using descriptive statistics to summarize PASI score for each visit by PS0016 randomized treatment group and the dose adjustment categories as defined in Section 4.10 along with the All Subjects (ie All BKZ) group. This will be based on observed data only.

8.2.1 Psoriasis Area and Severity Index

The individual scores for the PASI for each body region (redness, thickness and scaliness severity scores and area of involvement score [A]), and the derived total PASI score (from 0 to 72) will be listed for each subject by PS0016 randomized treatment group and visit. The listing will include the change from PS0016 Baseline and percentage change from Baseline for the total score only. Subjects achieving a PASI50, PASI75, PASI90 and PASI100 response at each visit will be flagged in the listing. Missing data will not be imputed for the listings.

Descriptive statistics (including 95% CI) will be presented by PS0016 randomized treatment group and overall and by Dose adjustment, and by visit for absolute values, changes from PS0016 Baseline and percentage change from PS0016 Baseline (based on the total PASI score only). For the purpose of the tabulations the lower and upper 95% confidence limits will be truncated as follows:

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

The following figures will be presented:

- Combined individual (spaghetti) plots displaying percentage change from Baseline in PASI score versus time (visit) by PS0016 randomized treatment group (all subjects will be overlaid on the same plot with separate plots for each PS0016 randomized treatment group)
- Mean (with 95% CI) percentage change from Baseline in PASI score versus time (visit) by PS0016 randomized treatment group (both treatment groups will be overlaid on the same plot)

All tabulations and both individual and mean figures will be presented using the FAS with imputation and observed cases. All listings will be presented using the SS.

For subjects that discontinue the study, missing data will be imputed using LOCF as described in Section 4.2 for the tabulations and mean figures.

Missing data will not be imputed for the individual figures.

Furthermore, a supportive analysis specifically for adjusters will be performed in which PASI score will be summarized by visit, where Baseline is recalibrated for each individual subject and defined as the visit where the bimekizumab 320mg Q4W dose is initiated. The visits summarized

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will be in weeks relative to when the bimekizumab 320mg Q4W dose was started as opposed to the scheduled week of the PS0018 assessment. These summaries will be based on observed data only.

The PASI50, PASI75, PASI90, and PASI100 responses are based on at least 50%, 75%, 90%, and 100% improvement from Baseline in the PASI score. Thus, the following will apply:

- If the percentage improvement is ≥50% then the subject is a PASI50 responder
- If the percentage improvement is ≥75% then the subject is a PASI75 responder (and is a PASI50 responder also)
- If the percentage improvement is ≥90% then the subject is a PASI90 responder (and is a PASI50 and PASI75 responder also)
- If the percentage improvement is 100% then the subject is a PASI100 responder (and is a PASI50, PASI75 and PASI90 responder also)

The number and percentage of subjects achieving a PASI50, PASI75, PASI90, and PASI100 response will be tabulated by visit and overall and by PS0016 randomized treatment group and by Dose adjustment. The 95% CI for the percentage of responders will be calculated using a Wilson approximation and be included in the tabulation.

In addition, the percentage of responders (including 95% CI) will be plotted at each PS0018 visit for each response variable. Separate plots will be presented for each of PASI50, PASI75, PASI90 and PASI100 with both treatment groups overlaid on the same plot. These plots will be presented by PS0016 randomized treatment and by Dose adjustment separately.

For the purpose of the tabulation the lower and upper 95% confidence limits for the percentage of responders will be truncated at 0 and 100% respectively.

Missing data will be imputed using NRI as described in Section 4.2.1.1. Subjects with missing data will be regarded as non-responders for the PASI50, PASI75, PASI90, and PASI100 variables.

The tabulation will also be repeated using observed cases for both treatment assignments that will include a category for missing data. Those who discontinue will be counted in the missing category for this tabulation where applicable. For this tabulation based on observed cases, the denominator for the percentage of responders and non-responders, will be the number of subjects with nonmissing data at the visit.

8.2.2 Change in body surface area affected by psoriasis

The percentage BSA (0 to 100%) affected by psoriasis will be listed by PS0016 randomized treatment, by subject and visit including the percentage change from PS0016 Baseline. Missing data will not be imputed for the listing.

Descriptive statistics will be presented by PS0016 randomized treatment group and overall, by visit for both absolute values and percentage changes from Baseline.

Missing data for the tabulations will be imputed as described in Section 4.2.1.2. Tabulations (absolute values and percentage change from PS0016 Baseline) will be repeated using observed cases for both treatment assignments and will include the category missing.

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8.2.3 Investigator's Global Assessment

The results of the IGA will be listed by PS0016 randomized treatment group, subject and visit. A clinical response with regard to the IGA is defined as clear (0) or almost clear (1) with at least a 2 category improvement from Baseline. Subjects achieving a clinical response will be flagged in the listing at relevant visit timepoints. Missing data will not be imputed for the listing.

The number and percentage of subjects achieving an IGA response at each PS0018 visit will be summarized by PS0016 randomized treatment group and overall. The 95% CI for the percentage of responders will be included, calculated using a Wilson approximation. For the purpose of the tabulation the lower and upper 95% confidence limits for the percentage of responders will be truncated at 0 and 100% respectively.

Missing data will be imputed using NRI as described in Section 4.2.1.3. The tabulation will also be repeated using observed cases for both treatment assignments and will include a category for missing data; those who discontinue will be counted in the missing category for this tabulation where applicable. For the tabulation based on observed cases, the denominator for the percentage of responders and non-responders, will be the number of subjects with nonmissing data at the visit.

Shift tables will be presented for the IGA score, by PS0016 randomized treatment group and overall, at each PS0018 visit, compared to the PS0016 Baseline score.

In addition, a frequency table will be presented showing the number and percentage of subjects with each specific IGA score at each visit by PS0016 randomized treatment group. Both tabulations will include a category for missing data. The denominator for the percentages will be the number of subjects in the FAS, for each PS0016 randomized treatment group. No imputation for missing values will be done for these analyses.

8.2.4 Hospital Anxiety and Depression Scale

The HADS scores for anxiety HADS-A and depression HADS-D each range from 0 to 21with higher scores indicating worse state. A score below 8 is considered to be normal whereas a score of 15 and above is considered severe (Snaith and Zigmond, 1994). The individual items, associated item scores and calculation rules for the anxiety and depression domains are provided in Section 8.1.3.

The results of the HADS will be listed by PS0016 randomized treatment group, subject and visit including the individual item responses and the derived domain scores for HADS-A and HADS-D. Changes from Baseline will be calculated based on the domain scores only, and will be included in the listing. A Glossary will also be included.

Descriptive statistics will be presented by PS0016 randomized treatment group and overall, , by visit for both absolute values and changes from Baseline, separately for each domain HADS-A and HADS-D. Missing data will be imputed as defined in Section 4.2.1.3 and supportive summaries of observed cases will also be included for both treatment assignments.

The number and percentage of subjects with scores categories <8, ≥8 to <11, ≥15 and missing for the HADS-A and HADS-D will be summarized by PS0016 randomized treatment group and overall at each visit based on observed cases. The percentages will be based on the number of available observations at each visit.

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9 PHARMACOKINETICS

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

Individual blood sampling times and concentrations of bimekizumab will be listed by PS0016 randomized treatment group for the SS and will include the actual sampling time in weeks relative to the first PS0018 dose.

Individual concentrations will be summarized by PS0016 randomized treatment group at each scheduled visit based on the PK-PPS, using n, mean, median, SD, minimum, maximum, geometric mean, 95% CI for the geometric mean and geoCV (assuming log-normally distributed data).

Individual concentration versus time (week) profiles will be presented graphically in linear and semi-logarithmic scale with all subjects overlaid on the same plot (spaghetti plots) and separate plots for each treatment group. Geometric mean profiles of bimekizumab will also be presented on both linear and semi-logarithmic scale respectively with and without the corresponding lower and upper limit of the 95% CI for linear and semi-logarithmic plots respectively. Both treatment groups (PS0016 randomized treatment groups) will be overlaid on the same plot. All figures will include the LLOQ on the semi logarithmic plots.

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

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

$$geoCV = [100 \times \sqrt{(e^{SD^2} - 1)}] \quad [9]$$

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

10 IMMUNOLOGY

The results for the anti-drug (bimekizumab) antibody (ADA) measurements will be listed by PS0016 randomized treatment group and timepoint based on the SS, including the screening assay, confirmatory assay and titer (if applicable).

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

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The following definitions will be applied 2 ways: firstly including the PS0018 SFU visit, and then excluding the PS0018 SFU visit:

- An ADA status of positive will be concluded for any subject with an ADA level that is ACP and CP at any timepoint (PS0016 Baseline, Week 4 and Week 8, and all PS0018 visits)
- An ADA status of negative will be concluded for any subject with an ADA level that is either BCP or ACP and NCP at any timepoint (PS0016 Baseline, Week 4 and Week 8, and all PS0018 visits)
- A subject will be classified as having ADA positivity at PS0016 Baseline if the PS0016 Day 1, predose result is ACP and CP
- A subject will be classified as having treatment-induced ADA positivity when meeting one of the following criteria:
  - The PS0016 Baseline result is either BCP or ACP and NCP, and at least one PS0018 timepoint is ACP and CP
  - The PS0016 Baseline result is positive (ACP and CP) and at least one PS0018 measurement shows a pre-defined fold increase in titer from the Baseline value (the fold increase from PS0016 Baseline required to meet this criteria will be defined with the development of the assay and will be included in the TFLs)
- A subject will be classified as overall positive if at least one PS0018 measurement is ACP and CP (this includes subjects who have negative results at Baseline)
- A subject will be classified as overall negative if at all PS0018 visits the ADA status is negative (this includes subjects who have positive [ACP and CP] results at Baseline)

All listings, summaries and figures will include the PS0016 visits Baseline, Week 4 and Week 8 and all PS0018 visits.

The ADA status (positive/negative) will be summarized as a categorical endpoint (number and percentage of subjects) by PS0016 randomized treatment group for all timepoints and overall, based on the SS.

In addition, the first occurrence of treatment-induced ADA positivity (based on the definitions above) will be summarized (number and percentage of subjects) by PS0016 randomized treatment group at the visits PS0016 Baseline and Week 4 and Week 8 of PS0016 and additionally at each PS0018 visit, based on the SS. This tabulation will count the number of subjects at each PS0018 visit who fulfill at least one of the above defined criteria for treatment-induced positivity; subjects will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, subjects will be counted in the denominator (assuming a measurement is available). For all tabulations, percentages will be based on the number of observations at each visit.

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

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

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

11 SAFETY ANALYSES

All analysis of safety variables will be performed using the SS, unless otherwise stated. Changes from Baseline for all safety variables are changes from PS0016 Baseline.

11.1 Extent of exposure

11.1.1 Drug administration

All drug administration details (including date, time of injection, location, side of body and volume delivered) will be listed by subject and visit. The study medication will be given as 1 or 2 sc injections depending on dose, at each planned dosing visit (PS0018 Week 0, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 40 and Week 44).

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

$$\text{Date of last dose in PS0018} - \text{Date of first dose in PS0018} + 28 \quad [10]$$

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:

$$\text{Week 48 visit date} - \text{Date of first dose in PS0018} + 1 \quad [11]$$

For subjects who have died the exposure will be as follows:

$$\text{Date of death} - \text{Date of first dose in PS0018} + 1 \quad [12]$$

For subjects who switched dose during PS0018, the duration of dose within each dose interval (except the last dose interval) will be calculated as:

$$\text{Date of last dose in PS0018} - \text{Date of first dose in PS0018} + 1 \quad [13]$$

The dose taken in the last dose interval will be calculated as:

$$\text{Date of last dose in PS0018} - \text{Date of first dose in PS0018} + 28 \quad [14]$$

In this case duration of exposure will be calculated as the sum of the dose intervals for bimekizumab 160mg Q4W and 320mg Q4W, respectively.

Extent of exposure in PS0018 will be summarized using descriptive statistics and presented by bimekizumab 160mg Q4W, 320mg Q4W, respectively and All bimekizumab.

11.1.2 Subject time at risk

The subject time at risk represents the time a subject was at risk for having an AE and will be used to calculate the exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER) as described in Section 11.2.2.

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

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$$Time\ at\ risk = (Date\ of\ Last\ PS0018\ IMP - Date\ of\ First\ PS0018\ IMP) + 140 \quad [15]$$

This includes the duration of the SFU Period.

For subjects who switch dose during PS0018, time at risk will be derived in each dose interval and calculated as per equation [13] above, and equation [15] will be applied for the dose in the final dose interval.

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

$$Time\ at\ Risk = (Date\ of\ Last\ Contact - Date\ of\ First\ PS0018\ IMP) + 1 \quad [16]$$

This will apply for the following:

- For subjects that discontinue prematurely (ie, and no SFU data are available), the date of final contact refers to the date of the latest contact with the subject during the study PS0018 after which no further information or data are available. This will be reported on the study termination page of the electronic Case Report Form (eCRF).
- For subjects that have died during the study the date of last contact refers to the date of death

The sum of these exposure days at risk across subjects in the relevant PS0018 dose group is converted to years for the EAIR and EAER calculations described in Section 11.2.2.

Subject-years at risk is defined as the subject time (in days) at risk divided by 365.25. The days at risk and subject years at risk will be listed and summed by PS0018 dose at onset, together with the drug administration information (Section 11.1.1).

11.2 Adverse events

11.2.1 Definitions and classification of adverse events

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

Adverse events will be coded according to MedDRA® version 19.0. Treatment-emergent adverse events (TEAEs) will be defined as events that have a start date on or after the first administration of study treatment in PS0018 until the last received dose of study medication +140 days (which covers the 20-week SFU Period). Adverse events occurring after this date will not be classified as TEAEs and will therefore be excluded from the summary tables. TEAEs will be categorized according to the PS0018 dose at onset, ie, the last dose being received at the time of onset of the event. If a TEAE occurs on the same day as a change in dosage and it cannot be clearly established whether or not the TEAE started before or after dosing, because for example the time of the AE is missing, then the TEAE will be attributed to the treatment dose that the subject has just completed, unless the adverse event is related to the injection (ie higher level term (HLT) of "injection site reactions") or an anaphylactic reaction (Section 14.3.7.1), in which case the TEAE will be assigned to the treatment dose administered on that day. Tables will include columns for BKZ 160mg Q4W, BKZ 320mg Q4W, and All BKZ.

Any adverse events considered ongoing from PS0016 which do not worsen in severity during PS0018, or starting prior to first PS0018 dose will not be considered treatment emergent in PS0018 and will be tabulated separately.

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In order to evaluate if there is any difference in the TEAE profile of subjects who have dose adjustments, additional summaries will be generated based on Dose adjustment described in Section 3.6 for select tables as given in Section 11.2.3.

Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to PS0018 dosing. Handling of missing dates/times for classification of AEs as TEAEs is described in Section 4.2.4.

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

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

- Related
- Not related

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

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

- Mild
- Moderate
- Severe

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

All AE data will be presented as recorded in the database for the listings.

11.2.2 Calculation of exposure adjusted incidence and event rates

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

$$EAIR = 100 \times \frac{n}{\sum_{i=1}^{N} TExp,i} \quad [17]$$

In the above equation, N is the total number of subjects at risk (in each PS0018 dose group) and TExp,i is the time at risk for subject i, expressed in years. Subject time at risk represents the time a subject was at risk for having a TEAE calculated as follows:

- For subjects experiencing the specific TEAE the time at risk (TExp,i) is calculated from the time of the first PS0018 dose to the onset of the TEAE. If a subject has multiple events, the time at risk is calculated relative to the first occurrence of the TEAE being considered.
- For subjects who do not experience the specific TEAE the total time at risk (TExp,i) is calculated as described in Section 11.1.2.

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Exact Poisson 95% CIs (lower confidence limit [LCL], upper confidence limit [UCL]) for the EAIR will be calculated using the relationship between the Poisson and the chi-square distribution (Ulm, 1990; Fay and Feuer, 1997):

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \ , UCL = \frac{\chi^2_{2(n+1),1-\frac{\alpha}{2}}}{2} \quad [18]$$

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

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

$$EAER = 100 \times \frac{n_{AE}}{\sum_{i=1}^{N} \text{TRisk,i}} \quad [19]$$

where n_{AE} is the total number of TEAEs and TRisk,i is the time at risk for subject i, expressed in years (calculated as described in Section 11.1.2).

No CIs will be computed for EAER.

11.2.3 Presentation of adverse events

An overview of the number and percentage of subjects who experience TEAEs will be presented based on the SS. This tabulation will include the number and percentage of subjects with any TEAEs, serious TEAEs, related TEAEs, discontinuation due to TEAEs, severe TEAEs, AEs leading to death and TEAEs leading to death; event counts will also be included.

- The tabulation will be presented by PS0018 dose at onset.
- This tabulation will be repeated by Dose adjustment and PS0016 randomized treatment group.

In addition, the following summaries will be presented by PS0018 dose at onset, SOC, high level term (HLT) and PT, based on the SS:

- Incidence of TEAEs by PS0018 dose at onset, including the EAIR and EAER calculated as described in Section 11.2.2 for the 'Any TEAE' category only
- Incidence of TEAEs by PS0018 dose at onset, including the EAIR and EAER calculated as described in Section 11.2.2 for the 'Any TEAE' category only by overall ADA status (positive/negative)
- Incidence of TEAEs by Dose adjustment and PS0016 randomized treatment group
- Incidence of serious TEAEs by PS0018 dose at onset and Dose adjustment
- Incidence of TEAEs by relationship and PS0018 dose at onset
- Incidence of TEAEs by maximum relationship and PS0018 dose at onset
- Incidence of TEAEs by maximum intensity and PS0018 dose at onset
- Incidence of fatal TEAEs by relationship and PS0018 dose at onset

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- Incidence of serious TEAEs by relationship and PS0018 dose at onset
- Incidence of non-serious TEAEs above threshold of 5% of subjects by PS0018 dose at onset
- Incidence of non-serious TEAEs above threshold of 5% of subjects by relationship and PS0018 dose at onset
- Incidence of ongoing AEs from PS0016
- Incidence of ongoing AEs from PS0016 which do not worsen in severity, or AEs started prior to PS0018 dose, by PS0016 randomized treatment group

In addition, separate AE summaries by PS0018 dose at onset, SOC, HLT and PT will be included for the following AEs of special monitoring (AESM) further defined in Section 14.3.

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

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

The criteria for identifying AESM and additional criteria for reporting AESM are provided in Section 14.3.

Adverse event summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing frequency of PT in the 'BKZ 320mg' column for the PS0016 randomized treatment group. In the PS0018 dose at onset tables, the summaries will be presented in a similar manner in decreasing frequency of PT in the 'All BKZ' column.

For tables including only number and percentage of subjects, summaries will be ordered by alphabetical SOC, alphabetical HLT within SOC and decreasing incidence of PT within HLT and SOC in the 'All BKZ' column.

Any adverse events considered ongoing from PS0016 which do not worsen in severity during PS0018 dosing, or starting prior to first PS0018 dose will not be considered treatment emergent in PS0018 and will be tabulated separately.

The AEs will be listed by PS0016 randomized treatment group and include all subjects screened in the ES. The listing will include the onset date/time and outcome date/time of the event (including relative days), the AE duration (derived), dose at onset, days since first dose of study

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medication, days since most recent dose of study medication, pattern of event, intensity, relationship, action taken and outcome. In addition the listing will flag AEs that led to discontinuation, TEAEs, AESM, AEs of special interest (as reported on the eCRF) and SAEs.

A glossary of all TEAE terms will be provided including the SOC, HLT, PT and reported term.

11.3 Clinical laboratory evaluations

Laboratory data (clinical chemistry, hematology, and urinalysis) and changes from Baseline (if applicable) for numeric variables will be listed by PS0016 randomized treatment group and visit. Any laboratory variables with values that are BLQ or ALQ will be handled as described in Section 4.2.2 for calculation of changes from Baseline and for summary tables. Values outside the reference range for the numeric variables will be flagged in the listings.

Clinical chemistry and hematology variables will be summarized by PS0016 randomized treatment group at each visit, for both absolute values and changes from PS0016 Baseline.

Laboratory variables will be grouped according to the laboratory function panel and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory. For selected variables that are identified in Table 11–1, the change in category from Baseline will be presented in shift tables at all PS0018 visits.

The number and percentage of subjects with treatment-emergent markedly abnormal (TEMA) laboratory results will be tabulated by PS0016 randomized treatment group and visit. Markedly abnormal laboratory values will be defined as those categorized as Grade 3 and above based on the ranges defined as per the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (2016). These are provided in Table 14–2. The tabulation will include a category for the incidence of TEMA results over all visits which will also count unscheduled measurements.

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

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

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

Subjects with treatment-emergent liver function test abnormalities at any PS0018 visit will be summarized (number and percentage of subjects) by PS0016 randomized treatment group. The criteria for this tabulation are presented in Table 14–3.

Table 11–1: Clinical laboratory measurements

Category	Panel	Variable
Hematology	Red blood cell	RBC count, hemoglobin, hematocrit
	Red blood cell indices	MCH, MCHC, MCV
	Platelet	Platelets

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Table 11–1: Clinical laboratory measurements

Category	Panel	Variable
	White blood cell	WBC count
	White blood cell differential	Absolute counts: ANC, basophils, eosinophils, ALC, monocytes, atypical lymphocytes (if indicated) Percentages: neutrophils/leukocytes, basophils/leukocytes, eosinophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes.
Chemistry	Electrolytes	Sodium, chloride, potassium, calcium, magnesium
	Kidney function	BUN, creatinine
	Liver function	AST, ALT, GGT, ALP, LDH, total bilirubin (direct bilirubin, indirect bilirubin, if indicated)
	Lipids	Total cholesterol
	Metabolic function	Glucose
	Hormones	FSH[b]
	Fertility	Pregnancy test[a]
	Other	CRP
Urinalysis	Dipstick	pH, protein, blood, leukocyte esterase, nitrite, glucose
	Urine sediment (if indicated)	WBC, RBC, epithelial cells (squamous, transitional and renal tubular), hyaline casts, WBC casts, RBC casts, waxy casts, granular casts, calcium oxalate crystals, uric acid crystals, triphosphate crystals, yeast, bacteria, amorphous urates, amorphous phosphates

ALC=absolute lyphoctye count; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; FSH=follicle stimulating hormone; GGT=gamma glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell
a Pregnancy testing will consist of serum testing at the SFU Visit. The pregnancy test will be urine at all other visits and will be performed locally.
b The FSH test should only be performed on postmenopausal females who have been postmenopausal for ≥1 year and last menstrual cycle occurred <2 years ago.

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

11.4.1 Vital signs

Vital signs will be measured at every visit and will include:

- Systolic and diastolic blood pressure
- Pulse rate
- Body temperature (oral, axillary, or otic)

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Vital signs are to be measured prior to blood sampling, and prior to dosing, where applicable.

A by-subject listing of all vital sign measurements and changes from Baseline will be presented by PS0016 randomized treatment group and visit. The listing will include a flag for measurements identified as TEMA/potentially clinically significant (PCS) as calculated by the criteria outlined in Table 14–4.

Descriptive statistics will be reported for all vital sign measurements. Measured values and changes from Baseline will be summarized by vital signs variable and visit for each PS0016 randomized treatment group.

The number and percentage of subjects with TEMA/PCS vital sign values will be summarized by PS0016 randomized treatment group and variable at each visit and overall (ie across all PS0018 visits).

11.4.2 Body weight

A by-subject listing of body weight will be presented. No summary tabulations will be provided for this variable.

11.4.3 12-Lead Electrocardiograms

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

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

The results of all ECG variables will be reported in the by-subject listings. The listing will also include the change from Baseline for numeric parameters and will be presented by PS0016 randomized treatment group and visit.

Measured values and changes from Baseline will be summarized for each variable by PS0016 randomized treatment group and visit.

The following cut-points in QTcF (raw data and change from Baseline) will be summarized categorically by PS0016 randomized treatment group (number and percentage of subjects) and visit. The denominator for the percentages will be the number of subjects with a non-missing measurement for the variable at the specific visit.

Raw QTcF data:

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

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Change from Baseline QTcF:

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

Electrocardiogram findings will be listed separately.

11.4.4 Other safety variables

11.4.4.1 Physical examination

Physical examination will not be reported as part of the CSR.

11.4.4.2 Tuberculosis

Tuberculosis assessment by interferon gamma release assay

The TB assessment by interferon gamma release assay will be performed for all subjects. The test results will be listed for each subject by PS0016 randomized treatment group and visit, reported as positive, negative, or indeterminate.

Chest x ray for Tuberculosis

Chest x ray will be performed in PS0018 only when required to confirm or exclude TB. Any clinically significant findings on chest x ray will be documented in the eCRF as an AE and will thus be listed and summarized together with TEAEs as described in Section 11.2.3.

Tuberculosis questionnaire

The TB questionnaire results will be listed for each subject by PS0016 randomized treatment group and visit.

11.4.4.3 Columbia-Suicide Severity Rating Scale

The results of the C-SSRS will be listed for each subject by PS0016 randomized treatment group and visit.

12 OTHER ANALYSES

A listing of comments on the SS will be presented, if applicable.

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13 REFERENCES

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

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14 APPENDICES

14.1 Classification of markedly abnormal laboratory values based on CTCAE grades

The criteria for assessing laboratory values as markedly abnormal are presented in Table 14–2. Baseline in the table refers to PS0016 Baseline.

Table 14–2: Criteria for markedly abnormal laboratory tests

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

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Table 14–2: Criteria for markedly abnormal laboratory tests			
Category	**Panel**	**Variable**	**Criteria (CTCAE Grade 3 and above)**
	Lipids	Total cholesterol	>10.34 mmol/L

ALC= absolute lymphocyte count; ALP=alkaline phosphatase; ALT=alanine aminotransferase; ANC= absolute neutrophil count; AST=aspartate aminotransferase; GGT=gamma glutamyltransferase; RBC=red blood cell; ULN=upper limit of normal, WBC=white blood cell:

14.2 Treatment-emergent abnormal liver values

The criteria for identifying treatment-emergent liver function abnormalities are presented in Table 14–3. Subjects will be counted in all applicable categories for the tabulations ie, a subject with ≥5 x ULN in aspartate aminotransferase (AST) will also be counted in the ≥3 x ULN in AST category, the ≥3 x ULN in AST or alanine aminotransferase (ALT) category and the ≥5x ULN in AST or ALT category. Increases from Baseline are based on PS0016 Baseline.

Table 14–3: Definition of treatment emergent liver function values

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

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

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14.3 Adverse events of special monitoring

The following AESM are defined for bimekizumab and will be summarized separately as described in Section 11.2.3:

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

All AESM tabulations will be presented by Treatment at onset, SOC, HLT and PT, based on the SS, and will include the EAIR and EAER in the 'Any TEAE' categories only.

14.3.1 Major cardiovascular events

Major adverse cardiac events (MACE) will be presented in a table. The classification of an event as MACE is determined by an external cardiovascular event adjudication committee.

14.3.2 Serious infections, including opportunistic infections and tuberculosis

14.3.2.1 Serious infections

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

14.3.2.2 Fungal infections

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

14.3.2.3 Opportunistic infections

Opportunistic infections (including tuberculosis) will be summarized in a stand-alone table. The table will include all TEAEs identified using UCB-defined search criteria (refer to Excel spreadsheet on "OI - MedDRA v19.0.xlsx" in "Bimekizumab-Safety-Topics-of-Interest.docx").

The following steps are followed for identifying opportunistic infections:

Step 1: Refer to column B of the spreadsheet which identifies the Preferred Terms (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 to be considered an opportunistic infection.

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– 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 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, High Level Term (HLT), Lower Level Term (LLT), PT, AE start date, AE end date, seriousness, severity, relationship to study medication, action taken. Additionally, a column will be included where the study physician can document their decision on the case.
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. At quarterly Infectious Disease Committee (IDC) Meetings, outputs will be produced and reviewed by the study physician ahead of the IDC Meeting. The IDC will then agree on the final adjudication for each potential opportunistic infection. A final output for opportunistic infections will be produced and agreed upon between the study physician and the IDC prior to finalizing the database.
4. Study programming team incorporates these decisions into the AE dataset by merging the final 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 in Step 2 will be summarized as such in the stand-alone table, along with all events identified in Step 1 of this process.

The timing and frequency of Step 2 will be outlined 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 prior to the DMC meeting.

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 final study physician decisions (with IDC agreement) on the full set of case-by-case events, will be archived at the conclusion of the study.

14.3.3 Malignancies including lymphoma

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

- Malignant or unspecified tumours
- Malignant tumours

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

The output tables will include 2 different overall incidence rows:

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

14.3.4 Cytopenias

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

14.3.5 Neuropsychiatric events

This table is based on the SMQ of "Depression and suicide/self-injury" (all TEAEs that code to a PT included in the Scope=Broad and/or Scope=Narrow).

An external neuropsychiatric adjudication committee will evaluate potential neuropsychiatric events and determine whether any of those events were associated with suicidal ideation and behavior (SIB). If an event is adjudicated as SIB, further information will be provided. A separate listing for SIB events as determined by the adjudication committee will be included.

14.3.6 Inflammatory bowel disease

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

14.3.7 Anaphylactic reaction

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

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

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

Hypersensitivity reactions and anaphylactic reactions will be identified as follows:

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

  All TEAEs with onset (start date/time) within 24 hours after any administration of study medication, and which fulfill any of the 3 criteria described in Section 14.3.7.1 will be included in the summary table.

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

14.3.7.1 Anaphylactic reaction algorithm

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

A **narrow search** containing PTs that represent core anaphylactic reaction terms. If a subject reports any TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction and summarized as such in the table.

- Category A

5. Anaphylactic reaction
6. Anaphylactic shock
7. Anaphylactic transfusion reaction
8. Anaphylactoid reaction
9. Anaphylactoid shock
10. Circulatory collapse
11. Dialysis membrane reaction
12. Kounis syndrome
13. Shock
14. Shock symptom
15. Type I hypersensitivity

- A **broad search:** If a subject reports any TEAE which codes to a PT included in Category B **AND** reports any TEAE which codes to a PT included in Category C, **and both TEAEs have the same start date**, then both events will be flagged as anaphylactic reactions and summarized as such in the table.

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– **Category B**

1. Acute respiratory failure
2. Asthma
3. Bronchial oedema
4. Bronchospasm
5. Cardio-respiratory distress
6. Chest discomfort
7. Choking
8. Choking sensation
9. Circumoral oedema
10. Cough
11. Cyanosis
12. Dyspnoea
13. Hyperventilation
14. Irregular breathing
15. Laryngeal dyspnoea
16. Laryngeal oedema
17. Laryngospasm
18. Laryngotracheal oedema
19. Mouth swelling
20. Nasal obstruction
21. Oedema mouth
22. Oropharyngeal spasm
23. Oropharyngeal swelling
24. Respiratory arrest
25. Respiratory distress
26. Respiratory dyskinesia
27. Respiratory failure
28. Reversible airways obstruction
29. Sensation of foreign body
30. Sneezing
31. Stridor

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32. Swollen tongue
33. Tachypnoea
34. Throat tightness
35. Tongue oedema
36. Tracheal obstruction
37. Tracheal oedema
38. Upper airway obstruction
39. Wheezing

– **Category C**

1. Allergic oedema
2. Angioedema
3. Erythema
4. Eye oedema
5. Eye pruritis
6. Eye swelling
7. Eyelid oedema
8. Face oedema
9. Flushing
10. Generalised erythema
11. Injection site urticaria
12. Lip oedema
13. Lip swelling
14. Nodular rash
15. Ocular hyperaemia
16. Oedema
17. Periorbital oedema
18. Pruritis
19. Pruritis allergic
20. Pruritis generalised
21. Rash
22. Rash erythematous
23. Rash generalized

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24. Rash pruritic
25. Skin swelling
26. Swelling
27. Swelling face
28. Urticaria
29. Urticaria papular

– **Category D**

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

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

14.3.8 Hepatic events and drug-induced liver injury

Hepatic events will include:

- Events based on the SMQ = 'Drug related hepatic disorders – comprehensive search' (excluding sub-SMQs = 'Liver neoplasms, benign [incl cysts and polyps]' and 'Liver neoplasms, malignant and unspecified'). All AEs should be included in the tabulation (included those considered both related and not related to the IMP) which code to a PT included in the Scope=Narrow group within each SMQ.
- Hy's Law cases will also be summarized separately in a table of liver function abnormalities as described in Section 14.2 (with adjudication for potential drug-induced liver injury cases).

14.4 Treatment-emergent markedly abnormal vital signs values

The criteria for identifying TEMA/PCS vital signs values are provided in Table 14–4. Decreases and increases from Baseline are based on PS0016 Baseline.

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Table 14–4: TEMA/PCS criteria for vital signs

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

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

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15 AMENDMENTS TO THE SAP

15.1 Amendment 1

15.1.1 Rationale for the amendment

This SAP was amended in order to make minor corrections to the text that were noted during the dry run.

15.1.2 List of changes

Specific changes

Change #1: Section 1, 2nd paragraph.

The following bullet has been added:-

- Protocol amendment 3 dated 16 February 2018

Change #2: Section 3.2.2

The following section has been added:-

3.2.2 Daylight saving dates

Daylight saving dates will be considered in the calculation of the absolute scheduled and actual times and in the duration when this is based on times. Therefore, if any daylight saving change occurs during the study development, this will impact the description of the blood sample collections, the calculation of the PK parameters, and any AE duration in case the time is included in the calculation of the duration.

Change #3: Section 3.3, final sentence

The sentence has changed from:

- This will be labelled as PS0018 Week 0 in the tabulations, and will be included in any change from PS0016 Baseline summaries.

to

- The day of first dose will be labelled as PS0018 Week 0 in the tabulations, and will be included in any change from PS0016 Baseline summaries.

Change #4: Section 4.4

The second bullet has changed from:

- "If the early WD visit does not correspond to the day of a scheduled visit, all the efficacy, safety and other relevant assessments of the early WD visit should be mapped to the nearest scheduled visit, relative to the PS0018 Week 0 visit date, following the last scheduled visit where assessments are available."

to:

- "If the early WD visit does not correspond to the day of a scheduled visit, all the efficacy, safety and other relevant assessments of the early WD visit should be mapped to the nearest scheduled visit, relative to the PS0018 Week 0 visit date, following the last scheduled visit where assessments are available."

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Change #5: Section 4.4

Two further bullets, and a sentence have been added:-

- If an EW visit mapping results in data being mapped to a visit where the specific assessment is not actually collected per the protocol schedule of assessments, these data will not be included in the summary statistics and will be listed only.
- The only exception to the above rule is for ADA (for both BKZ and CZP) assessments, in which all early withdrawal visit assessments will be assigned to the next scheduled visit at which ADA are assessed. The rationale for this is that ADA positivity is summarized over a given study period. As part of that summary, a table indicating the first visit at which ADA positivity is observed will be presented. In order to match the number of subjects who were ADA positive at specific visits with the overall positivity for the period, it is necessary to ensure that ADA positivity is attributed to a visit where ADA antibody assessments were performed.

Assessments from the EW visit will be displayed as the mapped visit and will be flagged in the by-visit data listings.

Change #6: Section 11.2.3

Two bullets have been removed:-

- Incidence of non-serious TEAEs by PS0018 dose at onset and Dose adjustment
- Incidence of non-serious TEAEs by relationship and PS0018 dose at onset

Change #7: Section 11.2.3

One bullet has been added:-

- Incidence of ongoing AEs from PS0016

Change #8: Section 14.3.4

The second sentence has changed from:

- "Only serious TEAEs will be included in the tabulation"

to:

- "Serious and non-serious TEAEs will be included in the tabulation"

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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.

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Approval Signatures

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