# STATISTICAL ANALYSIS PLAN

**Study: PS0032**

**Product: Bimekizumab**

# A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN ADULT KOREAN STUDY PARTICIPANTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in adult Korean study participants with moderate to severe plaque psoriasis



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# TABLE OF CONTENTS

# VERSION HISTORY

| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| 1 | 08 Nov 2021 | Not Applicable | Original version |
| Amendment 1 | | • Updated algorithmic approach in section 6.1.6<br>• The outputs for SFU data in section 5.1.1.1.3 and section 5.6.3.1.1<br>• Baseline of PSD calculation and compliance/completion rate definitions in section 5.4.1.1.4<br>• Minor update of descriptions in section 5.5.2<br>• AE outputs update in section 5.6.2.2<br>• Updated definition of CTCAE grade in section 6.1.8<br>• Additional descriptions of unscheduled visit in section 5.1<br>• Updated eDISH descriptions and additional figure<br>• Updated PHQ-9 output<br>• Added HAC materials in section 5.6.2.3.8<br>• Added descriptions of re-screened listing<br>• Updated descriptions of exclusion of PK concentrations data at section 5.7.1.1<br>• Updated numbering of section 5.6.3.4~5.6.3.9<br>• Update format throughout the document | |

| SAP Version | Approval Date | Change | Rationale |
|---|---|---|---|
| | | • Update analysis population used in section 5.6.2.2<br>• Add "if applicable" to the TEAE analysis of during/post COVID-19 pandemic in section 5.2.1<br>• Add "unless otherwise specified" to state that SFU will be included for most summaries except for two figures in section 5.6.3.1.1<br>• Additional descriptions for handling more than one set of PSD scores are added in section 5.4.1.1.4<br>• Additional sensitivity analysis of DLQI response excluding study participants with a missing Baseline DLQI score is added in section 5.4.1.3 | |



# LIST OF ABBREVIATIONS

## List of Abbreviations

| | |
|---|---|
| ACP | Above The Cut Point |
| ADAb | Antidrug Antibody |
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| BCP | Below The Cut Point |
| BLQ | Below the Level of Quantification |
| BMI | Body Mass Index |
| BSA | Body Surface Area |
| CFS | COVID-19 Free Set |
| CI | Confidence Interval |
| CMH | Cochran-Mantel-Haenszel |

## List of Abbreviations

| | |
|---|---|
| COVID-19 | Coronavirus disease 2019 |
| CP | Confirmed Positive |
| CSR | Clinical Study Report |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | Coefficient of Variation |
| CV-CAC | Cardiovascular Event Adjudication Committee |
| DLQI | Dermatology Life Quality Index |
| DMC | Data Monitoring Committee |
| EAER | Exposure-Adjusted Event Rate |
| EAIR | Exposure-Adjusted Incidence Rate |
| ES | Enrolled Set |
| FAS | Full Analysis Set |
| IBD | Inflammatory Bowel Disease |
| IBD-CAC | Inflammatory Bowel Disease Adjudication Committee |
| IGA | Investigator's Global Assessment |
| IGRA | Interferon-Gamma Release Assay |
| IMP | Investigational Medicinal Product |
| LLoQ | Lower Limit of Quantification |
| LOCF | Last Observation Carried Forward |
| MACE | Major Adverse Cardiac Event |
| MAP | Managed Access Program |
| MAR | Missing at Random |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Multiple Imputation |
| NCP | Not Confirmed Positive |
| OR | Odds Ratio |
| PASI | Psoriasis Area and Severity Index |
| PD | Pharmacodynamic |
| PEOT | Premature End of Treatment |
| PHQ | Patient Health Questionnaire |
| PK | Pharmacokinetic |

## List of Abbreviations

| | |
|---|---|
| PK-PPS | Pharmacokinetic Per Protocol Set |
| PPS | Per Protocol Set |
| PSD | Patient Symptom Diary |
| P-SIM | Patient Symptom and Impact Measure |
| PSO | Psoriasis |
| Q4W | every 4 weeks |
| QOL | Quality of Life |
| RS | Randomized Set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SMQ | Standardized MedDRA Query |
| sc | Subcutaneous |
| SFU | Safety Follow-Up |
| SS | Safety Set |
| TB | Tuberculosis |
| TEAE | Treatment-Emergent Adverse Event |
| TE-SAE | Treatment-Emergent Serious Adverse Event |
| TEMA | Treatment-Emergent Markedly Abnormal |
| WHO-DD | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

PS0032 is a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in adult Korean study participants with moderate to severe plaque psoriasis. This Statistical Analysis Plan (SAP) prespecifies the analyses for endpoints in PS0032, including PK, safety, efficacy, quality of life (QOL), and immunogenicity. Results obtained from the analyses in this SAP will serve as the basis of the clinical study report (CSR) for PS0032. The SAP is based on the following study document: Protocol Amendment 3, 16 Aug 2021.

## 1.1 Objectives and Estimands/Endpoints

**Table 1: Objectives and Estimands/Endpoints**

| Objectives | Estimands / Endpoints |
|---|---|
| **Primary** | |
| Primary Objective:<br>To evaluate the efficacy of bimekizumab compared with placebo | Primary Estimand:<br>• Treatment: Bimekizumab 320mg Q4W for 16 weeks<br>• Target Population: adult Korean study participants meeting the protocol-specified inclusion/exclusion criteria<br>• Endpoints:<br>o Co-Primary Endpoint 1: Psoriasis Area and Severity Index (PASI) 90 response at Week 16<br>o Co-Primary Endpoint 2: Investigator's Global Assessment (IGA) 0/1 (clear or almost clear with at least a 2-category improvement from Baseline) response at Week 16<br>• Intercurrent event handling:<br>o Co-Primary Endpoint 1: An intercurrent event is defined as discontinuation of investigational medicinal product (IMP) prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving PASI90 response at Week 16 and not discontinuing IMP through Week 16. Study participants with intercurrent event of discontinuation of IMP prior to Week 16 will be considered nonresponders (i.e. negative clinical outcome).<br>o Co-Primary Endpoint 2: An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving IGA 0/1 response at Week 16 and not discontinuing IMP through Week 16. Study participants with intercurrent event of discontinuation of IMP prior to Week 16 will be considered nonresponders (i.e. negative clinical outcome).<br>• Population level summary: odds ratio comparing bimekizumab to placebo |

## Table 1: Objectives and Estimands/Endpoints

| Objectives | Estimands / Endpoints |
|---|---|
| **Secondary** | |
| Secondary Objective(s):<br>To evaluate the efficacy of bimekizumab compared with placebo at achieving complete skin clearance (PASI100 or IGA 0)<br><br>To evaluate the efficacy of bimekizumab compared with placebo at achieving rapid response (PASI75)<br><br>To evaluate the efficacy of bimekizumab compared with placebo on itch, pain, and scaling<br><br>To evaluate the efficacy of bimekizumab compared with placebo on the change in psoriatic scalp disease in study participants with scalp psoriasis (PSO) at Baseline<br><br>To assess the effect of bimekizumab compared with placebo on quality of life (QOL) | Secondary Estimands:<br>• Treatment: Bimekizumab 320mg Q4W for 16 weeks<br>• Target Population: adult Korean study participants meeting the protocol-specified inclusion/exclusion criteria<br>• Endpoints:<br>o PASI100 response at Week 16<br>o IGA 0 (clear with at least a 2-category improvement from Baseline) response at Week 16<br>o PASI75 response at Week 4<br>o Patient symptom diary (PSD) (also published as Patient Symptom and Impact Measure [P-SIM] [Gottlieb et al, 2020]):<br>▪ PSD (P-SIM) response for itch at Week 16<br>▪ PSD (P-SIM) response for pain at Week 16<br>▪ PSD (P-SIM) response for scaling at Week 16<br>o Scalp IGA 0/1 (clear or almost clear with at least a 2-category improvement from Baseline) response at Week 16 for study participants with scalp PSO at Baseline<br>o Dermatology Life Quality Index (DLQI) 0/1 response at Week 16<br>• Intercurrent event handling:<br>An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving response at Week 16 and not discontinuing IMP through Week 16. Study participants with intercurrent event of discontinuation of IMP prior to Week 16 will be considered nonresponders (i.e. negative clinical outcome).<br>• Population level summary: odds ratio comparing bimekizumab to placebo |

## Table 1: Objectives and Estimands/Endpoints

| Objectives | Estimands / Endpoints |
|---|---|
| To evaluate the effect of bimekizumab compared with placebo on percent change from Baseline in body surface area (BSA) affected by PSO | • Treatment: Bimekizumab 320mg Q4W for 16 weeks<br>• Target Population: adult Korean study participants meeting the protocol-specified inclusion/exclusion criteria<br>• Endpoint:<br>Percent change from Baseline in BSA affected by PSO at Week 16<br>• Intercurrent event handling:<br>A hypothetical strategy will be implemented in which the estimand targets the treatment difference in a scenario where an intercurrent event does not occur, such that outcomes for study participants without an intercurrent event are as observed, and outcomes for study participants with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16 by imputing data following an intercurrent event using last observation carried forward (LOCF).<br>• Population level summary: difference in the adjusted means between bimekizumab and placebo |
| To evaluate the safety of bimekizumab | • Incidence of treatment-emergent adverse events (TEAEs) throughout the study<br>• Incidence of treatment-emergent serious adverse events (TE-SAEs) throughout the study<br>• Incidence of TEAEs leading to permanent discontinuation of IMP throughout the study |
| To assess the effect of bimekizumab on depression occurrence or worsening | • Change from Baseline in Patient Health Questionnaire (PHQ)-9 at Week 16 |
| **Tertiary/Exploratory** | |
| To evaluate the PK of bimekizumab in study participants with moderate to severe PSO | • Plasma bimekizumab concentrations over the study duration |
| To evaluate the immunogenicity of bimekizumab | • Anti-bimekizumab antibody status over the study duration |

**Table 1: Objectives and Estimands/Endpoints**

| Objectives | Estimands / Endpoints |
|---|---|
| To assess the efficacy of bimekizumab compared with placebo over time | • PASI75 response over time<br>• PASI90 response over time<br>• PASI100 response over time<br>• Absolute and percent change from Baseline in PASI score over time<br>• Percentage of study participants with absolute PASI score ≤1, ≤2, ≤3, and ≤5 over time<br>• Time to PASI50, PASI75, PASI90, and PASI100 response<br>• IGA 0/1 response (with at least 2-category improvement from Baseline) over time<br>• IGA 0 response (with at least 2-category improvement from Baseline) over time<br>• Scalp-specific IGA (scalp IGA) 0/1 response (clear or almost clear with at least 2-category improvement from Baseline for participants with scalp PSO at Baseline) over time<br>• Percentage of study participants with absolute BSA affected by PSO=0%, ≤1%, ≤3% and ≤5% over time<br>• Percentage of study participants achieving a DLQI Total Score of 0 or 1 over time<br>• Change from Baseline in DLQI Total Score over time<br>• PSD (P-SIM) response rates over time<br>• Change from Baseline in PSD (P-SIM) scores over time |
| To further evaluate the safety of bimekizumab compared with placebo over time | • Selected safety topics of interest TEAEs<br>• Change from Baseline in laboratory variables (hematology and biochemistry)<br>• Incidence of markedly abnormal laboratory values<br>• Change from Baseline in vital signs<br>• Incidence of markedly abnormal vital signs<br>• Change from Baseline in ECG parameters<br>• ECG outliers<br>• Change from Baseline in PHQ-9<br>• Incidence of PHQ-9 scores ≥15 and ≥20<br>• Incidence of suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent (from C-SSRS) |



## 1.2 Study design

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of bimekizumab compared with placebo in adult Korean study participants with moderate to severe plaque PSO. The aim of this study is to bridge the existing evidence of efficacy and safety of bimekizumab from the Phase 3 program with limited

Korean study participation to a Korean population of study participants with moderate to severe PSO.

The study population consists of adult Korean study participants (≥19 years of age) with a diagnosis of moderate to severe plaque PSO (Baseline PASI ≥12 and BSA affected by PSO ≥10% and IGA score ≥3 on a 5-point scale) who are candidates for systemic PSO therapy and/or phototherapy.

This study will include 3 periods [Figure 1]:

- Screening Period (2 to 5 weeks)
- Treatment Period (16 weeks)
- Safety Follow-Up (SFU) Period (20 weeks after the last dose of IMP)

One rescreening may be allowed after consultation with the Medical Monitor.

After completion of the Screening Period, eligible study participants will be allowed to enroll into the study. Approximately 45 adult Korean study participants will be randomized 2:1 to receive the following blinded IMP regimens during the Treatment Period:

- Bimekizumab 320mg every 4 weeks (Q4W) administered subcutaneous (sc) injection (30 study participants)
- Placebo Q4W administered sc injection (15 study participants)

During the Treatment Period, IMP will be administered at the study site.

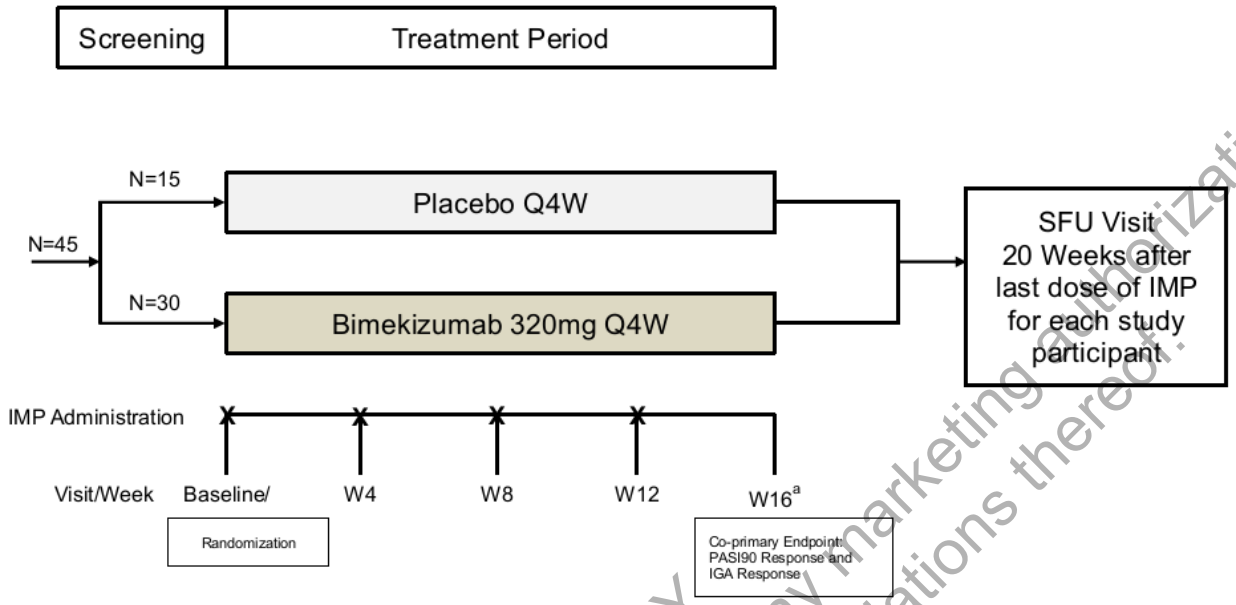
Study participants who have completed the 16-week Treatment Period may choose to enter into a Managed Access Program (MAP) to receive open-label treatment with bimekizumab or enter the SFU.

All study participants choosing not to transition into a MAP will have a SFU Visit 20 weeks post last dose of IMP. Safety assessments will be made by ongoing monitoring and evaluation of AEs and other safety topics of interest specific to bimekizumab.

Study participants withdrawing early from IMP will undergo the premature end of treatment (PEOT) Visit assessments and be asked to continue in the SFU Period.

A study participant is considered to have completed the study if he/she has completed the 16 week treatment period, regardless of entry into the MAP or completion of the SFU period.

**Figure 1 Study schematic**




IGA= Investigator's Global Assessment; IMP=investigational medicinal product; MAP=managed access program; PASI=Psoriasis Area and Severity Index; PEOT=Premature End of Treatment; Q4W=every 4 weeks; SFU=Safety Follow-Up; W=Week
[a] If a participant completes Week16 and is provided the continued treatment with bimekizumab as part of the MAP, SFU is not required.



# 2 STATISTICAL HYPOTHESES

The co-primary efficacy endpoints for this study are PASI90 response and IGA 0/1 response at Week 16.

**PASI90:**

The null hypothesis is that there is no difference between bimekizumab and placebo in the PASI90 response at Week 16; namely the odds ratio (OR) for bimekizumab group compared with placebo group is equal to one:

$H_{PASI}(0)$: $OR = 1$

The alternative hypothesis is that there is difference between bimekizumab and placebo in the PASI90 response at Week 16; namely the OR for bimekizumab group compared with placebo group is not equal to one:

$H_{PASI}(1)$: $OR \neq 1$

**IGA 0/1:**

The null hypothesis is that there is no difference between bimekizumab and placebo in the IGA 0/1 response at Week 16; namely the OR for bimekizumab group compared with placebo group is equal to one:

$H_{IGA0/1}(0)$: $OR = 1$

The alternative hypothesis is that there is difference to the IGA0/1 response at Week 16; namely the OR in favor of IGA 0/1 response for bimekizumab group compared with placebo group is not equal to one:

$H_{IGA0/1}(1)$: $OR \neq 1$

The statistical analyses of these two co-primary endpoints will be performed using Type 1 error rate at a two-sided alpha level of 0.05. To account for multiplicity and control the Type 1 error rate, superiority of bimekizumab relative to placebo will only be declared if both PASI90 response and IGA 0/1 response are statistically significant in favor of bimekizumab.

# 3 SAMPLE SIZE DETERMINATION

Sample size and power calculations are performed based on a total of 45 study participants being randomly assigned in a 2:1 ratio at Baseline to one of the following treatment groups:

- Bimekizumab 320mg Q4W (30 study participants)
- Placebo (15 study participants)

The primary efficacy analysis is based on the comparison of bimekizumab to placebo for the co-primary efficacy endpoints of PASI90 and IGA 0/1 response at Week 16. The assumed responder rates for PASI90 at Week 16 are 70% and 13.3% for bimekizumab and placebo, respectively. Based on the number of study participants planned, this equates to 21 and 2 responders in the bimekizumab and placebo treatment groups, respectively. In the global Phase 3 bimekizumab PSO program, the PASI90 responder rate ranged from 85% to 90%. The assumption here is relatively low to account for increased variability due to a small sample size and the possibility of missing data due to COVID-19. Additionally, the placebo PASI90 responder rate assumption is higher than observed in the Phase 3 program to account for potential variability due to small sample size. These assumptions are conservative against a bimekizumab treatment effect.

The power to show statistical superiority of bimekizumab relative to placebo at a 2-sided significance level of 0.05 under these assumptions is 95% for PASI90 at Week 16. As the Phase 3 studies demonstrated similar responder rates between PASI90 and IGA 0/1, this calculation is considered sufficient to justify the sample size. These calculations were performed using nQuery Advisor® 7.0 based on a two-group continuity corrected chi-square test of equal proportions (with unequal n).

# 4 POPULATIONS FOR ANALYSIS

## 4.1 Analysis Sets

### 4.1.1 Enrolled Set

The Enrolled Set (ES) will consist of all study participants who have given informed consent.

### 4.1.2 Randomized Set

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

### 4.1.3 Safety Set

The Safety Set (SS) will consist of all study participants that received at least 1 dose of the IMP.

### 4.1.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized study participants that received at least 1 dose of the IMP and have a valid measurement of the co-primary efficacy variables at Baseline.

### 4.1.5 Per Protocol Set

The Per-Protocol Set (PPS) will consist of all study participants in the RS who had no important protocol deviations affecting the co-primary efficacy variables. Exclusions from the FAS will be considered important protocol deviations that also result in exclusion from the PPS.

Important protocol deviations will be predefined, and study participants with important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding the data.

### 4.1.6 Pharmacokinetics Per-Protocol Set

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized study participants who received at least 1 dose of the IMP and provided at least 1 quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration.

### 4.1.7 COVID-19 Free Set

The COVID-19 Free Set (CFS) will consist of all study participants randomized into the study and who have no COVID-19 impact through Week 16. This analysis set will be used for sensitivity analysis of the co-primary efficacy endpoints.

# 5 STATISTICAL ANALYSES

## 5.1 General Considerations

All analyses will be performed using SAS® version 9.4 or higher (SAS Institute, Cary, NC, US).

Summary statistics will consist of frequency tables for categorical variables. For continuous variables, summary statistics will consist of the number of available observations, arithmetic mean, standard deviation, median, minimum, and maximum, unless stated otherwise.

For categorical variables, the number and percentage of study participants in each category will be presented. Unless otherwise noted, the denominator for percentages should be based on the number of study participants included in the respective analysis set. Study participants with missing data will be accounted for using the following approaches:

- For summaries of demographics and Baseline characteristics: summarize percentages based on all study participants in the analysis set and include a “Missing” category (corresponding to study participants with missing data for the variable being summarized) as the last row in the list of categories being summarized.
- For summaries of efficacy and safety endpoints, unless otherwise specified: summarize percentages based only on those study participants with observed data for the variable being summarized. As the denominator may be different from the number of study participants in the analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be “n/Nsub (%).”

Percentages will be presented to 1 decimal place. If the percentage is 100%, do not present a decimal. If the percentage is 0, do not present the percentage. Typically, the % sign should be presented in the column header, but not with each individual value.

For bimekizumab PK concentrations, summary statistics will include geometric mean, geometric coefficient of variation (CV), 95% confidence intervals for geometric mean, arithmetic mean, SD, median, minimum, and maximum. All summaries of PK variables will be based on the observed values. No imputation will be used.

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

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

Derived variables in general will display the mean, SD and median to 1 more decimal place than the variables used in the derivation. If the number of decimal places reported in the raw data is varied then use either the maximum raw number of reported decimal places or 3, whichever is the lowest, as a guide for the descriptive statistics.

Statistical tests of efficacy variables will be presented as two-sided p-values rounded to three decimal places. P-values less than 0.001 will be presented as "<0.001" and p-values greater than 0.999 will be presented as ">0.999."

Per protocol, visit windows of ±3 days from the first dose (W0) to the Week 16 visit are permissible; for SFU Visit, permissible window is ±7 days from last dose + 20 weeks. For by-visit presentations, data from unscheduled visits should generally not be included. If the data of unscheduled visit is the only record prior to first IMP administration, it will be an exception and treated as baseline value. In case of repeated laboratory tests at a particular visit, the last measurement should generally be used for visit presentation in by-visit summaries.

In cases where vendor data is assigned to an unscheduled visit instead of a scheduled visit, the assessments will be mapped into the scheduled visit if the assessment dates fall into the permissible window, as detailed above.

A complete set of data listings containing all documented data and all calculated data (eg, change from Baseline) will be generated.

### 5.1.1 General study level definitions

#### 5.1.1.1 Analysis Time Points

##### 5.1.1.1.1 Relative day

Relative day will be calculated as the algorithm below:

If the event occurred on or after the date of first study drug administration, then the following calculation is used:

$$Relative\ Day = Date_{event} - Date\ of\ first\ dose + 1$$

If the event occurred before the date of first study drug administration, then the following calculation is used:

$$Relative\ Day = Date_{event} - Date\ of\ first\ dose$$

Relative days that occur before the date of first study drug administration will be preceded by a "-", when present in listings.

If the event occurred after the date of last study drug administration, then the following calculation is used:

$$Relative\ Day = Date_{event} - Date\ of\ last\ dose$$

Relative days that occur after the date of last study drug administration will be preceded by a "+", when present in listings.

Relative day will only be computed for fully completed dates and will be missing for partial dates.

#### 5.1.1.1.2 End date of the Treatment Period

The end date of the Treatment Period will be either the date of Week 16 visit for study participants completing the Treatment Period, or the date of the PEOT for study participants who discontinued during the Treatment Period. If a study participant does not have a Week 16 visit/PEOT, then either the date of the last scheduled or unscheduled visit during the Treatment Period or the date of last known dose of study drug during the Treatment Period, whichever is later, will define the end date of the Treatment Period.

#### 5.1.1.1.3 Study periods

The study consists of the following periods:

- Screening Period: the Screening Period will last 2 weeks, but can be extended up to a total of 5 weeks in cases where a laboratory assessment needs to be repeated or to allow washout of prohibited medications. The Screening Period starts from the ICF date and ends one day before the first IMP administration date.
- Treatment Period: the Treatment Period starts from the date of first IMP administration and ends at the Week 16 visit date or PEOT date.
- SFU Period: Only applicable to the study participants not entering the MAP. The SFU starts one day after the end date of Treatment Period (Week 16 date or PEOT date) and ends at the SFU Visit (scheduled to be 20 weeks from final dose of IMP).

SFU data will be listed only, with the exception of the figures of ALT/AST values for participants with at least one markedly abnormal value and the inclusion of AEs with onset during the SFU period, which will be included in selected summaries, detailed in section 5.6.2.2.

A study participant will be considered to have completed a period if they complete the last scheduled study visit for that period.

#### 5.1.1.1.4 Mapping of assessments performed at Early Discontinuation Visit

If the PEOT visit occurs at a scheduled visit as outlined in the schedule of assessments, then no mapping is necessary, and any PEOT assessments should correspond to that scheduled visit.

Premature study withdrawal visit assessments that occur on a date after a scheduled visit will be assigned to the next scheduled site visit per the protocol following the last visit where assessments were available. This approach means that there is a chance that data will be mapped to a visit where a given assessment was not actually collected per the protocol schedule of assessments. Such data will not be summarized in by-visit tables (though it will be available in the listings).

The only exception to the above rule is for anti-bimekizumab antibody assessments, in which all early withdrawal visit assessments will be assigned to the next scheduled visit at which antibimekizumab antibodies are assessed. The rationale for this is that anti-bimekizumab antibody positivity is summarized over a given study period. As part of that summary, a table indicating the first visit at which anti-bimekizumab antibody positivity is observed will be prepared. In order to match the number of study participants who were anti-bimekizumab antibody positive at specific visits with the overall positivity for the period, it is necessary to ensure that anti-bimekizumab antibody positivity is attributed to a visit where such assessments were performed.

All by-visit summaries will contain nominal visits only. Unscheduled visits will not be mapped to scheduled visits. However, in cases where vendor data is assigned to an unscheduled visit instead of a scheduled visit, the assessments will be mapped into the scheduled visit if the assessment dates fall into the permissible window, as detailed in section 5.1.

Note that based on the early withdrawal mapping conventions described above, a mapped early withdrawal visit is considered as observed at that visit and should be summarized as such in the tables.

#### 5.1.1.1.5 Definition of Baseline values

A Baseline value for clinical variables is defined as the latest measurement on or prior to the first dosing day of study medication, regardless of the time of the measurement, for the Treatment Period. If a Baseline assessment is taken on the same day as first administration of study medication, it is eligible to be used as the Baseline value, even in the case that the time of the assessment is recorded as taking place after the time of first study medication administration. One exception to this rule is plasma concentration. If Baseline plasma concentration is measured at a time after the first administration of study medication, then it will not be eligible to be considered as a Baseline plasma concentration. Such cases will be discussed with the quantitative clinical pharmacologist.

If a Baseline measurement is missing or not collected, and a Screening value is available, the Screening value will be utilized as Baseline instead. If no measurement is available prior to receiving study medication, then the Baseline value is treated as missing.

Baseline values for component scores should be computed using components from the same visit where the relevant measurements were recorded prior to dosing. For example, if the Screening visit has all of the components, but the Baseline visit is missing one or more components, the Baseline value for the component score should be calculated using the Screening visit values.

#### 5.1.1.2 Protocol Deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the primary efficacy, key safety, or other PK outcomes for an individual participant. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document at study start. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented to confirm exclusion from analysis sets.

#### 5.1.1.3 Treatment assignment and treatment groups

It is expected that study participants receive treatment as randomized and hence safety analyses will be based on the SS, as randomized. However, if after unblinding it is determined that study participants randomized to placebo received bimekizumab at any time, then for safety analyses these study participants will be reallocated to the appropriate bimekizumab treatment group, unless otherwise specified. Study participants randomized to bimekizumab will only be reallocated to the placebo group if they never received bimekizumab.

Efficacy analyses should be performed according to randomized treatment and not actual treatment received.

#### 5.1.1.4 Center pooling strategy

No pooling of centers is planned for this study.

#### 5.1.1.5 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Medical procedures will not be coded.

For MedDRA, version 19.0 or later will be used. For WHO-DD, version Mar/2021 or later will be used.

#### 5.1.1.6 Multicenter studies

The data from all centers will be pooled for the purposes of the analysis. No exploration of treatment by center interaction will be investigated.

#### 5.1.1.7 Handling of dropouts or missing data

Details about approaches to handle missing data are described in this section.

##### 5.1.1.7.1 Efficacy missing data

An intercurrent event is defined as discontinuation of IMP prior to Week 16.

For study participants who experience an intercurrent event, the intercurrent event date is defined as:

Last study treatment date + 28 days (dosing interval) + 3 days (visit window)

For both co-primary endpoints (PASI90 and IGA 0/1 at Week 16), participants with an intercurrent event will be considered as nonresponder.

For secondary efficacy binary endpoints (PASI100 response at Week 16, IGA 0 response at Week 16, PSD [P-SIM] [itch, pain, and scaling] response at Week 16, Scalp IGA 0/1 response at

Week 16, and DLQI 0/1 response at Week 16), study participants with intercurrent event will be handled using the same approach as the co-primary endpoints.

For PASI75 response at Week 4, a study participant will be considered a nonresponder only if the intercurrent event date occurs prior to the date of the Week 4 assessment.

Any missing data for the primary and secondary binary endpoints not associated with discontinuation of IMP will also be imputed as a nonresponse.

For the secondary continuous endpoint (percent change from baseline in BSA affected by PSO), participants with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16 by imputing data following an intercurrent event using LOCF (see section 5.4.1.2.2). In addition, missing data not associated with discontinuation of IMP will also be imputed using LOCF.

For all tertiary endpoints, all data collected after an intercurrent event will be treated as missing and subject to imputation as described in section 5.5.

#### 5.1.1.7.2 PK missing data

Pharmacokinetic analyses will be based on observed data; no data will be imputed. If plasma concentration measurements are below the lower limit of quantification (LLOQ), then for calculation of the derived statistics the result will be set to half of the LLOQ.

#### 5.1.1.7.3 Incomplete dates and times

Partial dates may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- 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 and time:

- If only the month and year are specified and the month and year of the first dose of IMP is not the same as the month and year of the start date, then use the 1st of the month, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month).
- If only the month and year are specified and the month and year of the first dose of IMP is the same as the month and year of the start date, then use the date of the first dose of IMP. If this results in an imputed start date that is after the specified end date, then use the 1st of the month, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month).
- If only the year is specified, and the year of the first dose of IMP is not the same as the year of the start date then January 01 will be used.
- If only the year is specified, and the year of the first dose of IMP is the same as the year of the start date, then the date of the first dose of IMP will be used. If this results in an imputed start date that is after the specified end date, then January 01, or the date of screening if this is later will be used (if the latter imputation results in an end date that is earlier than the start date, then January 01 will be used).

- If the start date is completely unknown, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of Screening if this is later.

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

## 5.2 Participant Dispositions

The number of study participants screened and screen failures and the primary reason for screen failure are summarized for all participants screened.

The number and percentage of study participants who completed or prematurely discontinued the treatment period, as well as the reason for discontinuation will be summarized based on the RS. The number of study participants who completed the SFU and the number of study participants who enter the MAP will also be summarized.

The number and percentage of study participants who discontinued due to AEs will be separately summarized based on the RS.

The disposition of study participants for all study participants screened will include the number of study participants included in each analysis set (RS, SS, FAS, PPS, CFS and PK-PPS) overall.

The following listings will be presented:

- Study participants who did not meet study eligibility criteria (ES)
- Study participants disposition (ES)
- Study discontinuation (RS)
- Visit dates (RS)
- Study participants analysis sets (RS)
- Rescreened Subjects (ES)

### 5.2.1 COVID-19 impact analysis

The World Health Organization (WHO) declared the novel COVID-19 outbreak a global pandemic on 11 Mar 2020. For the purposes of summarizing disposition with respect to COVID, post-COVID refers to an event or record reported after the date when WHO declares the global pandemic has ended. If the WHO has not declared an official end date by the end of the study, an alternative end date may be used at the discretion of study team.

If no suitable end date exists, the global pandemic will be considered ongoing, and the summaries by during and post-pandemic period described below will not be produced.

To assess the impact of the COVID-19 pandemic on the study, the following summaries will be presented (if there is a suitable pandemic end date):

- A summary of study participant disposition based on enrollment during and post COVID-19 pandemic
- A summary of study participant demographics based on enrollment during and post COVID-19

Treatment emergent AE data will also be analyzed during and post COVID-19 pandemic if applicable, details can be found in 5.6.2.2.

The following summary will also be provided:

- A summary of study visits impacted, and type of impact by the COVID-19 pandemic

## 5.3 Primary Endpoints Analysis

The co-primary efficacy variables for this study are PASI90 response and IGA 0/1 response at Week 16 and the corresponding analyses are based on the RS.

### 5.3.1 Definition of endpoints

#### 5.3.1.1 PASI90 at Week 16

PASI90 is defined to be equal to 1 if the percentage improvement from Baseline in the PASI scores is 90% or greater and 0 if the percentage improvement from Baseline is less than 90%. This definition is introduced for the purpose of identifying study participants who respond to the treatment
(1 = responder, 0 = non-responder).

$$Percent\ Improvement\ from\ Baseline = 100 \times \frac{Baseline\ PASI - Post\ Baseline\ Timepoint\ PASI}{Baseline\ PASI}$$

The PASI is the most commonly used and validated assessment for grading the severity of PSO in clinical studies (Feldman, 2004). The PASI quantifies the severity and extent of the disease and weighs these with the percentage of BSA involvement. The PASI will be completed by the Investigator electronically at the visits specified in the protocol schedule of assessment.

The percent area of involvement (BSA%) is estimated across 4 body areas: head, upper extremities, trunk, and lower extremities. Assessors will enter the degree of involvement for a given region on a scale of 0 to 6 (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). This degree score is used in the calculation of PASI score as shown in Table 2. The total percent body surface area (BSA) of PSO involvement will also be estimated as a number between 0 and 100.

The Investigator assesses the average redness, thickness, and scaliness of lesions in each body area (each on a 5-point scale); 0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked. The PASI score ranges from 0 to 72, with a higher score indicating increased disease severity. Detailed information of PASI scores could be found in 6.1.5.1.

**Table 2: Body areas for calculation of percent BSA for PASI**

| Body area | Details of area | BSA | Degree of involvement of body area[a] |
|---|---|---|---|
| Head | Face, back of head | 10% | 0 to 6 |
| Upper extremities | Left, right, upper, lower, flexor surface, extensor surface | 20% | 0 to 6 |
| Trunk | Front, back, groin | 30% | 0 to 6 |
| Lower extremities | Left, right, upper, lower, flexor surface, extensor surface, including buttocks | 40% | 0 to 6 |
| Total | | 100% | |

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

#### 5.3.1.2 IGA 0/1 (clear or almost clear with at least a 2-category improvement from Baseline) at Week 16

IGA 0/1 response is defined as clear [0] or almost clear [1] with at least a 2-category improvement from Baseline at Week 16.

A static IGA for PSO will be used to assess disease severity in all study participants during the study. The IGA will be completed at the visits specified in the protocol schedule of assessments.

The Investigator will assess the overall severity of PSO using the following 5-point scale presented in Table 3 below.

**Table 3: Five-point IGA**

| Score | Short descriptor | Detailed descriptor |
|---|---|---|
| 0 | Clear | No signs of PSO; postinflammatory 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, moderate scaling |
| 4 | Severe | Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions |

IGA=Investigator's Global Assessment; PSO=psoriasis

### 5.3.2 Main analytical approach

The primary estimand for the co-primary endpoints is defined as follows:

- Treatment: Bimekizumab 320mg Q4W for 16 weeks
- Target Population: adult Korean study participants meeting the protocol-specified inclusion/exclusion criteria
- Intercurrent event handling:

  An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving PASI90/IGA 0/1 response at Week 16 and not discontinuing IMP through Week 16. Study participants with intercurrent event of discontinuation of IMP prior to Week 16 will be considered nonresponders (i.e. negative clinical outcome).
- Population level summary: odds ratio comparing bimekizumab to placebo

In the above scenario, missing data at Week 16 that are not preceded by an intercurrent event, as well as any data after an intercurrent event, will be imputed as non-responders. While this approach is described as a composite strategy for intercurrent event handling, it is equivalent to applying non-responder imputation (NRI).

The primary analysis of the co-primary endpoints will be based on the Cochran-Mantel-Haenszel (CMH) test. The evaluation of superiority to placebo will use treatment comparisons based on the CMH test using the p-value for the general association. The odds ratio and associated confidence interval (CI) based on the Wald test will be presented. If one of the treatment groups has 0 or very low response where CMH is no longer an appropriate method, Fisher's exact test will be applied and the odds ratio will not be calculated.

The number and percentage of study participants who are PASI90 responders at Week 16 will be summarized. IGA 0/1 response will be summarized in the same manner as the PASI90 responder variable.

A line plot of the PASI90 and IGA 0/1 responder rate over time by treatment group will be produced.

By-study participant listings of PASI and IGA responder variables, PASI and IGA data will be provided.

### 5.3.3 Sensitivity analysis

Sensitivity analysis based on observed cases will be performed. Study participants with missing data or who have prematurely discontinued IMP will be treated as missing. The same CMH test as in the primary efficacy analysis will be used. The odds ratio comparing bimekizumab to placebo based on FAS and PPS will be summarized for both PASI90 and IGA 0/1. The odds ratio and associated CI based on the Wald test will be presented. If one of the treatment groups has 0 or very low response where CMH is no longer an appropriate method, Fisher's exact test will be applied and the odds ratio will not be calculated.

Supplementary analysis for the co-primary endpoints will be produced on the FAS, PPS, and COVID-19 Free set. The analysis method applied will be the same as used for the primary analysis.

## 5.4 Secondary Endpoints Analysis

The secondary efficacy variables will be analyzed for all study participants in the RS. No formal statistical testing will be conducted for the secondary efficacy variables however nominal p-values for the comparison of bimekizumab to placebo will be produced. The secondary endpoints will be derived in the following subsections.

### 5.4.1 Secondary endpoint(s)

#### 5.4.1.1 Definition of endpoint(s)

##### 5.4.1.1.1 PASI100 at Week 16

Detailed information for PASI can be found in section 5.3.1.1 and 6.1.5.1.

The binary response variable PASI100 is defined to be equal to 1 if the percentage improvement from Baseline in the PASI scores is 100% and 0 if the percentage improvement from Baseline is less than 100%.

This definition is introduced for the purpose of identifying study participants who respond to the treatment (1 = responder, 0 = non-responder).

##### 5.4.1.1.2 IGA 0 at Week 16

Detailed information for IGA score can be found in 5.3.1.2.

The binary response variable IGA 0 response is defined as clear [0] with at least a 2-category improvement from Baseline at Week 16.

##### 5.4.1.1.3 PASI75 at Week 4

Detailed information for PASI can be found in 5.3.1.1and 6.1.5.1.

The binary response variable PASI75 is defined to be equal to 1 if the percentage improvement from Baseline in the PASI scores is 75% or greater and 0 if the percentage improvement from Baseline is less than 75%.

This definition is introduced for the purpose of identifying study participants who respond to the treatment (1 = responder, 0 = non-responder).

##### 5.4.1.1.4 PSD (P-SIM) response for itch, pain and scaling at Week 16

The PSD (P-SIM) consists of 14 items, measuring the following PSO-related signs, symptoms, and functional impacts: redness, scaling, cracking, lesions, thickening, itch, pain, burning, dryness, irritation, sensitivity, fatigue, embarrassment, and choice of clothing. Each item is assessed for severity/impact level over a recall period of the past 24 hours on a 0 to10 scale, where 0 means no symptoms or impact and 10 means very severe symptoms or worst impact.

Weekly averages will be derived for each of the items of the PSD for weeks matching the post-Baseline dosing weeks up to Week 16. A weekly average is the sum of the scored item over the course of the study week divided by the number of days on which the item was completed. The weekly averages will be relative to the respective visit date except for Baseline, which will be

anchored to the first dose of study drug. A weekly average will only be calculated if at least 4 non-missing values (not necessarily consecutive) are available. Otherwise, the PSD weekly average for the given question will be set to missing.

Baseline will be computed as the average from the last 7 consecutive day period prior to the Baseline visit in which there are at least 4 non-missing entries. That is, to start, we consider the last 7 consecutive days prior to the Baseline visit, but not including the Baseline visit day itself. If there are at least 4 non-missing values (not necessarily consecutive), then the Baseline average will be calculated. If there are less than 4 values, the 7 consecutive day period will move one day earlier. If there are at least 4 non-missing values (not necessarily consecutive) in that period, then the Baseline average will be calculated. This will continue until there are at least 4 non-missing values in a 7 consecutive day period in the 14 days prior to Baseline. If there is no period in which there are at least 4 non-missing entries, then the Baseline value will be set to missing.

If more than one set of PSD scores are submitted on a particular date, only the record where the submission date matches the expected PSD entry date will be used in the calculation of weekly scores.

Each of three PSD response scores -itch, pain, and scaling- will be characterized in terms of the cumulative percent of study participants demonstrating a pre-specified point improvement at Week 16. The thresholds for the PSD response score of itch, pain, and scaling are 4.00. For this responder analysis, it will be limited to the study participants with a Baseline PSD response score at or above the applicable threshold score (4.00).
PSD compliance rate and completion rate at Baseline and Week 16 for each of the 3 items (Pain, Itch, and Scaling) will be derived as follows:

Compliance rate: the percentage of study participants in the RS with a non-missing weekly item score at each visit.
Completion rate: the percentage of study participants who have completed a particular visit with a non-missing weekly item score.

#### 5.4.1.1.5 Scalp IGA 0/1 at Week 16

A static IGA for scalp PSO will be used to assess disease severity on the scalp.

The scalp IGA will be assessed for all study participants at Baseline. The scalp IGA will be completed by the Investigator electronically. Only study participants with a scalp IGA score >0 at Baseline will have the scalp IGA assessed at later visits as specified in the protocol schedule of assessments.

Scalp lesions will be assessed in terms of clinical signs of redness, thickness, and scaliness using a 5-point scale (Table 4).

**Table 4: Scalp IGA**

| Score | Short descriptor | Detailed descriptor |
|---|---|---|
| 0 | Clear | Scalp has no signs of PSO; postinflammatory hyperpigmentation may be present |

| | | |
|---|---|---|
| 1 | Almost clear | Scalp has no thickening; normal to pink coloration; no to minimal focal scaling |
| 2 | Mild | Scalp has just detectable to mild thickening; pink to light red coloration; predominately fine scaling |
| 3 | Moderate | Scalp has clearly distinguishable to moderate thickening; dull to bright red, moderate scaling |
| 4 | Severe | Scalp has severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions |

PSO=psoriasis

The binary response variable Scalp IGA response at Week 16 is defined as clear [0] or almost clear [1] with at least a 2-category improvement from Baseline to Week 16. For analysis purposes, the evaluation of scalp IGA response will be limited to study participants with a Baseline scalp IGA of at least 2. Therefore, if a study participant has a score of 2 at Baseline, they can only be considered a responder if their IGA is 0 (thereby meeting the criterion for a 2-category improvement from Baseline). Study participants with a Baseline scalp IGA of 1 will be assessed per the protocol but will not be part of the scalp IGA analysis.

#### 5.4.1.1.6 DLQI 0/1 response at Week 16

The DLQI questionnaire is used for patients with psoriasis and consists of 10 questions. This is a validated, quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment, as assessed over the past week.

The scoring of each answer for the DLQI is as follows:

**Table 5: Dermatology Life Quality Index**

| **DLQI Scoring** | |
|---|---|
| **Response** | **Score** |
| Very much | 3 |
| A lot | 2 |
| A little | 1 |
| Not at all | 0 |
| Not relevant | 0 |

| | |
|---|---|
| Question unanswered | 0 |
| Q7: "prevented work or studying" = yes | 3 |

The DLQI total score is calculated by adding the score of each question. The maximum score is 30, and the minimum score is 0. The higher the score, the more quality of life is impaired.

Meaning of DLQI Scores:

0-1 = no effect at all on patient's life

2-5 = small effect on patient's life

6-10 = moderate effect on patient's life

11-20 = very large effect on patient's life

21-30 = extremely large effect on patient's life

This categorization will not be utilized in the analysis.

Because Q7 has a sub-question (referred to as Q7a here) after the leading yes/no question, some clarifying rules for scoring are provided:

- If Q7 is marked as "yes", a score of 3 is given regardless of the responses to Q7a.
- If Q7 is marked as "no", "not relevant", or is missing and Q7a is "A lot", a score of 2 is given.
- If Q7 is marked as "no", "not relevant", or is missing and Q7a is "A little", a score of 1 is given.
- If Q7 is marked as "no", "not relevant", or is missing and Q7a is "Not at all", a score of 0 is given.
- If Q7 is marked as "no" or "not relevant" and Q7a is missing, a score of 0 is given.
- If Q7 is missing and Q7a is missing, Q7 is considered unanswered (see below for details on how this impacts the overall DLQI score).

If 1 question is left unanswered, this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If 2 or more questions are left unanswered, the questionnaire is not scored.

A DLQI total score of 0 or 1 indicates no impact of the disease on patient's life.

The binary response variable DLQI 0/1 response (defined as a DLQI total score of 0 or 1) at Week 16 will be evaluated as a secondary endpoint.

#### 5.4.1.1.7 Percentage of Body Surface Area (BSA) affected by PSO at Week 16

The percentage BSA affected by PSO is recorded as a number between 0 and 100 recorded at visits where skin is assessed.

The percent change from baseline in BSA is defined as:

$$Percent\ change\ from\ Baseline\ = 100 \times \frac{Post\ Baseline\ BSA - Baseline\ BSA}{Baseline\ BSA}$$

#### 5.4.1.2 Main analytical approach

##### 5.4.1.2.1 Binary endpoints

The binary secondary efficacy endpoints include:

- PASI100 response at Week 16,
- IGA 0 response at Week 16,
- PASI75 response at Week 4,
- PSD [P-SIM] [itch, pain, and scaling] response at Week 16,
- Scalp IGA 0/1 response at Week 16,
- DLQI 0/1 response at Week 16

These secondary endpoints will have the same estimand structure as for the co-primary endpoints, which is defined as follows:

- Treatment: Bimekizumab 320mg Q4W for 16 weeks
- Target Population: adult Korean study participants meeting the protocol-specified inclusion/exclusion criteria
- Intercurrent event handling:
  - PASI100 response at Week 16, IGA 0 response at Week 16, PSD [P-SIM] [itch, pain, and scaling] response at Week 16, Scalp IGA0/1 response at Week 16, DLQI 0/1 response at Week 16

    An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving response at Week 16 and not discontinuing IMP through Week 16. Study participants with intercurrent event of discontinuation of IMP prior to Week 16 will be considered nonresponders (i.e. negative clinical outcome).
  - PASI75 response at Week 4

    An intercurrent event is defined as discontinuation of IMP prior to Week 4. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving response at Week 4 and not discontinuing IMP through Week 4. Study participants with intercurrent event of discontinuation of IMP prior to Week 4 will be considered nonresponders (i.e. negative clinical outcome).
- Population level summary: odds ratio comparing bimekizumab to placebo

In the above scenario, missing data at the time point of interest that are not preceded by an intercurrent event, as well as any data after an intercurrent event, will be imputed as non-responders. While this approach is described as a composite strategy for intercurrent event handling, it is equivalent to applying non-responder imputation (NRI).

The number and percentages of PASI100, IGA 0, PSD [itch, pain, and scaling] responders, Scalp IGA, DLQI 0/1 responders at Week 16 and PASI75 responder at Week 4 will be reported for each treatment group.

The evaluation of superiority to placebo will use treatment comparisons based on the CMH test using the nominal p-value for the general association. The odds ratio and associated confidence interval (CI) based on the Wald test will be presented. If one of the treatment groups has 0 or very low response where CMH is no longer an appropriate method, Fisher's exact test will be applied and the odds ratio will not be calculated.

A line plot of the responder rate over time by treatment group will be produced.

By-study participant listings of the secondary efficacy binary variables will be provided.

#### 5.4.1.2.2 Continuous endpoint

The continuous secondary efficacy endpoint is the percent change from Baseline in BSA affected by PSO at Week 16.

The estimand to define the treatment effect of interest for the continuous secondary efficacy endpoint is as follows:

- **Treatment**: 320mg bimekizumab Q4W for 16 weeks.
- **Target Population**: adult Korean study participants meeting the protocol-specified inclusion/exclusion criteria.
- **Intercurrent event handling**: A hypothetical strategy will be implemented in which the estimand targets the treatment difference in a scenario where an intercurrent event does not occur, such that outcomes for study participants without an intercurrent event are as observed, and outcomes for study participants with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16 by imputing data following an intercurrent event using LOCF.
- **Study participant-level summary measure**: Difference in the adjusted means between bimekizumab and placebo.

For the continuous change from Baseline efficacy endpoint, percent change from Baseline in BSA affected by PSO at Week 16, an analysis of covariance (ANCOVA) model will be used with fixed effects of treatment and Baseline value as a covariate. Missing data will be imputed via LOCF.

### 5.4.1.3 Sensitivity analysis

For all secondary efficacy endpoints, sensitivity analysis based on observed cases will be performed. Study participants with missing data or who have prematurely discontinued IMP will be treated as missing. The same analysis method applied for the primary endpoints will be used for binary endpoints and ANCOVA model for continuous endpoint as in the secondary efficacy analysis will be used.

An additional sensitivity analysis will be performed on DLQI 0/1 at Week 16 which will exclude study participants with a missing Baseline DLQI score. Missing baseline DLQI scores can be due to study participants not completing an assessment until after the first dosing visit or due to late entry of the intended Baseline scores. The scores should be entered directly into the database by the study participant at the Baseline visit, however due to some technical problems for a few subjects this was not possible, and the scores were collected on paper and entered at a later date.

As only the date that the scores were entered electronically is captured in the database, these records are considered post-baseline for the purpose of analysis.

#### 5.4.1.4 Supplementary analyses

No supplementary analysis will be conducted.

## 5.5 Tertiary/Exploratory Endpoint(s) Analysis

The tertiary efficacy variables will be analyzed for all study participants in the RS.

### 5.5.1 Binary endpoints

Binary (responder) variables as listed below will be summarized using frequency tables by treatment group for each visit. Missing data that are not preceded by an intercurrent event, as well as any data following an intercurrent event will be imputed as non-response. While this approach is described as a composite strategy for intercurrent event handling, it is equivalent to applying non-responder imputation (NRI). Observed case results will also be displayed:

- PASI75/90/100 response over time
- IGA 0/1 & IGA 0 response over time
- PSD (P-SIM) response for each item over time
- Scalp IGA 0/1 response over time
- Percentage of study participants with absolute PASI score ≤1, ≤2, ≤3, and ≤5 over time
- Percentage of study participants with absolute BSA affected by PSO=0%, ≤1%, ≤3% and ≤5% over time
- DLQI 0/1 response over time

The following endpoints will be derived using observed data only (no imputation):
PSD (P-SIM) Itch, Pain and Scaling Compliance rate at Baseline and Week 16
PSD (P-SIM) Itch, Pain and Scaling Completion rate at Baseline and Week 16

Figures displaying the response over time using NRI data will be produced for PASI, IGA, Scalp IGA and DLQI 0/1 response variables.

### 5.5.2 Continuous endpoints

Continuous variables will be summarized using descriptive statistics by treatment group for each visit. No imputation will be applied to continuous variables, only observed data will be summarized:

- Absolute and percent change from Baseline in PASI score over time
- Absolute and percentage change in BSA affected by PSO over time
- Change from Baseline in DLQI Total Score over time
- Absolute and percent change from Baseline in PSD (P-SIM) scores for each item over time

Figures displaying the results over time will be produced for mean percent improvement from baseline in PASI score and mean percent change from baseline in BSA respectively.

In addition, the entire distribution of data for PSD response based on each of the items will be evaluated via continuous plots showing the absolute change from Baseline on the X-axis and the percent of study participants experiencing that change on the Y-axis. This distribution curve will reveal the extent to which overall results are driven by outliers who improve or worsen more than others. The cumulative distribution function (CDF) is the probability that the variable takes a value less than or equal to x. That is:

$x \mapsto Fx(x) = P(X \leq x)$where the right-hand side represents the probability that the random variable X takes on a value less than or equal to x. The probability that X lies in the interval [a, b] is therefore:

$$Fx(b) - Fx(a) \text{ if } a < b$$

Cumulative distribution plots will be provided for absolute change from Baseline in PSD scores at Week 16 for each PSD item.

### 5.5.3 Time to PASI50/70/90/100 response

Time to PASI50, PASI75, PASI90, and PASI100 response (in days) during the Treatment Period will each be calculated as:

Date of first PASI xx response – Date of first study drug administration + 1.

with xx representing 50, 70, 90, 100 respectively. All visits including unscheduled visit are considered.

Time to PASI50, PASI75, PASI90, and PASI100 response will be estimated using the Kaplan-Meier product-limit method for each treatment group. Study participants who discontinue IMP prior to achieving a response will be censored at the date of the last observed PASI assessment on or prior to the date of IMP discontinuation. Study participants who complete the study without achieving the given response will be censored at the date of the last observed PASI assessment in the Treatment Period. Study participants will be censored at Baseline (Day 0) if there is no Baseline PASI assessment or no post-Baseline PASI assessment in the Treatment Period.

Kaplan-Meier plots of time to PASI responses will also be provided by treatment group. In these Kaplan-Meier plots, the line will start at 0 (since there are no responders at Week 0) and will increase over time, representing time to achieving the response.

The median time to response, including the 2-sided 95% CI, will be calculated for each treatment group.

## 5.6 Safety Analyses

Safety variables will be analyzed for all study participants in the SS.

### 5.6.1 Extent of Exposure

Summaries for exposure will be provided. This consists of a descriptive summary of study medication duration in days. In addition, total study medication duration and time at risk will be

summarized in years by treatment group. The cumulative study medication duration will be summarized for study participants exposed for given durations of time, with four weekly categories through Week 16:

- >0 week
- ≥4 weeks
- ≥8 weeks
- ≥12 weeks
- ≥16 weeks

Definitions for study medication duration (days) during the Treatment Period are provided as follows:

Study medication duration (days):

- Date of last dose – date of first dose + 28 days

The use of +28 days reflects the dosing interval of Q4W.

Note: For participants who died during the treatment period, the calculation reverts to:

- Date of death – date of first dose + 1

Time at Risk (Days) during the Treatment Period:

For study participants who complete the final visit (week 16) of the Treatment Period:

- Date of Week 16 visit – Date of first dose +1

For study participants who discontinue on or prior to the final visit of the Treatment Period, use the minimum of the following:

- Planned total number of days in the Treatment Period (112 days)
- Date of last clinical contact – Date of first dose +1

For study participants who died during the Treatment Period:

- Date of death – date of first dose +1

Date of last clinical contact for each study participant in the Treatment Period is defined as the maximum of last visit date in the Treatment Period, last imputed AE start date, date of study termination or completion, last date of study drug administration.

Time at Risk (Days) during the Treatment Period + SFU:

For study participants who complete the final visit (week 16) of the Treatment Period and enter the MAP:

- Date of Week 16 visit – Date of first dose +1

For study participants who do not enter the MAP, use the minimum of the following:

- Date of last dose – Date of first dose +141
- Date of last clinical contact – Date of first dose +1

For study participants who died prior to the end of time at risk as defined above:

- Date of death – date of first dose +1

Date of last clinical contact for each study participant in the Treatment Period + SFU is defined as the maximum of: last visit date including SFU, last imputed AE start date, date of study termination or completion, last date of study drug administration.

### 5.6.2 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 19.0).

#### 5.6.2.1 Data considerations

Treatment-emergent AEs are defined as those AEs that have a start date on or following the first dose of IMP through the to the end of the time at risk, as defined in section 5.6.

The rules for imputing partial start or stop dates are outlined in 5.1.1.7.3. If it is not possible (due to partial dates) to determine whether an AE is treatment-emergent then it will be assumed to be a TEAE. If the intensity of an AE is unknown, it will be considered as severe. If the relationship to study drug is missing, it will be considered as related.

Treatment-emergent AEs will be summarized as study participant incidence (number and percentage of study participants experiencing the AE) and AE frequencies (number of AEs including repeat events) by treatment group.

Selected AE summaries will include the exposure-adjusted incidence rate (EAIR) and the exposure-adjusted event rate (EAER). The 95% CIs will be reported for the EAIR only.

The EAIR is the total number of study participants with a specific AE divided by the total time at risk across all study participants. If a study participant has multiple events, the time of exposure is calculated to the first occurrence of the AE being considered. If a study participant has no events, the total time at risk is used. The EAER is the total number of AEs including repeat occurrences in individual study participants divided by the total time at risk across all study participants. Exposure adjusted rates (EAIR and EAER) will be scaled to 100 participant-years. Study participant time at risk represents the time a participant is at risk for having an AE. These definitions will be used in calculations of exposure-adjusted rates for adverse events.

Details of the calculations for exposure adjusted rates (EAIR and EAER) can be found in section 6.1.5.2.

The following PTs will be used to classify COVID-19 adverse events:

- Corona virus infection
- Coronavirus test positive

A separate summary and by-study participant listing will be produced for COVID-19 TEAEs.

To assess the impact of COVID-19 mass vaccination on TEAEs, a sensitivity analysis will present all TEAEs excluding TEAEs assessed as exclusively related to COVID-19 vaccine by the investigator. TEAEs recorded as related to both study medication and COVID-19 vaccination

will not be excluded. A complementary table and listing of TEAEs related to COVID-19 vaccine will be presented.

Another sensitivity analysis will present all TEAEs excluding TEAEs with start date on or up to 5 days after date of COVID-19 vaccine. Note that study participants may receive more than one administration of COVID-19 vaccine. A complementary table and listing of TEAEs with start date on or up to 5 days after date of COVID-19 vaccine will also be presented.

#### 5.6.2.2 AE Summaries

The AE summaries listed below will be provided based on incidence during the Treatment Period.
The following summaries will be provided by treatment group. In addition, all summaries of TEAEs based on "100 subject years" will include EAIR (with 95% confidence interval) and EAER.

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT
- Incidence of Serious TEAEs per 100 subject years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Discontinuation per 100 subject years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Death by SOC, HLT, and PT
- Incidence of TEAEs by Maximum Relationship by SOC, HLT, and PT
- Incidence of COVID-19 TEAEs by SOC, HLT, and PT
- Incidence of TEAEs by during and post COVID-19 pandemic by SOC, HLT, and PT (if applicable, see section 5.2.1)
- Incidence of Related Serious TEAEs by SOC, HLT, and PT
- Incidence of TEAEs by Maximum Intensity, SOC, HLT, and PT
- Incidence of TEAEs by decreasing frequency of PT
- Incidence of Non-Serious TEAEs by SOC, HLT, and PT
- Incidence of Non-Serious TEAEs by Maximum Relationship SOC, HLT, and PT
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by SOC and PT
- Incidence of Serious TEAEs by Relationship SOC and PT
- Incidence of Related TEAEs by SOC, HLT, and PT
- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT and by Time of Onset Relative to Anti-bimekizumab Antibody Status (subjects treated with BKZ)
- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT and by Time of Onset Relative to Neutralizing Anti-bimekizumab Antibody Status (subjects treated with BKZ)

In addition, the AE summaries listed below will be provided based on the incidence in the Treatment + SFU Period.

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT
- Incidence of Serious TEAEs per 100 subject years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Discontinuation per 100 subject years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Death by SOC, HLT, and PT

A by-study participant listing of TEAEs which code to the "Infections and Infestations" SOC and Emerged within 30 days of when a CTCAE Grade 3 or 4 Neutrophil Value Occurred will be presented.

The AE summaries listed below will be provided to assess the impact of COVID-19 mass vaccination on TEAEs through the Treatment Period.

- Incidence of TEAEs Excluding TEAEs Exclusively Related to COVID-19 Vaccine by SOC, HLT, and PT (all SS)
- Incidence of TEAEs Exclusively Related to COVID-19 Vaccine by SOC, HLT, and PT (all participants in the SS who received at least one COVID-19 vaccine during the study)
- Incidence of COVID-19 Vaccine Interval Censored TEAEs by SOC, HLT, and PT (all SS)
- Incidence of COVID-19 Vaccine Interval TEAEs by SOC, HLT, and PT (all participants in the SS who received at least one COVID-19 vaccine during the study)

A by-study participant listing of TEAEs related to COVID-19 vaccine and a listing of COVID-19 vaccine interval TEAEs will be presented.

#### 5.6.2.3 Other safety topics of interest

The following are AEs of other safety topics of interest that require special statistical analyses.

The AE summaries described below will be provided based on incidence in the Treatment Period.

A by-study participant listing of all AEs of safety topics of interest will be presented by type of safety topics of interest.

##### 5.6.2.3.1 Infections (serious, opportunistic, fungal and TB)

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

Fungal infections will be summarized in a stand-alone table. The table will include all TEAEs (serious and non-serious) which code into the High Level Group Term "Fungal infectious disorders"

Opportunistic infections (including tuberculosis [TB]) will be summarized in a stand-alone table. The table will include all opportunistic infection TEAEs identified using UCB-defined search criteria which were adjudicated as opportunistic infections.

##### 5.6.2.3.2 Malignancies

These events will be presented in the following tables:

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

SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each SMQ.

Note that the events included in the "Malignancies" table will be a subset of the events included in the "Malignancies (including unspecified)" table. While the "Malignant tumours (SMQ)" is most relevant, "Malignant or unspecified tumours (SMQ)" must be reviewed for potential malignancies.

The output table will include 2 different overall incidence rows:

- The first overall incidence row will summarize "Any Malignancy" and this row will summarize the incidence of all AEs flagged for inclusion in the table (using the appropriate SMQ depending on the table), regardless of the High Level Term (HLT) it codes to.
- The second overall incidence row will summarize "Any Malignancy excluding non melanomic skin cancers HLT" and this row will summarize the incidence of AEs flagged for inclusion in the table (using the appropriate SMQ depending on the table), excluding those which code to an HLT of "Skin neoplasms malignant and unspecified (excl melanoma)".

#### 5.6.2.3.3 Major adverse cardiac event

Potential cardiovascular events are adjudicated by the independent Cardiovascular Event Adjudication Committee (CV-CAC) according to the CV-CAC Charter (version 6.0). Adjudicated events are classified by the CV-CAC to one of the event types as defined in Table 6. The classification of an event as a Major Adverse Cardiac Event (MACE) is also determined by the CV-CAC. Events which are classified by the CV-CAC as any of the events types identified in the third column of Table 6 will be considered an extended MACE. Note that extended MACE is determined programmatically and includes a broader scope definition of MACE.

MACE as determined by the CV-CAC will be presented in a table and listing. Extended MACE will be presented separately in a table and listing.

Another table and listing will present the adjudicated cardiovascular events by type. For each cardiovascular event type, the individual PTs which fall within each event type will be summarized. This listing will indicate whether each event was determined to be a MACE and/or an extended MACE.

Additionally, a listing of all events identified for potential review by the CV-CAC will be produced. This listing will indicate whether each event was identified by the CV-CAC Chair for full committee review.

**Table 6: Cardiovascular event classifications**

| Event Type Code | Event Type | Extended MACE |
|---|---|---|
| 1 | Non-Fatal Myocardial Infarction (MI) | Yes |
| 2 | Non-Fatal Stroke: hemorrhagic | Yes |
| 3 | Non-Fatal Stroke: ischemic | Yes |

**Table 6: Cardiovascular event classifications**

| Event Type Code | Event Type | Extended MACE |
|---|---|---|
| 4 | Non-Fatal Stroke: embolic | Yes |
| 5 | Non-Fatal Stroke: undeterminable | Yes |
| 6 | Hospitalization or ER for Unstable Angina with urgent revascularization | Yes |
| 7 | Hospitalization or ER for Unstable Angina without urgent revascularization | No |
| 8 | Hospitalization for Heart Failure | Yes |
| 9 | Transient Ischemic Attack (TIA) | No |
| 10 | Coronary Revascularization Procedures (e.g. percutaneous coronary intervention, coronary artery bypass grafting) | Yes |
| 11 | Urgent Revascularization Procedures (i.e. due to symptoms of brain ischemia or pending infarction) | Yes |
| 12 | Arrhythmia (not associated with ischemia) | No |
| 13 | Peripheral Arterial Event | No |
| 14 | Venous Thromboembolic Event: pulmonary embolism (PE) | No |
| 15 | Venous Thromboembolic Event: deep vein thrombosis (DVT) | No |
| 16 | Venous Thromboembolic Event: PE and DVT | No |
| 17 | Other CV Event | No |
| 18 | Death due to Myocardial Infarction (MI) | Yes |
| 19 | Death due to Stroke | Yes |
| 20 | Sudden Cardiac Death | Yes |
| 21 | Other CV Death (e.g. heart failure, pulmonary embolism, cardiovascular procedure-related) | Yes |
| 22 | Cardiovascular: Undetermined Cause of Death (i.e. cause of death unknown) | Yes |
| 23 | Non-Cardiovascular Death | No |
| 24 | Non-Cardiovascular Event | No |
| 99 | Inadequate information to adjudicate | No |

CV=Cardiovascular; DVT=Deep Vein Thrombosis; ER=Emergency Room; MACE= Major Adverse Cardiac Event; MI=Myocardial Infarction; PE=Pulmonary Embolism; TIA=Transient Ischemic Attack.
MACE is determined by the adjudication committee and is not identified programmatically based on event type.



#### 5.6.2.3.4 Neutropenia

A table will be based on the following PTs (regardless of seriousness):

- Autoimmune neutropenia

- Band neutrophil count decreased
- Cyclic neutropenia
- Febrile neutropenia
- Idiopathic neutropenia
- Neutropenia
- Neutropenic infection
- Neutropenic sepsis
- Neutrophil count decreased

#### 5.6.2.3.5 Suicidal Ideation and Behavior

Potential neuropsychiatric events are adjudicated by the independent Neuropsychiatric Adjudication Committee according to the Neuropsychiatric Adjudication Committee (version 8.0). Adjudicated events are classified by the Committee as Suicidal or Non-suicidal. Adjudicated events are also further classified by the Committee to one of the event types as defined in Table 7. Suicidal Ideation and Behavior (SIB) is defined as events classified by the Committee as Suicidal.

A table and listing will present SIB events.

Another table and listing will present the adjudicated neuropsychiatric events by type. For each neuropsychiatric event type, the individual PTs which fall within each event type will be summarized. This listing will indicate whether each event was determined to be Suicidal or Non-Suicidal. For event type suicidal ideation, the listing will also indicate if intent was present and if the suicidal ideation was clinically significant.

Additionally, a listing of all events identified for potential review by the Committee will be produced. This listing will indicate whether each event was identified by the Neuropsychiatric Event Adjudication Committee Chair for full committee review.

**Table 7: Neuropsychiatric event classifications**

| Event Type Code | Event Classification | Event Type |
|---|---|---|
| 1 | Suicidal | Suicidal events/completed suicide |
| 2 | Suicidal | Suicide attempt |
| 3 | Suicidal | Preparatory acts toward imminent suicidal behavior |
| 4 | Suicidal/Non-suicidal[a] | Suicidal ideation |
| 7 | Non-suicidal | Nonsuicidal Self-injurious behavior |
| 8 | Non-suicidal | Nonsuicidal Other |
| 99 | Not applicable | Inadequate information to adjudicate |

[a] Suicidal ideation event types can be classified by the Neuropsychiatric Adjudication Committee as Suicidal or Non-suicidal depending on whether intent to die was present.

#### 5.6.2.3.6 Inflammatory bowel disease

Selected gastrointestinal events are adjudicated by the independent Inflammatory Bowel Disease (IBD) Adjudication Committee (IBD-CAC) according to the IBD-CAC Charter (version 3.0). Adjudicated events are classified by the IBD-CAC into one of the diagnostic types as defined in Table 8. The events will further be classified as definite, probable or possible IBD.

An overview of adjudicated IBD events will be stratified by subjects with or without a previous medical history of IBD. Previous medical history of IBD will be determined using the information recorded on the Extra-Articular Assessment at Screening CRF page ("Does subject have a history of IBD?"). This overview table will present events adjudicated by the IBD-CAC as either possible, probable or definite IBD. Definite and probable IBD will also be aggregated and summarized in this table. In addition, this table will summarize each IBD event classification (possible, probable or definite) separately.

Another table and listing will present the adjudicated IBD events by type. For each IBD event type, the individual PTs which fall within each event type will be summarized.

Additionally, a listing of all events identified for potential review by the IBD-CAC will be produced. This listing will indicate whether each event was identified by the IBD-CAC Chair for full committee review.

A further supportive listing will present the individual diagnostic criteria met for each adjudicated IBD event.

**Table 8: IBD event classifications**

| Event Type Code | Event Type (Classification and diagnosis) | Classification |
|---|---|---|
| 1 | Possible Inflammatory Bowel Disease – Crohn's Disease | Possible |
| 2 | Probable Inflammatory Bowel Disease – Crohn's Disease | Probable |
| 3 | Definite Inflammatory Bowel Disease – Crohn's Disease | Definite |
| 4 | Possible Inflammatory Bowel Disease – Ulcerative Colitis | Possible |
| 5 | Probable Inflammatory Bowel Disease – Ulcerative Colitis | Probable |
| 6 | Definite Inflammatory Bowel Disease – Ulcerative Colitis | Definite |
| 7 | Possible Inflammatory Bowel Disease – type unclassified | Possible |
| 8 | Probable Inflammatory Bowel Disease – type unclassified | Probable |
| 9 | Definite Inflammatory Bowel Disease – type unclassified | Definite |
| 10 | Symptoms not consistent with Inflammatory Bowel Disease | Not applicable |
| 11 | Possible Inflammatory Bowel Disease – Microscopic Colitis | Possible |
| 12 | Probable Inflammatory Bowel Disease – Microscopic Colitis | Probable |
| 13 | Definite Inflammatory Bowel Disease – Microscopic Colitis | Definite |

**Table 8: IBD event classifications**

| Event Type Code | Event Type (Classification and diagnosis) | Classification |
|---|---|---|
| 14 | Possible Inflammatory Bowel Disease – no further differentiation possible | Possible |
| 15 | Probable Inflammatory Bowel Disease – no further differentiation possible | Probable |
| 16 | Definite Inflammatory Bowel Disease – no further differentiation possible | Definite |
| 99 | Not enough information to adjudicate | Not applicable |

IBD=inflammatory bowel disease.
Note: IBD diagnoses of "microscopic colitis" and "no further differentiation possible" were added in an adjudication charter amendment, accounting for the event type numbering.

#### 5.6.2.3.7 Hypersensitivity (including anaphylaxis)

A separate table will be prepared based on the MedDRA anaphylaxis Algorithm (see section 6.1.9) for acute anaphylactic events (reported on the same day as when an injection was administered or one day after). An AE glossary table will also be produced to summarize the MedDRA coding for these events. The glossary table will include the following fields: reported term, PT, LLT, HLT, and SOC.

A separate table will be prepared to summarize hypersensitivity events, identified using the SMQ "Hypersensitivity (SMQ)". All TEAEs which code to a PT included in the Scope=Narrow search will be included in this table. In addition, a separate table will be prepared to summarize serious hypersensitivity events, identified using the SMQ "Hypersensitivity (SMQ)". All serious TEAEs which code to a PT included in the Scope=Narrow search will be included in this table. An AE glossary table will also be produced to summarize the MedDRA coding for these events. The glossary table will include the following fields: reported term, LLT, PT, HLT, and SOC.

Furthermore, a separate table will be prepared to summarize injection site reactions, identified using the HLTs: "Administration site reactions NEC" and "Injection site reactions".

#### 5.6.2.3.8 Hepatic events and DILI

A table for hepatic events will be created based on the SMQ of "Drug related hepatic disorders - comprehensive search (SMQ)". However, these 2 sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)". For each of the above SMQs, include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow.

Note that all AEs meeting the above criteria are to be included. It should not be limited to events that the investigator determined to be related to study drug.

Cases of potential Hy's Law will be reported separately in a liver function test table.

In addition, potential Drug Induced Liver Injury (pDILI) events are adjudicated by the independent Hepatology Adjudication Committee (HAC) based on liver function test (LFT) elevations according to the HAC Charter (version 3.0). Adjudicated events will receive a causality assessment score as defined in Table 9 indicating the likelihood of the LFT elevations being a drug-induced liver injury related to the blinded investigational medicinal product.

A table will summarize the maximum final causality score and likelihood category for study participants with adjudicated events. Additionally, a listing of all study participants with events identified for potential review by the HAC will be produced. This listing will indicate the final causality assessment score. If a study participant has more than one causality assessment score, the worst score will be presented.

**Table 9 Causality assessment scoring by HAC for drug-induced liver injury**

| Causality Score | Numeric Causality Score | Likelihood (%) |
|---|---|---|
| Definite | 1 | >95 |
| Highly likely | 2 | 75-95 |
| Probable | 3 | 50-74 |
| Possible | 4 | 25-49 |
| Unlikely | 5 | <25 |
| Insufficient Data | 99 | NA |



### 5.6.3 Additional Safety Assessments

#### 5.6.3.1 Clinical laboratory evaluations

Laboratory values, including markedly abnormal laboratory values will be presented descriptively by treatment group for SS. Tables of markedly abnormal laboratory values (see section 6.1.7.1) and those based on CTCAE grade (see section 6.1.8) will only include selected variables.

##### 5.6.3.1.1 Laboratory values over time

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. For tables where multiple measurements over a period of time are considered (as in shift tables), unscheduled and repeat visits will be considered as long as they were collected in the period being summarized. All summaries will be presented in International System of Units and will be based on observed case values. In the case where laboratory values are below the LLQ, then these will be set to the midpoint between 0 and the lower limit of quantification for the purpose of summarizing the data.

The following summaries will be presented for data collected during the Treatment Period, SFU data will be included in listings only (unless otherwise specified).

- A summary of the absolute and change from Baseline values in each laboratory variable by treatment group and visit.
- A summary of the number and percentage of study participants experiencing markedly abnormal values at any time while on treatment (assessment on or following the first dose

of study treatment through to the end of the time at risk (see section 5.6.1)) by laboratory variable and treatment group

- A summary of the number and percentage of study participants with a given CTCAE grade (0,1,2,3, or 4) based on minimum/maximum post-baseline value by laboratory variable and treatment group
- A shift table of the number and percentage of study participants experiencing CTCAE grade 0,1,2,3, or 4 values (as applicable) at Baseline to maximum post-Baseline CTCAE grade, by laboratory variable and treatment group
- A figure presenting neutrophil CTCAE grade over time for study participants with at least one markedly abnormal neutrophil value (Grade 3 or above).
- Spaghetti plots presenting ALT values over time for study participants with at least one markedly abnormal ALT value (Grade 3 or above) (Including SFU).
- Spaghetti plots presenting AST values over time for study participants with at least one markedly abnormal AST value (Grade 3 or above) (Including SFU).
- A by-study participant listing of all laboratory data (including urinalysis) will be provided. This listing will be presented by treatment group and will include: center, subject identifier, age, sex, race, weight, visit, laboratory variable, result (with abnormal values flagged as "L" or "H" accordingly) and unit.

The table for elevated liver function tests (LFTs) will contain data beyond the CTCAE Grade 3 thresholds in order to allow for a more thorough review of elevated LFTs. There will be one table which will list the count and percentage of study participants meeting the below criteria at any time during the study:

- AST: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- AST or ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- Bilirubin: >1.5xULN, >2xULN
- ALP: >1.5xULN

The detailed information of markedly abnormal values criteria can be found in 6.1.7.1.

The following definition of potential drug induced liver injuries (pDILI) will be used:

- [AST ≥3xULN or ALT ≥3xULN] and Total Bilirubin ≥1.5xULN
- [AST ≥3xULN or ALT ≥3xULN] and Total Bilirubin ≥2xULN
- [AST ≥3xULN or ALT ≥3xULN] and Total Bilirubin ≥2xULN in the absence of ALP ≥2xULN (Hy's law)

A table for potential drug induced liver injuries (pDILI) will be presented by treatment group for study participants with at least one post-Baseline liver laboratory assessment. Number and percentage of study participants meeting laboratory criteria for pDILI for at least 1 visit and reporting at least 1 symptom potentially associated with hepatitis or hypersensitivity according to

the Investigator on the pDILI CRF will be presented. Study participants who potentially meet Hy's law criteria at least 1 time during exposure. To be counted as potential Hy's Law, all criteria must be met at the same visit.

Two figures of evaluation of drug-induced serious hepatotoxicity (eDISH) will be created.

- eDISH for maximum Total Bilirubin (y-axis) versus maximum alanine/aspartate aminotransferase (ALT/AST), whichever is higher. Maximum bilirubin and maximum ALT/AST are values of each ULN on a log 10 scale.
- eDISH for maximum Total Bilirubin versus maximum alanine/aspartate aminotransferase (ALT/AST). In this figure, each participant is plotted based on their maximum concurrent total bilirubin (y-axis) and transaminase (ALT or AST, whichever is higher), where maximum concurrent is defined as maximum total bilirubin elevation occurring on or within 30 days after the maximum ALT or AST elevation. The transaminase elevation has to occur first.

#### 5.6.3.2 Vital Signs

##### 5.6.3.2.1 Vital Sign Values Over Time

The following vital signs variables will be summarized: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C) and heart rate (beats/min). The following summaries will be provided for the SS:

- A summary of the absolute and change from Baseline value for each vital sign variable by treatment group and visit during the Treatment Period

##### 5.6.3.2.2 Individual Subject Changes of Vital Sign Values

- A summary of the number and percentage of study participants experiencing at least one markedly abnormal value for a vital sign variable during the Treatment Period by treatment.

The detailed information of markedly abnormal values criteria could be found in 6.1.7.2.

#### 5.6.3.3 Electrocardiograms

Electrocardiogram data will be analyzed by treatment group and visit for SS.

A summary of the number and percentage of study participants with normal, abnormal ECG results, as determined by the central reader will be presented for all applicable visits through the Treatment Period.

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

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

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

The number and percentage of study participants who meet the ECG outlier criteria at any assessment post first dose through the Treatment Period will be summarized.

A separate by-study participant listing of all 12-lead ECG data will be provided based on interpretation from central reader.

#### 5.6.3.4 Assessment and management of TB and TB risk factors

A summary of the number and percentage of study participants with negative, positive, and indeterminate IGRA (Interferon-Gamma Release Assay) or Quantiferon Gold Plus results at all applicable visits through the Treatment Period will be presented. If multiple results are present at a visit, only the last result will be used in the summary.

A by-study participant listing of the "Evaluation of signs and symptoms of tuberculosis" questionnaire data and IGRA/Quantiferon Gold Plus results will be provided by treatment group.

A by-study participant listing of the result of chest x-ray for tuberculosis will be provided by treatment group.

#### 5.6.3.5 Physical examination

Physical examinations include general appearance; ears, nose, and throat; eyes, hair, and skin; and assessments of the respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, and neurological (including limb reflexes) systems, as well as mental status.

Abnormal results of the physical examination together with details of abnormalities: abnormality clinically significant or not, will be listed by study participants and visit for SS.

#### 5.6.3.6 Patient Health Questionnaire 9 (PHQ-9) scores

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. The PHQ-9 scores for depression range from 0 to 27 with higher scores indicating worse state. A score of 5-9 is considered to be minimal symptoms of depression. A score of 10 to 14 is considered minor depression, dysthymia, or mild major depression. A score of 15 to 19 is considered to indicate moderately severe major depression, and a score ≥20 is considered to be severe major depression.

Change from Baseline in PHQ-9 is derived as post-Baseline score minus Baseline score and will be summarized by treatment group.

PHQ-9 is a Safety parameter described on the Safety Population by actual treatment group. Nevertheless, identification of observable data and implementation of LOCF imputation is done the same way as Efficacy parameters.

A Table presenting the number of study participants with PHQ-9 total score ≥15 and ≥20 at all scheduled visits (including Screening, Baseline and each visit through the Treatment Period) and overall at any post-baseline visit will be provided by treatment group using observed case data.

A by-study participant listing of the PHQ-9 questionnaire data will be provided by treatment group including the increase of PHQ-9 scores from the previous visit.

#### 5.6.3.7 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening. The pregnancy test will be urine at all other visits.

A by-study participant listing of the pregnancy test data will be provided by treatment group.

#### 5.6.3.8 Childbearing potential and lifestyle

Childbearing potential and lifestyle will be collected at Screening. A by-study participant listing will be provided for all the study participants screened.

#### 5.6.3.9 Columbia Suicide Severity Rating Scale (C-SSRS)

Suicidal ideation and behavior will be assessed by using the C-SSRS. The questionnaire will be administered and assessed by trained study personnel. This scale will be used to assess suicidal ideation and behavior that may occur during the study. Results of the C-SSRS will be summarized using the number of study participants and percentage with (i) suicidal ideation, (iii) suicidal behavior, (iii) suicidal ideation or behavior, and (iv) self-injurious behavior without suicidal intent.

Suicidal ideation is defined as an event in any of the following 5 categories:

- [redacted]

Suicidal behavior is defined as an event in any of the following 4 categories:

- [redacted]

Suicidal behavior or ideation is defined as an event in any of the above 9 categories.

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

The incidence of study participants with suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior will be summarized during the treatment period by treatment group.

A by-study participant listing of the C-SSRS questionnaire data will be provided by treatment group. This listing will be repeated for study participants with positive responses.

## 5.7 Other Analyses

Pharmacokinetics and immunogenicity analyses are included in this section.

### 5.7.1 Other endpoints and/or parameters

#### 5.7.1.1 Pharmacokinetics

Pharmacokinetic variables will be analyzed for all study participants in the PK-PPS who are treated with bimekizumab.

All plasma concentration data will be reported in ug/mL in the tables, figures, and listings.
If the dosing for a visit is +/- 21 days out of window then the plasma concentration from that visit and all subsequent visits will be excluded from PK summaries.
If the PK sampling date is >1 day after the dosing date the data point will be excluded from the PK summaries.
All PK concentrations will be listed.

No imputation will be used for missing samples. However, plasma concentrations below the limit of quantification (BLQ) will be set to ½ of LLOQ in the calculation of the derived statistics (which will include number of values, geometric mean & its 95% CI, geometric coefficient of variation, mean, SD, median, minimum, and maximum). Geometric mean and its 95% CI, geometric CV, mean and SD will be calculated if at least ⅔ of the values of interest is above the LLOQ and n>=3; otherwise, only number of values, median, minimum, and maximum will be presented.

All concentrations obtained at the SFU visit will be listed only.

The geometric mean of bimekizumab plasma concentration (with 95% CI) time curve will be plotted on linear and semi-logarithmic scales. The table summary and figure will be repeated by anti-bimekizumab antibody status (positive, negative, missing). The missing group will not be displayed if <5% of study participants are categorized in the missing group.

The ADAb status (positive, negative, or missing) will be considered in a cumulative manner at each time point:

- A study participant will be counted as positive from the first visit at which the study participant achieved a positive ADAb sample result to the end of the treatment period (regardless of any missing/inconclusive or negative ADAb sample result).
- If a study participant has only negative ADAb samples or only one missing/inconclusive sample with negative ADAb samples up to that timepoint, the study participant will be classified as negative.
- Otherwise, the study participant will be classified in the missing ADAb category.

The table summary and figure will also be repeated by neutralizing anti-bimekizumab antibodies (NAb) status: (ADAb negative, NAb positive, ADAb positive/NAb negative, missing; section 5.7.2).

#### 5.7.1.2 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

#### 5.7.1.3 Genomics

Genetics are not evaluated in this study.

#### 5.7.1.4 Immunogenicity

**Anti-bimekizumab antibodies**

The ADAb will be assessed using a 3-tiered assay approach: Screening, confirmatory, and titration assays.

Screening, confirmatory and titer cut points of the respective assays will be determined by the bioanalytical laboratory. The relevant statistical reports will be provided as part of the bioanalytical reports.

ADAb samples are analyzed on the SS but are only analyzed for study participants on bimekizumab.

The Screening cut point will be used to determine the ADAb status in the test sample as "Positive Screen" (PS) or "Negative Screen" (NS). For samples presenting anti-bimekizumab antibody levels that are PS, further confirmatory assay will be performed, and the result of which will be reported as either "Positive Immunodepletion" (PI) or "Negative Immunodepletion" (NI).

The ADAb status for each visit will be derived as following:

- ADAb negative - sample values that are either NS or PS and NI.
- Inconclusive - sample values that are either NS or PS and NI and where the bimekizumab concentration exceeds the validated ADAb assay drug tolerance limit.
- ADAb positive - sample values that are PS and PI (regardless of availability of a titer value).
- Missing – if sample is not in one of the above categories.

For the overall ADAb status, a study participant will be classified as follows, excluding any assessments at SFU:

- **Positive** if the study participant has at least 1 positive sample at any time in the treatment period (regardless of having missing/inconclusive data).
- **Negative** if the study participant has all their samples negative or only 1 missing/inconclusive sample with all other negative ADAb samples.
- **Missing** if the study participant has missed more than 1 sample result for ADAb assessment (or have more than 1 inconclusive sample) and all other available ADAb samples are negative during the period of interest.

PI samples will be titrated and the ADAb titer reported. The PI samples will also be subject to a neutralizing (NAb) assay to evaluate whether the anti-bimekizumab antibody neutralizes the target binding of bimekizumab (IL17A or IL17F or both) in-vitro.

The following rule will be implemented for by-visit ADAb summaries where applicable:

- If the ADAb sample is collected within ±14 days (excluding the SFU visit) relative to the visit date at which the drug was administered, the ADAb result for that sample will be associated with the scheduled visit and summarized accordingly.
- In all cases, this will include unscheduled assessments (if a dose was administered at an unscheduled visit).

Summaries of cumulative ADAb status and time to treatment-emergent positivity will use all available data.

In addition, the ADAb status will be further classified according to the following ADAb categories:

- **Category 1: Pre ADAb negative – treatment-emergent ADAb negative**: Includes study participants who are negative at Baseline and antibody negative at all sampling points post treatment (excluding SFU). This group also includes study participants who have missing/inconclusive pre-treatment sample (e.g. either missing/inconclusive or insufficient volume) at baseline with all post-baseline samples as ADAb negative.
- **Category 2: Pre ADAb negative – treatment-emergent ADAb positive**: Includes study participants who are negative at Baseline and antibody positive at any sampling point post treatment (excluding SFU). This group also includes study participants who have a missing pre-treatment sample (either missing or insufficient volume) at Baseline with one or more ADAb positive post-treatment samples.
- **Category 3: Pre ADAb positive – treatment reduced ADAb**: Includes study participants who are positive at Baseline, and antibody negative at all sampling points post treatment (excluding SFU).
- **Category 4: Pre ADAb positive – treatment unaffected ADAb positive**: Includes study participants who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with titer values of the same magnitude as Baseline (i.e. less than a predefined fold difference from the Baseline value). For the purposes of this study, this is set at an increase of less than the validated Minimum Significant Ratio (MSR) from baseline.
- **Category 5: Pre ADAb positive – treatment boosted ADAb positive**: Includes study participants who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with increased titer values compared to Baseline (greater than or equal to a predefined fold difference increase from Baseline value which is defined within the validation of the assay). For the purposes of this study, this is set at an increase greater than or equal to the validated MSR from Baseline.

  Note: For any study participant who is positive at Baseline and positive at a post-Baseline time point, but for whom titers are not available to determine treatment unaffected or treatment boosted status, the study participant will be considered as treatment boosted assuming no other samples are available.
- **Category 6: Inconclusive**: Includes study participants who have a positive pre-treatment sample and some post-treatment samples are missing, while other post-treatment samples are ADAb negative.
- **Category 7: Total treatment-emergent**: Category 2 and 5 combined: Includes study participants who are pre ADAb negative – treatment emergent ADAb positive (Category 2) and pre ADAb positive – treatment boosted ADAb positive (Category 5).
- **Category 8: Total prevalence of pre-ADAb positivity**: (Categories 3, 4, 5 and 6 combined): Study participants that are tested ADAb positive at Baseline.

- **Category 9: Missing:** Includes study participants who have a negative or a missing/inconclusive pre-treatment sample and some post-treatment samples are missing/inconclusive, while other post-treatment samples are ADAb negative.

The following analyses will be prepared on the SS:

- A summary table displaying the number and percentage of study participants with ADAb status (positive, negative or missing) at each visit (excluding SFU) and overall. The overall summary will be presented for both visit during the treatment period and any visit during the study (including Baseline but excluding the SFU visit).
- A table displaying the number (%) of study participants with the first occurrence of ADAb treatment-emergent positivity during the study (i.e., including Baseline visit) will be summarized. This summary will include the following categories:
  - Any ADAb+: ADA positive sample regardless of category during the treatment period,
  - ADAb Category 2: Pre ADAb negative – treatment-emergent ADAb positive,
  - ADAb Category 5: Pre ADAb positive – treatment-boosted ADAb positive (if this category represents at least 10% of the study participants, otherwise results are to be merged with Category 2). For this category, the first occurrence of a boosted result is considered.

  The table will include the number and percentage of study participants with first occurrence of any ADAb+ sample, and also study participants who are either treatment-emergent ADAb positive or treatment-boosted ADAb positive for the first time at the specified time point in the study and will include the cumulative number and percentage of study participants with any ADAb+ sample and treatment-emergent ADAb positive results at each time point.
- A boxplot of the ADAb titer by time of occurrence of ADAb positivity will be created. The ADAb titer results will be presented on the log-scale. The time to occurrence is defined as the time in weeks from Baseline until the visit of interest when a sample is ADAb positive. Study participants who do not have any ADAb positivity will be excluded from the plot.
- A summary table of the number and percentage of study participants in each of the 9 ADAb categories will be tabulated.
- The time to achieving treatment-emergent anti-bimekizumab antibody positivity, separated by treatment group and Categories 2 & 5 above, will be analyzed based on Kaplan-Meier methods. Participants will be considered to have an event at the time point at which treatment emergent anti-bimekizumab antibody positive is first achieved (taking the MSR into consideration for Category 5). Participants classified as treatment-emergent ADAb negative will be censored at the time of the last available ADAb result.
- Individual plots (one plot by study participant) of bimekizumab concentrations/ADAb titer (log-scale) and PASI % change from baseline will be created. All 3 endpoints will be plotted on the Y-axis by visit (x-axis) for the full treatment period, including the SFU. Plots should be labeled and grouped into the 9 ADAb categories and display vertical tick-marks on the x-axis corresponding to dosing events.

- A spaghetti plot of ADAb titer (log-scale) by visit (x-axis) will be presented for all ADAb positive study participants defined as being in Categories 2 & 5 above:
- A figure will summarize efficacy response (PASI75, PASI90 and PASI100 responders) versus ADAb titer quartiles. The x-axis will display the ADAb titer quartiles at Week 16 (categorized as negative, Q1, Q2, Q3 and Q4) and the y-axis will display percentage of PASI75/90/100 responders at Week 16.
- Three figures (side by side) summarizing the time course of efficacy response (PASI75, PASI90 & PASI100 responders at Week 16) by overall ADAb status (3 lines per plot) will be created.

  The missing group will not be displayed on the figure if the group represents <5% of study participants.
- Finally, all individual study participants-level ADAb results (including SFU) will be listed including the Screening assay, confirmatory assay, ADAb status, and titers if applicable. *NB*: titer results will only be available if the confirmatory assay is positive. The listing will also include flags for ADAb measurements that were excluded from the by-visit summaries. The reason for exclusion will be one of the following:
  - Sample collected out of window relative to current dose (or visit),
  - More than one sample obtained at the same visit.

### 5.7.2 Neutralizing anti-bimekizumab antibodies (NAbs)

NAbs will be assessed using IL-17AA- and IL-17FF-specific assay methods. NAb results will be positive or negative to each specific NAb assay or both.
Any NAb results derived from samples with drug concentrations > the drug tolerance limits of the NAb assays will be labeled "inconclusive". All inconclusive results will be regarded as missing.

Study participants will be assigned an overall NAb classification, inclusive of Baseline and post-Baseline results but excluding SFU as follows:

- NAb negative: No NAb positive samples for IL-17AA and IL-17FF at Baseline or post-Baseline. This group will also include study participants who have only 1 missing sample and all other available samples during the period of interest are negative. Study participants who are NAb negative will be classified as follows:
  - ADAb positive / NAb negative: ADAb positive study participants who are 1) NAb negative for all available ADAb positive samples or 2) with only one missing NAb sample and all other evaluated ADAb positive samples are NAb negative.
  - ADAb negative: if the study participant has all the samples as ADAb negative or only one missing/inconclusive sample with all other available samples as negative ADAb.
- NAb positive: One or more positive samples (IL-17AA positive, IL-17FF positive, or both) at Baseline or post-Baseline (regardless of missing samples). Study participants who are NAb positive will be further classified as follows:

  - Positive for IL-17AA only: one or more positive samples for IL-17AA at baseline or post-baseline. No positive samples for IL-17FF
  - Positive for IL-17FF only: one or more positive samples for IL-17 FF at baseline or post-baseline. No positive samples for IL-17AA
  - Positive for both IL-17AA and IL-17FF: one or more positive samples for both IL-17AA and IL-17FF at baseline or post-baseline
- NAb Missing:
  - >1 relevant NAb samples are missing and other available NAb samples during the period of interest are negative, e.g., missing or insufficient sample left for NAb testing.
- A listing will be produced to summarize the NAb status overall in the study. The listing will summarize the following information for each study participant assessed for Nab (including SFU data):
  - Subject identifier
  - Visit
  - Study week
  - Laboratory sampling date and time
  - Time since previous dose (weeks)
  - Bimekizumab plasma concentration level at visit (ug/mL)
  - ADAb titer at visit
  - IL-17AA NAb status and corresponding IL-17AA signal/negative control result
  - IL-17FF NAb status and corresponding IL-17FF signal/negative control result.
- A table will provide the following overall summary statistics:
  - The number and percentage (based on the total number of study participants randomized to bimekizumab) of study participants confirmed as ADAb positive and negative up to Week 16
  - The number and percentage (based on both the total number of study participants randomized to bimekizumab and the number of ADAb positive study participants) of study participants who are NAb positive, NAb negative and missing up to Week 16.

In addition, the following analysis will be performed to assess the impact of NAb status on efficacy measures:

Three figures (side by side) summarizing the time course of efficacy response (PASI75. PASI90 & PASI100 responders at Week 16) by NAb status (ADAb negative; NAb positive; ADAb positive/NAb negative; missing).

## 5.8 Subgroup analyses

No subgroup analysis will be conducted.

## 5.9 Interim Analyses

After all study participants complete the week 16 visit, a final Week 16 analysis will be performed. A final analysis and final CSR will also be prepared once all data (through the SFU visit for study participants not entering the MAP) have been collected.

## 5.10 Data Monitoring Committee (DMC) or Other Review Board

No Data Monitoring Committee will be conducted.

# 6 SUPPORTING DOCUMENTATION

## 6.1 Appendix 1 Additional analysis specifications

### 6.1.1 Baseline characteristics and demographics

All summaries detailed in this section will be performed on the RS by treatment group. Summaries for demographics and other baseline characteristics will also be repeated on SS. If the RS and SS analysis sets are identical, the SS summary will not be produced.

#### 6.1.1.1 Demographics

Demographic variables will be summarized by treatment group and overall.

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

- Age at the time of study entry (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m$^2$)

BMI (kg/m$^2$) will be calculated as:

$$BMI = \frac{Weight\ (kg)}{(Height\ (m))^2}$$

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

- Age group (18-<65, 65-<85, ≥85 years)
- Age group (≤18, 19-<65, ≥65 years)
- Age group (<40, 40-<65, ≥65 years)
- Body weight (≤100 kg, >100 kg)
- Body Weight (≤120 kg, >120 kg)
- Gender
- Race
- Ethnicity
- BMI (<25 kg/m2, 25 to <30 kg/m2, ≥30 kg/m2)

By-study participant listings of demographics for all study participants screened will be provided.

#### 6.1.1.2 Other baseline characteristics

Baseline characteristics will be summarized by dose group and overall including but not limited to:

- PSO history parameters including duration of disease, calculated as date of randomization – date of PSO first diagnosis
- PSO BSA (%)
- PASI score
- PASI score (<20, ≥20)
- DLQI total score
- DLQI total score (=0, >0)
- PSD items: Pain, Itch, Scaling
- Duration of disease (<median, ≥median)
- IGA score
- Scalp involvement (yes, no)
- PHQ-9 total score
- Prior biologic therapy (Yes, No, Missing)
- Prior primary failure to biologic (Yes, No, Missing)
- Prior anti-TNF therapy (Yes, No, Missing)
- Prior phototherapy or chemotherapy (Yes, No, Missing)
- Any prior systemic therapy (Yes, No, Missing)

Baseline scalp involvement is based on the number of participants achieving scalp IGA>0.

If the date of onset of plaque PSO is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing). If the date of randomization is missing, then the duration of disease will be derived using the date of Screening.

Continuous variables will be summarized descriptively. Categorical variables will be summarized using frequency counts and percentages.

### 6.1.2 Protocol deviations

A summary, using the RS, displaying the number and percentage of study participants with an important protocol deviation (including a summary of study participants excluded from the PPS or PK-PPS due to important protocol deviations) by treatment group will be provided.

Important protocol deviations will be categorized as follows:

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

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

The impact on study conduct of the Coronavirus Disease 2019 (COVID-19) global pandemic will be assessed and captured as: confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 without infection or any other deviation from the protocol due to COVID-19.

### 6.1.3 Medical history and concomitant diseases

Previous and ongoing medical history will be summarized by dose group for the RS by SOC and PT using MedDRA version 19.0. Medical procedures are not coded.

The following listings for medical history and concomitant diseases will be provided: medical history, psoriasis history, concomitant medical procedures, previous and ongoing medical history glossary, previous and ongoing medical history conditions, and procedure history.

### 6.1.4 Prior/concomitant/follow-up medications

Medication start and stop dates will be compared to the date of first dose of treatment to allow medications to be classified as either Prior or Concomitant. Detailed information of imputation methods for missing or partial dates could be found in 5.1.1.7.3.

Prior medications include any medications that started prior to the start date of study medication.

Concomitant medications are medications taken at least one day in common with the study medication dosing period, which the dosing period starts from the date of first dose to the date of last dose plus 28 days.

The number and percentage of study participants taking prior medications will be summarized by treatment group, overall and by Anatomical Therapeutic Chemical classification (ATC) class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term. The number and percentage taking concomitant medications will be summarized similarly.

Past psoriasis medications will be captured separately and will also be summarized by treatment group. These medications are not subject to dictionary coding. In addition, study participants who failed past psoriasis biologic treatment will be summarized by reason of failure as captured on the Psoriasis Treatment History CRF module.

By-study participant listings of all Prior and Concomitant medications, prior and concomitant medications glossary will be provided.

The number and percentage of study participants with concomitant vaccines for COVID-19 will be summarized by treatment group, overall and by World Health Organization Drug Dictionary Standardised Drug Grouping (SDG), presenting SDG subgroup, and preferred term. The SDG subgroup Vaccines for COVID-19 will be used to identify vaccines for COVID-19 using the narrow scope; this subgroup is divided further into separate subgroups which is the level that will be presented. The number of individual occurrences of the vaccine for COVID-19 will also be summarized.

A by-study participant listing of all Concomitant vaccines for COVID-19 will be provided.

### 6.1.5 Data derivation rules

#### 6.1.5.1 PASI

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

The various body regions are weighted to reflect their respective proportion of BSA. The composite PASI score is then calculated by multiplying the sum of the individual-severity scores for each area by the weighted area-of-involvement score for that respective area, and then summing the four resulting quantities as follows (note for R, T, and S scores are as follows: 0 = one, 1 = slight, 2 = moderate, 3 = marked, and 4 = very marked):

$$PASI = (0.1 \times (R_h + T_h + S_h) \times A_h) + (0.2 \times (R_u + T_u + S_u) \times A_u) + (0.3 \times (R_t + T_t + S_t) \times A_t) + (0.4 \times (R_l + T_l + S_l) \times A_l)$$

where

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

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

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

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

The highest potential PASI score is 72 for severe disease; the lowest is 0 for no psoriasis lesions. PASI scores are treated as continuous. The percent improvement in PASI scores from Baseline will be computed as:

$$Percent\ Improvement\ from\ Baseline = 100 \times \frac{Baseline\ PASI - Post\ Baseline\ Timepoint\ PASI}{Baseline\ PASI}$$

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

If a study participant is missing 1 or 2 severity measurements for a certain region, the average of the remaining severity measurement(s) within that region will be utilized to substitute for the missing severity measurement(s) in that region. If the area of affected skin and/or all severity measurements for up to 2 regions are missing, then the missing (R+T+S) x A for a region will be substituted by the average of the available (R+T+S) x A. Otherwise, the PASI will be set to missing.

#### 6.1.5.2 Exposure-adjusted rates

The EAIR is defined as the number of study participants (n) with a specific AE adjusted for the exposure and will be scaled to 100 participant-years:

$$EAIR = 100 \times n \Big/ \sum_{i=1}^{N} (T_{\mathrm{Exp}(i)})$$

Where $T_{\mathrm{Exp}(i)}$ is the exposure time for the ith participant and N is the number of participants at risk.

If a study participant has multiple events, the time of exposure is calculated to the first occurrence of the AE being considered. If a study participant has no events, the total time at risk is used. Exact Poisson 95% confidence intervals for incidence rates are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 1990; Fay and Feuer, 1997):

$$LCL = \chi^2_{2n,\alpha/2}/2$$

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

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

The EAER will be the number of AEs including repeat occurrences in individual participants divided by the total time at risk scaled to 100 participant-years and calculated using:

$$EAER = 100 \times N_{AE} \Big/ \sum_{i=1}^{N} (T_{\mathrm{Risk}(i)})$$

where $N_{AE}$ is the total number of AEs, $T_{\mathrm{Risk}(i)}$ is the time at risk for then $i^{th}$ participant, and N is the total number of participants at risk.

No confidence interval will be computed for EAER.

### 6.1.6 AEs of Special Interest

Hy's Law:

– Potential Hy's Law, defined as ALT or AST ≥3×ULN with coexisting total bilirubin ≥2×ULN in the absence of ALP ≥2×ULN, with no alternative explanation for the biochemical abnormality (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the study participant.

The detailed information of analysis for Hy's law can be found in 5.6.3.1.1

### 6.1.7 Potentially Clinically Significant Criteria for Safety Endpoints

#### 6.1.7.1 Markedly abnormality criteria for laboratory data

Markedly abnormal values are defined as those with a severity of Grade 3 and above based on the common terminology criteria for adverse events (CTCAE) criteria (U.S. Department of Health and Human Services 2017). Definitions of markedly abnormal values using the Grade 3 cut points are given in the tables below for age ranges of ≥17 years (Table 10 for markedly abnormal hematology values, Table 11 for markedly abnormal biochemistry values, and Table 12 for markedly abnormal liver function test values). Tables summarizing markedly abnormal values should include a summary (counts and percentages) of markedly abnormal labs observed at any time while on treatment (i.e., treatment-emergent markedly abnormal [TEMA]). For this summary, Baseline values are not considered. The laboratory results classified as Grade 3 or Grade 4 will be summarized and listed separately.

**Table 10: Definition of Markedly Abnormal Hematology Values**

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

**Table 11: Definition of Markedly Abnormal Biochemistry Values**

| | Conventional | Standard | |
|---|---|---|---|

| Parameter Name | Unit | Criteria | Unit | Criteria | Abnormal Designation |
|---|---|---|---|---|---|
| Creatine | mg/dL | >3.0 x ULN | umol/L | >3.0 x ULN | AH |
| Glucose | mg/dL | <40 | mmol/L | <1.7 | AL |
| | | >250 | | >13.9 | AH |
| Calcium | mg/dL | <7.0 | mmol/L | <1.75 | AL |
| | | >12.5 | | >3.1 | AH |
| Magnesium | mg/dL | <0.9 | mmol/L | <0.4 | AL |
| | | >3.0 | | >1.23 | AH |
| Potassium | mmol/L | <3.0 | mmol/L | <3.0 | AL |
| | | >6.0 | | >6.0 | AH |
| Sodium | mmol/L | <130 | mmol/L | <130 | AL |
| | | >155 | | >155 | AH |
| Cholesterol | mg/dL | >400 | mmol/L | >10.34 | AH |
| Triglycerides | mg/dL | >500 | mmol/L | >5.7 | AH |

**Table 12 Definition of Markedly Abnormal Liver Function Test Values**

| Parameter Name | Conventional | | Standard | | Abnormal Designation |
|---|---|---|---|---|---|
| | Unit | Criteria | Unit | Criteria | |
| Alkaline Phosphate | U/L | >5.0 x ULN | U/L | >5.0 x ULN | AH |
| ALT | U/L | >5.0 x ULN | U/L | >5.0 x ULN | AH |
| AST | U/L | >5.0 x ULN | U/L | >5.0 x ULN | AH |
| Total Bilirubin | mg/dL | >3.0 x ULN | mg/dL | >3.0 x ULN | AH |
| GGT | U/L | >5.0 x ULN | U/L | >5.0 x ULN | AH |

Abbreviations: AH=abnormal high; AL=abnormal low; ALT= alanine aminotransferase; AST = aspartate aminotransferase; dL = deciliter; GGT: gamma-glutamyltransferase; L = liter; mg = milligram; mmol = millimoles; µg = microgram; ULN = upper limit of normal.

#### 6.1.7.2 Markedly abnormality criteria for vital signs

The definitions of markedly abnormal vital sign values are provided below:

**Table 13: Definitions of Markedly Abnormal Blood Pressure Values**

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

### 6.1.8 Definition of CTCAE grades

**Table 14: Definitions of CTCAE grades by biochemistry parameter**

| Parameter (unit) | Definition | Unit | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|---|
| Creatinine | High | umol/L | >ULN-1.5 x ULN | (>1.5-3.0) x ULN | (>3.0-6.0) x ULN | 6.0 x ULN |
| Sodium | Low | mmol/L | 130-<LLN | N/A | 120-<130 | <120 |
| Sodium | High | mmol/L | >ULN-150 | >150-155 | >155-160 | >160 |
| Potassium | Low | mmol/L | 3.0-<LLN | 3.0-<LLN | 2.5<3.0 | <2.5 |
| Potassium | High | mmol/L | >ULN-5.5 | >5.5-6.0 | >6.0-7.0 | >7.0 |
| Calcium | Low | mmol/L | 2.0-<LLN | 1.75-<2.0 | 1.5-<1.75 | <1.5 |
| Calcium | High | mmol/L | >ULN-2.9 | >2.9-3.1 | >3.1-3.4 | >3.4 |
| Magnesium | Low | mmol/L | 0.5-<LLN | 0.4-<0.5 | 0.3-<0.4 | <0.3 |
| Magnesium | High | mmol/L | >ULN-1.23 | N/A | >1.23-3.30 | >3.30 |
| Cholesterol | High | mmol/L | >ULN-7.75 | >7.75-10.34 | >10.34-12.92 | >12.92 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Triglycerides | High | mmol/L | 1.71-3.42 | >3.42-5.7 | >5.7-11.4 | >11.4 |

**Table 15: Definitions of CTCAE grades by hematology parameter**

| Parameter (unit) | Definition | Unit | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|---|
| Hemoglobin | Low | g/L | 100-<LLN | 80-<100 | <80 | N/A |
| Hemoglobin | High | g/L | >0-20 above BL | >20-40 above BL | >40 above BL | N/A |
| Platelets | Low | $10^9$/L | 75-<LLN | 50-<75 | 25-<50 | <25 |
| WBC | Low | $10^9$/L | 3-<LLN | 2-<3 | 1-<2 | <1 |
| WBC | High | $10^9$/L | N/A | N/A | >100 | N/A |
| Lymphocytes | Low | $10^9$/L | 0.8-<LLN | 0.5-<0.8 | 0.2-<0.5 | <0.2 |
| Lymphocytes | High | $10^9$/L | N/A | >4-20 | >20 | N/A |
| Neutrophils | Low | $10^9$/L | 1.5-<LLN | 1.0-<1.5 | 0.5-<1.0 | <0.5 |

Note that study participants who meet the decreased potassium criterion of 3.0< LLN, which is specified as the decreased potassium lab criterion for both CTCAE Grade 1 and Grade 2, will be counted as Grade 2.

### 6.1.9 MedDRA algorithmic approach to anaphylaxis

The SMQ *Anaphylactic reaction* consists of three parts (select the terms according to the applicable MedDRA version):

- A **narrow search** containing PTs that represent core anaphylactic reaction terms (Category A – core anaphylactic reaction terms)

| For MedDRA v19.0: |
|---|
| Anaphylactic reaction |
| Anaphylactic shock |
| Anaphylactic transfusion reaction |
| Anaphylactoid reaction |
| Anaphylactoid shock |
| Circulatory collapse |
| Dialysis membrane reaction |
| Kounis syndrome |
| Shock |

| |
|---|
| Shock symptom |
| Type I hypersensitivity |

- A **broad search** that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction and categorized in B, C or D
  - **Category B (Upper Airway/Respiratory Terms)**

| **For MedDRA v19.0:** | |
|---|---|
| Acute respiratory failure | Nasal obstruction |
| Asthma | Oedema mouth |
| Bronchial oedema | Oropharyngeal spasm |
| Bronchospasm | Oropharyngeal swelling |
| Cardio-respiratory distress | Respiratory arrest |
| Chest discomfort | Respiratory distress |
| Choking | Respiratory failure |
| Choking sensation | Reversible airways obstruction |
| Circumoral oedema | Sensation of foreign body |
| Cough | Sneezing |
| Cyanosis | Stridor |
| Dyspnoea | Swollen tongue |
| Hyperventilation | Tachypnoea |
| Irregular breathing | Throat tightness |
| Laryngeal dyspnoea | Tongue oedema |
| Laryngeal oedema | Tracheal obstruction |
| Laryngospasm | Tracheal oedema |
| Laryngotracheal oedema | Upper airway obstruction |
| Mouth swelling | Wheezing |

  - **Category C (Angioedema/Urticaria/Pruritus/Flush terms)**

| **For MedDRA v19.0:** | |
|---|---|
| Allergic oedema | Oedema |
| Angioedema | Periorbital oedema |
| Erythema | Pruritus |
| Eye oedema | Pruritus allergic |
| Eye pruritus | Pruritus generalised |
| Eye swelling | Rash |
| Eyelid oedema | Rash erythematous |
| Face oedema | Rash generalised |

| | |
|---|---|
| Flushing | Rash pruritic |
| Generalised erythema | Skin swelling |
| Injection site urticaria | Swelling |
| Lip oedema | Swelling face |
| Lip swelling | Urticaria |
| Nodular rash | Urticaria papular |
| Ocular hyperaemia | |

- **Category D (Cardiovascular/Hypotension terms)**

| **For MedDRA v19.0:** |
|---|
| Blood pressure decreased |
| Blood pressure diastolic decreased |
| Blood pressure systolic decreased |
| Cardiac arrest |
| Cardio-respiratory arrest |
| Cardiovascular insufficiency |
| Diastolic hypotension |
| Hypotension |

- An **algorithmic approach** which combines a number of anaphylactic reaction symptoms in order to increase specificity. A case must include one of the following where both occur on either the same day as when an injection was administered or one day after, and for scenarios where two events must have been reported, both events must have occurred within one day of each other (as anaphylaxis is an acute event, imputed dates should not be used in the algorithmic approach)**:**
  - A narrow term or a term from Category A;
  - A term from Category B - (Upper Airway/Respiratory) AND a term from Category C - (Angioedema/Urticaria/Pruritus/Flush);
  - A term from Category D - (Cardiovascular/Hypotension) AND [a term from Category B - (Upper Airway/Respiratory) OR a term from Category C - (Angioedema/Urticaria/ Pruritus/Flush)]

### 6.1.10 Treatment Compliance

Study treatment compliance will be calculated and summarized for the SS.

Treatment compliance will be calculated as:

$$(Actual\ number\ of\ completed\ injections / Expected\ number\ of\ injections) \times 100$$

In this study, Baseline visit and Weeks 4, 8, 12 are dosing visits. For study participants who complete all injections as planned, the expected number of injections is 8. For participants who permanently discontinue treatment, the number of expected injections is based on the time of early discontinuation relative to the dosing visits.

Compliance will be summarized descriptively by treatment group and overall. The number and percentage of study participants meeting certain compliance thresholds (<75% and ≥75%) will also be reported.

## 6.2 Appendix 2 Changes to Protocol-Planned Analyses

According to the protocol, for the secondary efficacy endpoint of percentage change from Baseline in BSA affected by PSO Week 16, the outcomes for study participants with an intercurrent event, which is defined as discontinuation of IMP prior to Week 16, will be imputed using multiple imputation (MI). Due to the small sample size of this study, MI approach may not be valid and will be changed using LOCF instead. In addition, missing data not associated with discontinuation of IMP will also be imputed using LOCF. The same update will be applied to PHQ-9, of which the missing data will be imputed using LOCF instead of MI approach.

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