STATISTICAL ANALYSIS PLAN

AMENDMENT 2

Study: PS0041

Product: Bimekizumab

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

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN CHINESE ADULT STUDY PARTICIPANTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

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VERSION HISTORY

SAP Version	Date	Change	Rationale
1	15 Dec 2023	Not Applicable	Original version
1.1	23 May 2024	Section 4.5.3.1: Typo in nR formula is corrected. Criteria to calculate nR for bilirubin is updated.	Typo.
		Section 4.5.3.2: Abnormal flag is removed from the vital signs listing	Abnormal range is not available in data.
		Section 6.13: Hemoglobin high criteria is updated to use ULN instead of baseline value	To keep consistency with global study
1.2	19 Jun 2024	Section 1.1: remove "(using weekly average)" for PSD	PSD is collected at site, weekly average is not applicable.
		Section 4.1.3: clarifications are added for PEOT remapping and unscheduled visits remapping	Added per request during DEM-A review to clarify and facilitate understanding.
		Section 4.1.4: add "study participants in AMS who started MTP will be included in MTP summaries".	Added per request during DEM-A review to update the summaries for MTP to be only for study participants who started MTP.
		Section 4.2.1.2: add "0/1"	Added per request during DEM-A review to clarify the definition is for IGA 0/1 response at Week 16.
		Section 4.2.2, 4.2.3.1, 4.2.3.2, 4.3.1.2: add risk difference and 95% CI	Added per request during DEM-A review as China agency (CDE) may request to report risk difference.
		Section 4.3.1.1.2: remove "or greater"	Updated per request during DEM-A review as greater than 100% is not valid.

SAP Version	Date	Change	Rationale
		Section 4.4.1: add summary of MTP data for Week 16 responders	Updated per request during DEM-A review to evaluate the maintenance of efficacy from BKZ 320mg Q4W to Q8W.
		Section 4.5.1: update extent of exposure calculation	Updated per request during DEM-A review to be same with the definition used in global pivotal studies.
		Section 4.5.2.4: add overview summary of safety topics of interest for the combined treatment period	Added per request during DEM-A review as the separate summary tables for each of the safety topics of interest would be removed.
		Section 4.5.3.1: add clarification to use central lab results in table summaries	Added per request during DEM-A review to clarify the lab results from local lab will not be used in table summaries.
		Section 6.8.5: add descriptive summary for DLQI score and change from baseline	Added new analyses per request during DEM-A review
1.3	24 Jul 2024	Section 1.2: “final dose” is replaced by “last dose” for SFU period. Section 1.2 and 4.1.3: Reference from protocol is updated.	Updated to be accurate.
		Section 3: MS is added; PK-PPS definition: “IMP” is replaced by “active IMP”	MS will be used for analysis of MTP based on study participants entering MTP. PK concentration is only valid for study participants receiving at least 1 dose of active IMP (BKZ).
		Section 4.1.1.2, 4.2.1.1, 4.2.3.1, 4.3.1.3.1, 4.5.2, 4.5.3, 4.6.1.1, 4.7, 6.6,	Updated to provide clarity.

SAP Version	Date	Change	Rationale
		6.7, 6.8: clarification is added	
		Section 4.1.4: updated treatment groups for MTP data based on MS	Updated as Maintenance Set was defined.
		Section 4.2.2: risk difference and 95% CI calculation is updated	Given that there are no stratification factors in the statistical model, it is appropriate to use the common risk difference in the PROC FREQ procedure
		Section 4.4.1: DLQI minimally clinical important difference (MCID) response over time is added. MS is used for MTP summaries based on Week 16 responders.	Added new analysis per request form team.
		Section 4.4.2: DLQI is added	Updated per request from team during SAP amendment 1 review
		Section 4.5: MS is used for MTP summaries	Updated as MS is defined for MTP summaries.
		Section 4.5.1: study medication duration and time at risk is updated	Updated to correct some algorithms.
		Section 4.5.2: risk difference formula is updated	Update to be same with the latest BKZ program convention.
		Section 4.5.2.4: separate tables for safety topics of interest are removed	As the sample size of this studies is not large, team decided to remove the separate tables and only keep the overview tables and the listings.
		Section 4.5.3.1: criteria for nR calculation is updated	Updated to correct the typo.

SAP Version	Date	Change	Rationale
		Section 4.5.3.2: body temperature is added	Updated as body temperature was collected in the study.
		Section 6.2, WHODD version is updated	Updated to be consistent with the latest BKZ program convention.
		Section 6.3, 6.4: MS is added. Section 6.4.2: wording is updated	Updated as MS was defined for analysis of MTP based on study participants entering MTP.
		Section 6.12: algorithmic is updated per the latest standards	Updated to be same with the latest BKZ program convention.
		Section 7: reference is added	Updated to add one new reference.
1.4	30 Jul 2024	Section 4.1.4: add "by treatment received at the start of the MTP"	Updated to provide clarity.
		Section 4.5.1: algorithmic is updated for time at risk for combined treatment period	Updated to clarify the algorithms.
		Section 4.5.2.4.2: added back "Any Malignancy excluding non melanomic skin cancers" Section 4.5.2.2: a listing for device deficiency is added	Updated to reflect the correct rule.
1.5	6 Aug 2024	Section 4.1: clarification is added (IMP means both bimekizumab and placebo). Section 4.5.1.3: logic is updated to follow pivotal study Section 6.8.1.1: clarification is added to define missing data in efficacy analysis	Updated to provide clarity.
Amend-1	14 Aug 2024	Clean version to be finalized	

SAP Version	Date	Change	Rationale
Amend-2	21 Nov 2024	Section 4.1.1.2 Additional rules have been incorporated into the definitions of the ITP and MTP study periods: For ITP: If the PEOT visit is not done, the ITP end date will be set to the date of premature study termination. For MTP: If the PEOT visit is not done, the MTP end date will be set to the date of premature study termination.	These rules are added to address scenarios where the PEOT visit is not conducted
		Section 4.2.2 Section 4.2.3.1 Section 4.3.1.2 In the circumstance where Fisher's exact test will be applied instead of the CMH test, the risk difference and its 95% will still be provided.	When Fisher's exact test is applied, the calculation of the risk difference and its associated 95% confidence interval remains feasible.
		Section 4.4.1 The following two endpoints are moved from tertiary endpoint to additional endpoint: • Percentage of study participants with absolute BSA =0%, ≤1%, ≤3% and ≤5% over time • DLQI minimally clinical important difference (MCID) response over time	In adherence to the study protocol, these two endpoints are not listed in the tertiary endpoint.
		Section 4.5.2.2 The following three TEAE tables are added: • Incidence of TEAEs per 100 participant years	The 3 tables were added to facilitate the comparation with global pivotal studies.

SAP Version	Date	Change	Rationale
		by SOC, HLT, and PT for the MTP • Incidence of TEAEs Leading to Study Discontinuation per 100 participant years by SOC, HLT, and PT for the ITP • Incidence of TEAEs Leading to Study Discontinuation per 100 participant years by SOC, HLT, and PT for the ITP and MTP combined	
		Section 4.5.2.4.3 Replace the term "MACE" with "Cardiovascular event" throughout the document.	The terms contained in the specified SMQs are of broader scope than MACE
		Section 4.5.2.2 The following are added: For summaries for the ITP, MTP, and Initial and Maintenance Period (combined), the TEAEs will be attributed according to their onset date and time at risk of each study participants for each period (see Section 4.5.1).	Added to clarify the rules used for summaries of TEAEs by period.
		Section 4.5.3.1 The following were added: For summaries for the ITP and Initial and Maintenance Period (combined) where multiple measurements across different visits are considered (as of markedly abnormal values tables, minimum/maximum post-baseline CTCAE tables, and shift tables), the laboratory results will be	Added to clarify the rules used for laboratory summaries by period.

SAP Version	Date	Change	Rationale
		attributed according to their sampling date and time at risk for each period (see Section 4.5.1).	
		Section 4.5.3.2 The following were added: For summaries for the ITP and Initial and Maintenance Period (combined) where multiple measurements across different visits are considered (as of markedly abnormal values tables), the vital sign results will be attributed according to their collection date and time at risk for each period (see Section 4.5.1).	Added to clarify the rules used for vital sign summaries by period.
		Section 4.6.1.4.1.1 The following were added: Since the bimekizumab concentration is not collected at the SFU visit, the ADAb status will be defined as ADAb-negative if the ADAb sample values are either NS, or PS and NI at the SFU visit.	Added since the bimekizumab concentration is not collected at the SFU visit and the concentration at the SFU is expected to be much lower than drug tolerance limit (200µg/mL).
		Section 6.6 Remove device deficient from the text since it is not relevant to the medical history content of this section	The listing of device deficiency has been mentioned in section 4.5.2.2
		Section 6.10 To add definition of markedly abnormal value to cholesterol Section 6.13	For consistency between the markedly abnormal in laboratory data (Section 6.10) and CTCAE grade 3 or 4 (Section 6.13).

SAP Version	Date	Change	Rationale
		To add definition of CTCAE grade to glucose	

1 INTRODUCTION

PS0041 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque psoriasis (PSO). This statistical analysis plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report (CSR). The SAP is based on the following study documents: Protocol Amendment 2, 19 Apr 2023.

1.1 Objectives and endpoints

Table 1-1 Objectives and Endpoints

Objectives	Endpoints
Primary	
Compare the efficacy of bimekizumab administered sc for 16 weeks versus placebo in the treatment of study participants with moderate to severe plaque PSO	**Co-primary endpoint 1:** Participant-level outcome: PASI90 response at Week 16 **Co-primary endpoint 2:** Participant-level outcome: IGA 0/1 response at Week 16
Secondary	
Key secondary	
Evaluate the efficacy of bimekizumab compared with placebo at achieving response (PASI75) at 4 weeks of treatment	• Participant-level outcome: PASI75 response at Week 4
Evaluate the efficacy of bimekizumab compared with placebo at achieving complete clearance (PASI100) at 16 weeks of treatment	• Participant-level outcome: PASI100 response at Week 16
Additional secondary	
Evaluate the effect of bimekizumab compared with placebo on itch, pain, and scaling, as assessed by the PSD (P-SIM) response, at 16 weeks of treatment	Reported by study participants using the PSD (also published as P-SIM [Gottlieb et al, 2020]): • Participant-level outcome: PSD (P-SIM) response for itch at Week 16 • Participant-level outcome: PSD (P-SIM) response for pain at Week 16 • Participant-level outcome: PSD (P-SIM) response for scaling at Week 16
Assess the safety of bimekizumab through 16 weeks of treatment	• Incidence of TEAEs through Week 16 • Incidence of serious TEAEs through Week 16 • Incidence of TEAEs leading to permanent discontinuation of IMP through Week 16

Objectives	Endpoints
Tertiary	
Assess the efficacy of bimekizumab in the treatment of study participants with moderate to severe plaque PSO over time	• IGA 0 response over time • IGA 0/1 response over time • PASI75 response over time • PASI90 response over time • PASI100 response over time • Percentage of study participants with absolute PASI score ≤1, ≤2, ≤3, and ≤5 over time • Time to PASI75, PASI90, and PASI100 response
Assess the effect of bimekizumab on scalp PSO over time in study participants with scalp PSO at Baseline	• Scalp IGA 0/1 response over time
Evaluate the effect of bimekizumab over time on itch, pain, and scaling, and other items assessed by the PSD (P-SIM)	For each PSD (P-SIM) item score: change from Baseline over time
Assess the effect of bimekizumab on health-related QoL over time	• DLQI 0/1 response over time
Assess the PK of bimekizumab over time	• Plasma bimekizumab concentrations over time
Assess the immunogenicity of bimekizumab prior to and following IMP administration	• Anti-bimekizumab antibody levels prior to and following IMP administration
Assess the safety and tolerability of bimekizumab throughout the study	• Severity and frequency of TEAEs • Selected safety topics of interest TEAEs • Change from Baseline in clinical laboratory values (chemistry, hematology) • Change from Baseline in vital signs • Clinically significant changes in physical examination findings

DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; IMP=investigational medicinal product; P-SIM=Psoriasis Symptom and Impact Measure; PASI=Psoriasis Area and Severity Index; PK=pharmacokinetic(s); PSD=Patient Symptom Diary; PSO=psoriasis; Q4W=every 4 weeks; QoL=quality of life; sc=subcutaneous(ly); scalp IGA=scalp-specific IGA; TEAE=treatment-emergent adverse event

Objectives	Endpoints

Note: During the 16-week Initial Treatment Period, study participants will receive either bimekizumab 320mg Q4W sc or placebo Q4W sc. During the Maintenance Treatment Period, study participants will receive treatment as described in Protocol Section 4.1.
Note: The PASI75/90/100 response is defined as a 75% or greater/90% or greater/100% improvement from Baseline in the PASI score.
Note: The IGA 0/1 response is defined as an IGA response of clear (0) or almost clear (1) with ≥2-category improvement relative to Baseline.
Note: The PSD (P-SIM) response for itch/pain/scaling is defined as a score that has improved (decreased) by ≥4 points from Baseline, and the study participant has not discontinued IMP.
Note: The IGA 0 response is defined as an IGA response of clear (0) with ≥2-category improvement relative to Baseline.
Note: The scalp IGA 0/1 response is defined as a scalp IGA response of clear (0) or almost clear (1) with a ≥2-category improvement from Baseline.
Note: The DLQI 0/1 response is defined as a DQLI total score equal to 0 or 1.

1.2 Study design

PS0041 is a Phase 3, multicenter, randomized, double blind, placebo controlled, parallel group study to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque PSO.

The study population consists of Chinese adult study participants (≥18 years of age) with a diagnosis of moderate to severe plaque PSO (Baseline PASI≥12 and Body Surface Area [BSA] affected by PSO≥10% and Investigator's Global Assessment [IGA] score ≥3 on a 5-point scale) who are candidates for systemic PSO therapy and/or phototherapy.

This study will include 4 periods: Screening Period (up to 5 weeks), Initial Treatment Period (16 weeks), Maintenance Treatment Period (16 weeks), and Safety Follow-Up (SFU) Period (17 weeks after the final dose of IMP [Figure 1-1]).

- Screening Period

The Screening Period will last up to a total of maximum 5 weeks (for example, in cases where a laboratory assessment needs to be repeated or to allow washout of prohibited medications). During the Screening Period, eligible study participants will be informed about the study and sign the Informed Consent Form (ICF). Following signed informed consent, all screening procedures and laboratory tests (hematology, urine, and biochemistry) will be performed per the Protocol Schedule of Activities (SoA). A study participant newly diagnosed with a latent TB infection (LTBI) as a result of a positive Interferon-Gamma Release Assay (IGRA) screening test, may be rescreened once and enrolled after receiving ≥4 weeks of appropriate LTBI therapy and after consultation with the Medical Monitor. Further details of rescreening are provided in the exclusion criteria in the Protocol.

After completion of the Screening Period, eligible study participants will be allowed to enroll into the study.

- Initial Treatment Period

During the 16-week Initial Treatment Period, approximately 120 Chinese adult study participants will be randomized 3:1 to receive the following blinded IMP regimens:

  - Bimekizumab 320mg administered sc every 4 weeks (Q4W) (90 study participants)

- Placebo administered sc Q4W (30 study participants)

IMP will be administered in the clinic by sc injection at the visits specified in the Protocol SoA. Study participants withdrawing early from the study will undergo the premature end of treatment (PEOT) visit assessments and will enter the SFU period.

- Maintenance Treatment Period

After completion of the Week 16 assessments, which are the last assessments in the 16-week Initial Treatment Period, study participants will enter the 16-week Maintenance Treatment Period. The first dose of IMP will be administered at Week 16 after all assessments are performed. During the Maintenance Treatment Period, study participants will return to the clinic Q4W up to Week 32 to maintain the study blind.

The treatment during the Maintenance Treatment Period (Week 16 to Week 32) will be based on the following rules:

- Study participants in the bimekizumab 320mg Q4W arm will receive bimekizumab 320mg every 8 weeks (Q8W). These study participants will also receive placebo injections at visits between dosing with bimekizumab to maintain blinding procedures.
- Study participants in the placebo arm will receive bimekizumab 320mg Q4W.

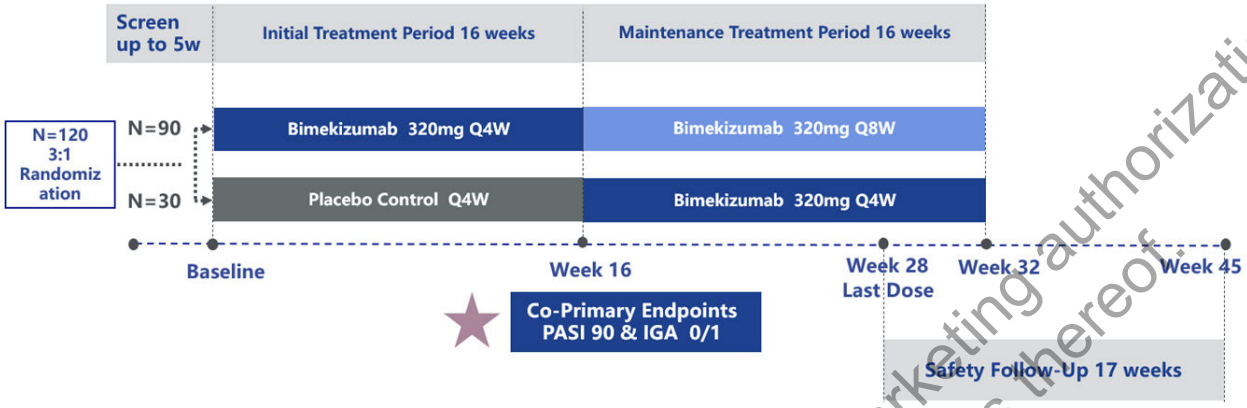
- SFU Period

After completion of the 16-week Maintenance Treatment Period, study participants will enter the SFU Period after the final dose of IMP.

Study participants withdrawing early from the study will undergo the PEOT Visit assessments and will enter the SFU Period.

All study participants, including those withdrawn from IMP, will have a SFU Visit 17 weeks after the last dose of IMP.

Figure 1-1: Study schematic



IGA 0/1=Investigator's Global Assessment response clear (0) or almost clear (1) with ≥2-category improvement relative to Baseline; PASI90=90% or greater improvement from Baseline in the Psoriasis Area and Severity Index score; Q4W=every 4 weeks; Q8W=every 8 weeks; w=week

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:

$H_{PASI90}(0)$: $OR=1$

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:

$H_{PASI90}(1)$: $OR\neq1$

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 between bimekizumab and placebo in the IGA 0/1 response at Week 16; namely the OR for bimekizumab group compared with placebo group is not equal to one:

$H_{IGA0/1}(1)$: $OR\neq1$

2.1 Multiplicity adjustment

The statistical analysis of the co-primary efficacy endpoints and key secondary endpoints will account for multiplicity and control the familywise Type I error rate at a 2-sided alpha level of 0.05 by using a fixed sequence testing procedure.

The hypotheses (H_1, H_2, H_3, H_4) comparing bimekizumab versus placebo will be tested at a 2-sided alpha level of 0.05.

The first 2 hypotheses (H_1 and H_2) will separately test whether bimekizumab is superior to placebo for PASI90 response and IGA 0/1 response at Week 16. These are the hypothesis tests corresponding to the co-primary endpoints. If both null hypotheses are rejected at a 2-sided alpha level of 0.05, that alpha will be passed to the next test in the sequence, allowing the testing procedure to proceed.

The hypotheses associated with the subsequent tests (H_3 and H_4) are for the 2 key secondary efficacy endpoints and are based on testing for superiority relative to placebo. See Table 2-1 for details on this procedure.

Table 2-1: Sequence of hypothesis testing

Hypothesis	Test
H_1 and H_2	PASI90 and IGA 0/1 response at Week 16
H_3	PASI75 response at Week 4
H_4	PASI100 response at Week 16

H=hypothesis; IGA 0/1=Investigator's Global Assessment response clear (0) or almost clear (1) with ≥2-category improvement relative to Baseline; PASI=Psoriasis Area and Severity Index; PASI75/90/100=75% or greater/90% or greater/100% improvement from Baseline in the PASI score

The hypothesis will be tested in the sequence as specified. The test will stop if the null hypothesis in previous step is not rejected using a 2-sided type I error rate of 0.05.

3 POPULATIONS FOR ANALYSIS

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

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

The Safety Set (SS) will consist of all study participants who receive ≥1 dose of IMP (bimekizumab or placebo).

The Full Analysis Set (FAS) will consist of all randomized study participants who receive ≥1 dose of IMP and have a valid measurement for each of the co-primary efficacy endpoints at Baseline.

The Active Medication Set (AMS) will consist of all study participants who receive ≥1 dose of active IMP (bimekizumab).

The Maintenance Set (MS) will consist of all study participants who receive ≥1 dose of active IMP (bimekizumab) in the Maintenance Treatment Period.

The Per-Protocol Set (PPS) will consist of all study participants in the RS who have no important protocol deviations affecting the co-primary efficacy endpoints. Important protocol deviations

will be predefined, and study participants with important protocol deviations will be evaluated during ongoing data cleaning meetings prior to database lock. The classification of PPS will be determined at blinded data evaluation meeting before unblinding of the data. The classification of study participants with important protocol deviations related to treatment group information will be re-determined after general unblinding.

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized study participants who receive ≥1 dose of active IMP (bimekizumab) and provide ≥1 quantifiable plasma concentration post dose without important protocol deviations that would affect the concentration.

4 STATISTICAL ANALYSES

4.1 General considerations

All analyses will be performed using SAS® version 9.4 (SAS Institute, Cary, NC, US). All tables and listings will use Courier New font size 9.

Descriptive statistics will be displayed to provide an overview of the study results. For continuous variables, descriptive statistics will consist of number of the study participants with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum.

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, descriptive statistics will include geometric mean, geometric coefficient of variation (CV), 95% confidence intervals (CIs) 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". Statistical comparisons will be two-sided and will be performed at the 0.05 level of significance.

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

Unless otherwise stated, the IMP administration in the Maintenance Treatment Period includes both active IMP (bimekizumab) and placebo injections for study participants randomized to BKZ Q4W in the initial treatment period and switch to BKZ Q8W in the Maintenance Treatment Period.

Per protocol, for visits from the first dose of IMP through Week 32, the visit window is ±4 days from the scheduled visit. For the SFU Visit, the visit window is ±7 days from the scheduled visit. All by-visit summaries will contain nominal (ie, scheduled) visits only. Unscheduled visits will not be mapped to scheduled visits except for assessments that occur within a 4-day time window of a scheduled visit and the relevant scheduled visit data is not available. In that case, the assessment will be mapped to the corresponding scheduled visit and will be used for the analysis. If multiple unscheduled visits are remapped to one scheduled visit, the data collected on a day nearest to the scheduled visit day will be used in the analysis. This will only occur for some vendor data (questionnaire data such as PASI, IGA, PSD, scalp IGA, and DLQI data).

4.1.1 Analysis time points

4.1.1.1 Relative day for listings

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

- If the event occurred on or after the date of first IMP administration and on or prior to the date of last IMP administration, then the following calculation is used:

  $$\text{Relative Day} = \text{Date}_x - \text{Date of first dose} + 1$$

  where Date_x is the start or stop date of interest and Date of first dose is the date of first IMP administration.

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

  $$\text{Relative Day} = \text{Date}_x - \text{Date of first dose}$$

  Relative days that occur before the date of first IMP administration should be preceded by a "-".

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

$$\text{Relative Day} = \text{Date}_x - \text{Date of last dose}$$

where Date_x is the start or stop date of interest and Date of last dose is the date of last IMP administration. Relative days that occur after the date of last IMP administration should be preceded by a "+".

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

4.1.1.2 Analysis periods

The following study periods are defined:

- Screening Period: starts at the time of the informed consent date and ends one day before the first IMP administration.
- Initial Treatment Period (ITP): starts on the day of the first IMP administration and ends prior the first IMP administration in the maintenance treatment period (first IMP in the maintenance treatment period typically occurs at Week 16, but for those that miss the Week 16 IMP administration, first IMP in the maintenance treatment period will be the first IMP administration after Week 16). For study participants that withdraw from the study prior to start of IMP in the maintenance treatment period, the ITP ends on the day of the PEOT Visit. If the PEOT visit is not done, the ITP end date will be set to the date of premature study termination.
- Maintenance Treatment Period (MTP): starts on the day and time of the first IMP administration in the MTP (first IMP in the MTP typically occurs at Week 16 after all clinical and safety assessments have been completed, but for those who miss the Week 16 IMP administration, first IMP in the MTP will be the first IMP administration after Week 16) and ends at the Week 32 visit. For study participants withdrawn from the study after Week 16 but before Week 32, the MTP will end at the PEOT Visit. If the PEOT visit is not done, the MTP end date will be set to the date of premature study termination.
- SFU Period: for participant who complete the study, in other words, complete all scheduled visit, up to and including Week 32, the SFU period starts on the day after Week 32 and ends on the day of the SFU visit. For participants who withdraw early from the study the SFU period start on the day of after PEOT Visit and ends on the day of the SFU visit.

Study participants will be considered to have completed a period if they complete the last scheduled study visit including the respective assessments for that period. It is possible for a study participant to discontinue the study after the Week 16 visit without entering the MTP. Therefore, study participants who discontinue after Week 16 assessments and who never start the MTP will be counted as having completed the ITP but having discontinued the overall study. If study participants miss the Week 16 visit, but start treatment in the MTP, they will still be considered to have completed ITP.

A study participant will be considered to have completed the study if he/she completes all scheduled visits, up to and including Week 32 (regardless of completion of the SFU Visit).

4.1.2 Definition of baseline values

A Baseline value for a study participant is defined as the latest measurement for that study participant up to and including the day of first IMP administration, unless otherwise stated. If a Baseline assessment is taken on the same day as first IMP administration, 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 IMP administration. This is considered acceptable as this measurement is still the best representation of the Baseline value of the given assessment since it is highly unlikely that the IMP could have an impact on any measurement in such a short period of time. However, such cases should be rare as study center personnel are instructed to do all assessments at the Baseline visit prior to administering IMP. One exception to this rule is plasma concentration. If Baseline plasma concentration is measured at a time after the first IMP administration, then it should not be eligible to be considered as a Baseline plasma concentration. Such cases should 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.

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 component scores on the Baseline visit cannot be derived due to missing components, the Baseline value for the component score should be calculated using the Screening visit values if the Screening visit has all of the components.

4.1.3 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. PEOT 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 regardless of the given assessment actually collected per the protocol SoA.

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 SoA. If that happens, those data will not be summarized in by-visit tables (though they will be available in the listings).

The only exception to the above rule is for anti-bimekizumab antibody assessments, in which all PEOT visit assessments will be assigned to the next scheduled visit at which anti-bimekizumab antibody are assessed.

All by-visit summaries will contain nominal visits only. Unscheduled visits will not be mapped to scheduled visits. However, in cases where vendor data (questionnaire data such as PASI, IGA, PSD, scalp IGA, and DLQI data) is assigned to an unscheduled visit instead of a scheduled visit, the assessments will be mapped into the scheduled visit if the assessments dates fall into the permissible window, as detailed in Section 4.1.

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

4.1.4 Treatment assignment and treatment groups

It is expected that study participants receive treatment as randomized for the ITP, or as assigned per protocol study design (via reallocation) for the MTP.

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 within the first 16 weeks, 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 treatment group if they never received bimekizumab.

Unless otherwise stated, the summary tables of safety analyses will be provided as:

- The ITP data will be displayed by Placebo and BZK 320mg Q4W columns based on the SS
- The MTP data will be displayed by BKZ 320mg Q4W and BKZ 320mg Q8W columns based on the MS by treatment received at the MTP
- The initial and maintenance treatment period data will be displayed by BKZ 320mg Q4W, BKZ 320mg Q8W, and BKZ 320mg Total columns based on the AMS

Study participants randomized to BKZ 320mg Q4W and received BKZ 320mg Q8W in the MTP will be represented in both the BKZ 320mg Q4W and BKZ 320mg Q8W treatment columns. BKZ 320mg Q8W column only presents the data after the switch from BZK 320mg Q4W to BZK 320mg Q8W. BKZ 320mg Q4W column will also include study participants that switch from Placebo to BKZ 320mg Q4W (only data after switch).

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

Unless otherwise stated, the summary tables of efficacy analyses will be provided as:

- The ITP data will be displayed by Placebo and BZK 320mg Q4W columns based on the RS
- The MTP data will be displayed by BKZ 320mg Q4W column and BKZ 320mg Q8W column based on the MS by treatment received at the MTP
- The initial and maintenance treatment period data will be displayed by Placebo/BKZ 320mg Q4W and BZK 320mg Q4W/Q8W columns based on the randomized treatment sequence by RS

For all TFLs for demographics, baseline disease characteristics, previous and ongoing medical history, prior and concomitant medications, and psoriasis treatment history, the summary will be displayed by Placebo/BKZ 320mg Q4W and BKZ 320mg Q4W/Q8W columns based on the randomized treatment sequence.

4.1.5 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.

4.1.6 Center pooling strategy

All centers will be pooled together for the analysis. No special centers pooling strategy is planned for this study.

4.2 Primary endpoints analysis

The co-primary efficacy endpoints for this study are PSAI90 response and IGA 0/1 response at Week 16.

4.2.1 Definition of endpoints

4.2.1.1 PASI90 response at Week 16

PASI90 response at Week 16 is defined to be equal to 1 if the percentage improvement from Baseline to Week 16 in the PASI scores is 90% or greater and 0 if the percentage improvement from Baseline to Week 16 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).

Detailed information of PASI scores and the definition of percentage improvement from Baseline can be found in Section 6.8.2.

4.2.1.2 IGA 0/1 response at Week 16

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

Detailed information of IGA can be found in Section 6.8.3.

4.2.2 Main analytical approach

The coprimary efficacy endpoints will be analyzed for all study participants in the RS. The primary analysis will be based on the Cochran-Mantel-Haenszel (CMH) test. Treatment comparisons will be made based on the CMH test using the p-value for the general association. Odds ratios and associated 95% CIs based on the Wald test will also be presented. Risk difference and associated 95% CI based on the Wald asymptotic between bimekizumab and placebo will be provided. If one of the treatment groups has 0 or very low response where CMH is no longer an appropriate method, Fisher's exact method will be applied instead, odds ratio and associated 95% CI will not be provided.

Non-responder imputation (NRI) will be used to account for missing data in the primary analysis. Specifically, any study participant who permanently withdraws from IMP prior to Week 16 or who has missing data for the co-primary efficacy variables at the Week 16 time point will be considered as a non-responder.

The number and percentage of study participants who are PASI90 responders at Week 16 will be summarized for the RS. IGA0/1 response will be summarized in the same manner as the PASI90 response.

Line plots of the mean percentage improvement from Baseline in PASI score over time by treatment group will be produced.

Line plots of the PASI90 and IGA0/1 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 for the RS.

4.2.3 Sensitivity analyses

[redacted]

[redacted]

4.3 Secondary endpoints analysis

4.3.1 Key secondary endpoints

4.3.1.1 Definition of endpoints

4.3.1.1.1 PASI75 response at Week 4

The binary response endpoint PASI75 at Week 4 is defined to be equal to 1 if the percentage improvement from Baseline to Week 4 in the PASI scores is 75% or greater and 0 if the percentage improvement from Baseline to Week 4 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).

Detailed information for PASI and the definition of percentage improvement from Baseline can be found in Section 6.8.2.

4.3.1.1.2 PASI100 response at Week 16

PASI100 response at Week 16 is defined to be equal to 1 if the percentage improvement from Baseline to Week 16 in the PASI scores is 100% and 0 if the percentage improvement from Baseline to Week 16 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).

Detailed information for PASI and the definition of percentage improvement from Baseline can be found in Section 6.8.2.

4.3.1.2 Main analytical approach

The key secondary efficacy endpoints will be analyzed for all study participants in the RS. The primary analysis will be based on the CMH test as specified in Section 4.2.2. If one of the treatment groups has 0 or very low response where CMH is no longer an appropriate method, Fisher's exact method will be applied instead, odds ratio and associated 95% CI will not be provided.

NRI will be used to account for missing data in the primary analysis. Specifically, any study participant who permanently withdraws from IMP prior to the given time point of interest or who has missing data for the key secondary efficacy variables at the given time point of interest will be considered as a non-responder.

The number and percentage of study participants who are PSAI75 responders at Week 4 and PASI100 responders at Week 16 will be summarized separately for the RS.

Line plots of the PASI100 responder rate over time by treatment group will be produced.

By-study participant listings of PASI75 and PAS100 responder variables will be provided for the RS.

4.3.1.3 Sensitivity analyses

Sensitivity analysis based on OC will be performed for the RS. Study participants with missing data or who have prematurely discontinued IMP will be treated as missing, and missing data will not be imputed. The same analysis method as described in Section 4.3.1.2 will be applied.

4.3.2 Additional secondary endpoints

The PSD (P-SIM) consists of 14 items, measuring the following PSO related signs, symptoms, and functional impacts: [redacted]. Each item is assessed for severity/impact level on a 0 to 10 scale, where 0 means no symptoms or impact and 10 means very severe symptoms or worst impact.

The additional secondary efficacy endpoints will be derived as follows:

- PSD (P-SIM) response for itch at Week 16: Itch score has improved (decreased) by ≥4 points from Baseline to Week 16, and the study participant has not discontinued IMP prior to Week 16. This will be assessed only in study participants with a Baseline itch score ≥4.
- PSD (P-SIM) response for pain at Week 16: Pain score has improved (decreased) by ≥4 points from Baseline to Week 16, and the study participant has not discontinued IMP prior to Week 16. This will be assessed only in study participants with a Baseline pain score ≥4.
- PSD (P-SIM) response for scaling at Week 16: Scaling score has improved (decreased) by ≥4 points from Baseline to Week 16, and the study participant has not discontinued IMP prior to Week 16. This will be assessed only in study participants with a Baseline scaling score ≥4.

[redacted]

[redacted]

4.4 Tertiary/Exploratory endpoints analysis

The tertiary efficacy endpoints in the Initial Treatment Period + Maintenance Treatment Period (combined) will be analyzed for all study participants in the RS.

4.4.1 Binary endpoints

The binary tertiary efficacy endpoints are listed as follows:

- IGA 0 response over time

  IGA 0 response is defined as IGA score of zero with at least a two-category improvement from Baseline at visit timepoint.

- IGA 0/1 response over time
- PASI75 response over time
- PASI90 response over time
- PASI100 response over time
- Percentage of study participants with absolute PASI score ≤1, ≤2, ≤3, and ≤5 over time
- Scalp IGA 0/1 response over time

  Details about scalp IGA can be found in section 6.8.4. Scalp IGA 0/1 response is defined as scalp IGA score of clear [0] or almost clear [1] with at least a two-category improvement from Baseline to each post baseline time point. For analysis purposes, the evaluation of scalp IGA 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 scalp IGA is 0 (thereby meeting the criterion for a two-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 0/1 response analysis.

- DLQI 0/1 response over time

  Details about DLQI can be found in section 6.8.5. DLQI 0/1 response is defined as DLQI absolute score of 0 or 1.

In addition to the aforementioned tertiary endpoints, the following summaries will be provided:

- Percentage of study participants with absolute BSA =0%, ≤1%, ≤3% and ≤5% over time
- DLQI minimally clinical important difference (MCID) response over time

  A study participant is considered to have achieved MCID if their individual improvement (decrease) from Baseline score is >=4 (Basra et al, 2015). A 4-point improvement in the DLQI score (DLQI response) has been reported to be meaningful for the study participant (within-study participant MCID). The summary of MCID will be restricted to study participants with a DLQI of at least 4 at Baseline to ensure that it is possible for the study participant to achieve the MCID.

Binary (response) endpoints will be summarized using frequency tables by treatment group for each visit.

All binary tertiary efficacy endpoints will be summarized based on imputed data (NRI) and OC data (ie, study participants with missing data or who have prematurely discontinued IMP are treated as missing, study participants with missing data will not be included in OC analysis), unless otherwise stated.

Summaries of MTP data among Week 16 responders only for PASI90, PASI100, IGA 0/1, IGA 0, Scalp IGA 0/1, DLQI 0/1 will be provided based on MS respectively.

Figures displaying the response over time using NRI data will be provided for PASI 90/100, IGA 0, IGA 0/1, Scalp IGA 0/1 and DLQI 0/1 response variables.

4.4.2 Continuous endpoints

The continuous tertiary efficacy endpoint is change from Baseline over time for each PSD (P-SIM) item score.

Continuous variables will be summarized using descriptive statistics by treatment group for each visit based on OC. Summaries of observed values and change from Baseline over time for DLQI score will also be provided.

In addition, cumulative distribution plots (see details in Section 4.3.2) will be provided for absolute and percent change from Baseline PSD at Week 16 for each item.

4.4.3 Time to PASI75/90/100 response

Time to PASI75/90/100 response (in days) during the ITP will each be calculated as:

$$Min\,(Date\ of\ first\ PASIxx\ response, Date\ of\ Week\ 16\ visit) - Date\ of\ First\ Dose\ +\ 1$$

with xx representing 75, 90, 100 respectively. All visits up to and including Week 16 visit (including unscheduled visits) will be considered.

Study participants who discontinue IMP without achieving a given PASI response (either PASI75, PASI90, or PASI100 response, respectively) prior to Week 16 visit will be censored at the date of the last observed PASI assessment on or prior to IMP discontinuation. Study participants who reach the Week 16 visit without achieving the given PASI response will be censored at the date of the last observed PASI assessment on or prior to the Week 16 visit. Study participants who miss the Week 16 visit but start the MTP without achieving a give PASI response will be censored at the date of the last observed PASI assessment on or prior to the first IMP administration in MTP. Study participants will be censored at Baseline if there is no Baseline PASI assessment or no post-Baseline PASI assessment.

Time to PASI75/90/100 response during the ITP will each be estimated and presented using the Kaplan-Meier product-limit method for each treatment group.

Kaplan-Meier plots of time to PASI responses will also be presented by treatment group. In these Kaplan-Meier plots, the line will start at 0 (since there are no responders at Day 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. Comparisons of bimekizumab versus placebo will be analyzed using a log-rank test.

4.5 Safety analyses

If not specified otherwise, all safety summaries and listings will be created for all study participants in the SS.

The MS will be used for summaries of safety that include data from the MTP and the AMS will be used for Initial and Maintenance Treatment Period (combined) summaries.

4.5.1 Extent of exposure

Summaries for exposure will be provided. This will consist of a descriptive summary of study medication duration in days. In addition, total study medication duration and time at risk will be summarized in participant-years by treatment group and treatment period (ie, the ITP, the MTP, the Initial and Maintenance Treatment Period (combined)). The cumulative study medication duration will be summarized for study participants exposed for given durations of time, the following categories for duration will be used:

- >0 weeks
- >=16 weeks
- >=24 weeks
- >=32 weeks

Definitions for study medication duration and time at risk in days are provided in this section. Time at risk will be summarized in participant-years. Time at risk in participant-years is calculated by dividing the time at risk in days by 365.25.

Throughout this section, date of last clinical contact for each study participant is defined as the maximum of [last study visit date including SFU visit (including unscheduled SFU), last AE start date (including imputed AE start dates), date of study termination or completion, last date of IMP administration].

4.5.1.1 Exposure during the ITP

Definitions for study medication duration (days) and time at risk (days) during the ITP are provided as follows:

Study medication duration (days)

$$Date\ of\ last\ dose\ in\ the\ ITP - date\ of\ first\ dose\ in\ the\ ITP + 28$$

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

- If the date of last dose in the ITP + 28 days extents to a date beyond the date of first dose of the MTP, then this calculation reverts to:

$$Date\ of\ first\ dose\ in\ the\ MTP - date\ of\ first\ dose\ in\ the\ ITP + 1$$

- For study participants who died during the ITP, if date of last dose in the ITP + 28 days extends beyond the date of death, then this calculation reverts to:

$$Date\ of\ death - date\ of\ first\ dose\ in\ the\ ITP + 1$$

- For study participants who discontinue the ITP early, if date of last dose in the ITP + 28 days extends beyond the date of the last visit (including PEOT, not including SFU), then this calculation reverts to:
  - $Date\ of\ last\ visit - date\ of\ first\ dose\ in\ the\ ITP + 1$

Time at risk (days)

For study participants who complete the final visit of the ITP (Week 16 visit) and continue to the MTP:

$$Date\ of\ first\ dose\ in\ the\ MTP - date\ of\ first\ dose\ in\ the\ ITP + 1$$

For study participants who died during the ITP:

$$Date\ of\ death - date\ of\ first\ dose\ in\ the\ ITP + 1$$

For study participants who discontinue the ITP early or who complete the ITP but not continue to the MTP, use the minimum of the following:

- *The total number of days in the ITP (112 days). For AEs that emerged after 112 days but still within the 119 days window, those AEs would be classified as TEAE, but will be excluded from the output based on the ITP. However, these AEs will be included in the AE summaries for Initial and Maintenance Treatment Period (combined).*
- $Date\ of\ last\ clinical\ contact - date\ of\ first\ dose\ in\ the\ ITP + 1$

4.5.1.2 Exposure during the MTP

Definitions for study medication duration (days) and time at risk (days) during the MTP are provided as follows:

Study medication duration (days)

$$Date\ of\ last\ active\ dose\ in\ the\ MTP - date\ of\ first\ dose\ in\ the\ MTP + 28$$

The use of 28 days assumes a Q4W dosing interval. This will be adjusted based on the dosing interval (eg, for Q8W use Date of last active dose in the MTP – date of first dose in the MTP + 56 days).

- If the date of last active dose in the MTP + 28 days (or 56 days in the case of Q8W dosing) extents to a date beyond the date of last visit in the MTP (including PEOT, not including SFU), then this calculation reverts to:

$$Date\ of\ last\ visit\ in\ the\ MTP - date\ of\ first\ dose\ in\ the\ MTP + 1$$

- For study participants who died during the MTP, if date of last active dose in the MTP + 28 days (or 56 days in the case of Q8W dosing) extends beyond the date of death, then this calculation reverts to:

$$Date\ of\ death - date\ of\ first\ dose\ in\ the\ MTP + 1$$

Time at risk (days)

For study participants who died during the MTP:

$$Date\ of\ death - date\ of\ first\ dose\ in\ the\ MTP + 1$$

For study participants who complete the MTP (not including SFU) as scheduled or who discontinue the MTP early, use the minimum of the following:

- $Date\ of\ last\ dose\ in\ the\ MTP - Date\ of\ first\ dose\ in\ the\ MTP + 119$
- $Date\ of\ last\ clinical\ contact - date\ of\ first\ dose\ in\ the\ MTP + 1$

4.5.1.3 Exposure during the Initial and Maintenance Treatment Period (combined)

Definitions for study medication duration (days) and time at risk (days) during the Initial and Maintenance Treatment Period (combined) are provided as follows:

Study medication duration (days)

Study medication duration will be summarized for BKZ 320mg Q4W, BKZ 320mg Q8W, and BKZ 320mg Total respectively:

- For BKZ 320mg Q4W:

  Include study medication duration in ITP for study participants who are randomized to BKZ 320mg Q4W in ITP (refer to section 4.5.1.1 – study medication duration) and study medication duration in MTP for study participants who are randomized to placebo in ITP and switch to BKZ 320mg Q4W in MTP (refer to section 4.5.1.2 – study medication duration)

- For BKZ 320mg Q8W:

  Include study medication duration in MTP for study participants who switch to BKZ 320mg Q8W in MTP (refer to section 4.5.1.2 – study medication duration)

- For BKZ 320mg Total:

  For study participants randomized to BKZ 320mg Q4W in the ITP:

  $$Date\ of\ last\ active\ dose - date\ of\ first\ dose\ in\ the\ ITP +$$
  28 (if last active dose was in the ITP) or 56 (if last active dose was in the MTP)

  - If the date of last active dose + 28 days (if last active dose was in the ITP) or 56 days (if last active dose was in the MTP) extends to a date beyond the date of last visit (including PEOT, not including SFU), then this calculation reverts to:

    $$Date\ of\ last\ visit - date\ of\ first\ dose\ in\ the\ ITP + 1$$

  - For study participants who died, if date of last active dose + 28 days (if last active dose was in the ITP) or 56 days (if last active dose was in the MTP) extends beyond the date of death, then this calculation reverts to:

    $$Date\ of\ death - date\ of\ first\ dose\ in\ the\ ITP + 1$$

  For study participants randomized to Placebo in ITP and switch to BKZ 320mg Q4W in MTP:

  Include study medication duration in MTP defined in section 4.5.1.2 – study medication duration.

Time at risk (days)

Time at risk will be summarized for BKZ 320mg Q4W, BKZ 320mg Q8W, and BKZ 320mg Total respectively:

- For BKZ 320mg Q4W:

  For study participants who are randomized to BKZ 320mg Q4W in ITP:

  - For study participants who complete the final visit of the ITP (Week 16 visit) and continue to the MTP

    $$Date\ of\ first\ dose\ in\ the\ MTP - date\ of\ first\ dose\ in\ the\ ITP + 1$$

  - For study participants who died during the ITP

    $$Date\ of\ death - date\ of\ first\ dose\ in\ the\ ITP + 1$$

  - For study participants who discontinue the ITP early or who complete the ITP but do not continue to the MTP, use the minimum of the following:

    $$Date\ of\ last\ dose\ in\ the\ ITP - \ Date\ of\ first\ dose\ in\ the\ ITP + 119$$

    $$Date\ of\ last\ clinical\ contact - date\ of\ first\ dose\ in\ the\ ITP + 1$$

  For study participants who are randomized to placebo in ITP and switch to BKZ 320mg Q4W in MTP:

  Include time at risk in MTP defined in section 4.5.1.2 – time at risk.

- For BKZ 320mg Q8W:

  Include time at risk in MTP for study participants who switch to BKZ 320mg Q8W in MTP (refer to section 4.5.1.2 – time at risk).

- For BKZ 320mg Total:

  For study participants randomized to BKZ 320mg Q4W in ITP:

  - For study participants who died before the final visit (not including SFU):

    $$Date\ of\ death - date\ of\ first\ dose\ in\ the\ ITP + 1$$

  - For all the other study participants including who discontinue early or who complete the MTP as scheduled, use the minimum of the following:

    $$Date\ of\ last\ dose - \ Date\ of\ first\ dose\ in\ the\ ITP + 119$$

    $$Date\ of\ last\ clinical\ contact - date\ of\ first\ dose\ in\ the\ ITP + 1$$

  For study participants who are randomized to Placebo in ITP and switch to BKZ 320mg Q4W in MTP:

  Include time at risk in MTP defined in section 4.5.1.2– time at risk

A by-study participant listing of exposure to study medications will be provided on the SS by treatment group.

4.5.2 Adverse events

An AE is any untoward medical occurrence in a study participant or clinical investigation study participant 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.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA version 19.0). All summaries will be provided by treatment group. The treatment group for each study participant will be defined as the treatment received at the onset of the AE. For study participants who switch treatment (ie, from placebo to bimekizumab or from bimekizumab Q4W to Q8W) at Week 16, any AEs that occur after initiation of the new treatment are attributable to the new treatment.

If an AE occurs on the date of a treatment switch, the event is attributed to the original treatment. The only exceptions are for the following types of events, which will be attributed to the new study treatment:

- Events that fulfill the anaphylaxis criteria for acute events (refer to Section 6.12)
- Events that fulfill the hypersensitivity reaction criteria (Hypersensitivity events will be identified using the "Hypersensitivity (Standardized MedDRA Query ([SMQ])". All TEAEs which code to a Preferred Term (PT) included in the Scope=Narrow search will be included.)
- Events with a High Level Term (HLT) of "Administration site reactions NEC"
- Events with an HLT of "Injection site reactions"

4.5.2.1 Data considerations

TEAEs are defined as those AEs that have a start date on or following the first dose of IMP through the final dose of IMP + 119 days (covering the 17-week SFU period). If it is not possible (due to partial dates) to determine whether or not an AE is treatment-emergent then it will be assumed to be a TEAE.

The rules for imputing partial AE start or stop dates are described in Section 6.8.1.2.

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

AEs will be presented as "number of study participants (percentage of study participants) [number of events]". In this style of output, "[number of events]" will include all cases of an AE including repeat occurrences in individual study participants, while "number of study participants" will count each study participant only once.

AE summaries by System Organ Class (SOC), High Level Term (HLT) and Preferred Term (PT) will be ordered alphabetically for SOC and HLT within SOC and in terms of decreasing frequency for PT within HLT in the bimekizumab treatment group, and in the event of ties, PT will be sorted alphabetically.

AE summaries by PT will be ordered in terms of decreasing frequency for PT within the bimekizumab treatment group, and in the event of ties, PT will be sorted alphabetically.

Study participant time at risk represents the time a study participant is at risk for having an AE. The definitions for study participant time at risk (in days) are outlined in Section 4.5.1. These definitions will be used for exposure-adjusted AE summaries.

Selected AE summaries will include the exposure-adjusted incidence rate (EAIR) with associated 95% CI and the exposure-adjusted event rate (EAER).

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 patient-years:

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

where N is the total number of study participants in the respective treatment group, and $T_{Exp(i)}$ is the time of exposure for each study participant. If a study participant has the specific AE being summarized, the time of exposure is censored at the date of the event (calculated as AE start date – date of first IMP administration + 1). If a study participant has multiple events, the time of exposure is calculated to the first occurrence of the AE being considered (calculated as AE start date for the first occurrence – date of first IMP administration + 1). If a study participant has no events, the total time at risk is used.

Exact Poisson 95% CIs for incidence rates are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 1990; Fay and Feuer, 1997):

$$LCL = \frac{\chi^2_{2n,\alpha/2}}{2 \times \sum_{i=1}^{n} \left(T_{Exp(i)}\right)}$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2 \times \sum_{i=1}^{n} \left(T_{Exp(i)}\right)}$$

where n is the number of study 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 χ^2.

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

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

where N_{AE} is the total number of AEs, T_{Risk} is the time at risk for each subject, and N is the total number of subjects at risk.

No CI will be computed for EAER.

Selected summaries will include the risk difference between bimekizumab and placebo. The risk difference (RD) is calculated as:

$$RD = IP_{BKZ} - IP_{PBO}$$

where IP_{BKZ} is the incidence proportion for the bimekizumab-treated group and IP_{PBO} is the incidence proportion for the placebo group. Note that incidence proportion simply refers to the percentage of study participants within the specified treatment group that experienced a given AE.

The standard error (SE) for the risk difference is calculated as follows:

$$SE_{RD} = \sqrt{\left(IP_{BKZ} \times \left(\frac{1 - IP_{BKZ}}{n_{BKZ}}\right)\right) + \left(IP_{PBO} \times \left(\frac{1 - IP_{PBO}}{n_{PBO}}\right)\right)}$$

where n_{BKZ} is the number of study participants in the bimekizumab-treated group and n_{PBO} is the number of study participants in the placebo group.

The corresponding CI for the risk difference is as follows:

$$CI_{RD} = RD \pm Z_{1-\alpha/2} \times (SE_{RD})$$

where $Z_{1-\alpha/2}$ is the Z statistic for the corresponding level of alpha. For the risk difference CIs calculated in this SAP, 1.96 will be used (corresponding to a two-sided alpha of 0.05 and 95% CI). The risk difference and corresponding CI will be displayed as percentage.

4.5.2.2 AE summaries

The following summaries will be provided in three different ways: by treatment for the ITP for the SS, by treatment for the MTP for the MS, by treatment for the Initial and Maintenance Treatment Period (combined) for the AMS. For summaries for the ITP, MTP, and Initial and Maintenance Period (combined), the TEAEs will be attributed according to their onset date and time at risk of each study participants for each period (see Section 4.5.1).

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 participant years by SOC, HLT, and PT

The following summaries will be provided in two different ways: by treatment for the ITP for the SS, and by treatment for the Initial and Maintenance Treatment Period (combined) for the AMS:

- Incidence of Serious TEAEs per 100 participant years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Permanent Discontinuation of IMP per 100 participant years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Study Discontinuation per 100 participant 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 Serious TEAEs by Relationship SOC, HLT, and PT – Note: For EudraCT reporting purposes
- Incidence of TEAEs Leading to Death by Relationship by SOC, HLT, and PT – Note: For EudraCT reporting purposes
- Incidence of TEAEs by Maximum Intensity, SOC, HLT, and PT
- Incidence of TEAEs by decreasing frequency of PT
- Incidence of TEAEs Above Reporting Threshold of 5% by SOC and 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 Non-Serious TEAEs Above Reporting Threshold of 5% by Relationship SOC and PT
- Incidence of Related TEAEs by SOC, HLT, and PT
- Incidence of Related TEAEs Above Reporting Threshold of 5% by SOC and PT

The following summary will be provided by treatment for the ITP for the SS:

- Incidence of TEAEs Above Reporting Threshold of 5% with Risk Differences by SOC and PT
- Incidence of Serious TEAEs and Risk Differences by SOC and PT

  The tables with risk differences will also be accompanied by figures (dot plots) which show the incidence of the AEs and corresponding 95% risk difference CIs. These will be ordered by descending order of risk difference (bimekizumab vs placebo).

The following summary will be provided for the Initial and Maintenance Treatment Period (combined) for the AMS by trough plasma concentration tertiles:

- TEAEs and infection TEAEs (TEAEs which code to the SOC of "Infections and infestations") will be summarized by bimekizumab trough plasma concentration tertiles based on Week 32 PK samples. Study participants with missing Week 32 PK samples will not be included.

  The summary will include the number of TEAEs and infection TEAEs, number of study participants with TEAEs and infection TEAEs, percentage of study participants with TEAEs and infection TEAEs, EAIR with 95% CI, and EAER. Infection TEAEs will be sorted by SOC, High Level Group Term (HLGT), HLT and PT. Fungal infections and candida infections will be identified based on MedDRA classification; a separate table does not need to be produced to summarize these events.

In addition, all summaries of TEAEs based on "100 participant years" will include EAIR (with 95% CI) and EAER.

By-study participant listings on all AEs, all serious AEs, and all deaths will be provided on the ES. By-study participant listings based on TEAEs related to study medication and TEAEs leading to study discontinuation will be provided on the SS. A by-study participant listing for device deficiency will also be provided based on the SS.

4.5.2.3 COVID-19 impact on AEs

Not applicable.

4.5.2.4 Other safety topics of interest

The following are AEs of other safety topics of interest that require special statistical analyses and will be provided based on 100 participant years by SOC and PT in two different ways: by treatment in the ITP for the SS, and by treatment in the Initial and Maintenance Treatment Period (combined) for the AMS.

There will be a table which displays the risk difference and the associated 95% CIs for each of the topics of interest in the ITP. A corresponding figure (with dot plots) will be prepared. A summary of each safety topics of interest in the Initial and Maintenance Treatment Period (combined) for the AMS will also be provided.

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

4.5.2.4.1 Infections (serious, opportunistic, fungal and Tuberculosis (TB))

Serious infections will be identified based on MedDRA classification (SOC "Infections and infestations") using the "Any Serious AE (SAE)" table.

Fungal infections will include all TEAEs (serious and non-serious) which code into the HLGT "Fungal infectious disorders".

Opportunistic infections (including tuberculosis) will include all opportunistic infection TEAEs identified using UCB-defined search criteria which were adjudicated as opportunistic infections.

4.5.2.4.2 Malignancies

These events will be identified 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.

"Any Malignancy excluding non melanomic skin cancers" will also be summarized based on SMQ="Malignant tumours (SMQ)", excluding those AEs which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

4.5.2.4.3 Cardiovascular events

For evaluation of potential major adverse cardiac event (MACE), cardiovascular events will include all TEAEs with PT of "Cardiac death" or "Sudden death" and TEAEs which code to a PT included in the Scope=Narrow group within the following SMQs:

- Central nervous system haemorrhages and cerebrovascular conditions (SMQ)
- Ischaemic heart disease (SMQ)
- Embolic and thrombotic events (SMQ)

4.5.2.4.4 Neutropenia

Neutropenia will include TEAEs with 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

4.5.2.4.5 Suicidal Ideation and Behavior (SIB)

SIB events will include all TEAEs which code to a PT included in the Scope=Narrow group within "Suicide/self-injury (SMQ)". Neuropsychiatric AEs will be identified based on MedDRA SOC psychiatric disorders using the "any TEAE table".

4.5.2.4.6 Inflammatory bowel disease (IBD)

IBD events will include all TEAEs with HLT "Colitis (excl infective)".

4.5.2.4.7 Hypersensitivity (including anaphylaxis)

Anaphylactic events will be identified based on the MedDRA anaphylaxis Algorithm (see Section 6.12) for acute anaphylactic events (reported on the same day as when an injection was administered or one day after).

Hypersensitivity events will be identified using the SMQ "Hypersensitivity (SMQ)". All TEAEs which code to a PT included in the Scope=Narrow search will be included. In addition, serious hypersensitivity events will be identified using the SMQ "Hypersensitivity (SMQ)". All serious TEAEs which code to a PT included in the Scope=Narrow search will be included.

Furthermore, injection site reactions will be identified using the HLTs: "Administration site reactions NEC" and "Injection site reactions".

4.5.2.4.8 Hepatic events and drug-induced liver injuries (DILIs)

Hepatic events will be identified 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.

Hepatic events (including DILI) will also be listed.

4.5.3 Additional safety assessments

4.5.3.1 Clinical laboratory evaluations

Laboratory values, including markedly abnormal laboratory values will be presented descriptively by treatment group for the SS.

Tables presenting markedly abnormal values and those based on CTCAE grade (see section 6.13) will only include selected laboratory variables.

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. Assessments collected at SFU visit should be included in by-visit tables. 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 SI units and will be based on observed case values. In the case where laboratory values are below the lower limit of quantification, then these will be set to the midpoint between 0 and the lower limit of quantification for the purpose of summarizing the data. Only central laboratory results will be used in table analysis, while local laboratory results will only be displayed in listings.

For summaries for the ITP and Initial and Maintenance Period (combined) where multiple measurements across different visits are considered (as of markedly abnormal values tables, minimum/maximum post-baseline CTCAE tables, and shift tables), the laboratory results will be attributed according to their sampling date and time at risk for each period (see Section 4.5.1).

The following analyses will be presented:

- A summary of the absolute and change from Baseline values in each laboratory variable by treatment group and visit for the SS displaying the Placebo/BKZ 320mg Q4W and BKZ 320mg Q4W/Q8W.
- A summary of the number and percentage of study participants experiencing markedly abnormal values at any time while on treatment (ie, assessment on or following the first dose of IMP through the last dose of IMP + 119 days, occurring at scheduled and unscheduled visits) by laboratory variable and treatment group. Baseline values and values observed more than 119 days after the last administration of IMP are not considered. Two separate tables will show results for the ITP (for the SS) and the initial and maintenance treatment period (combined) (for the AMS). See section 6.10.1 for the criteria for markedly abnormal values.
- 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. Two separate tables will show results for the ITP (for the SS) and the initial and maintenance treatment period (combined) (for the AMS).
- Shift tables of the number and percentage of study participants experiencing CTCAE grade 0,1,2,3, or 4 values (as applicable) at Baseline to minimum/maximum post-Baseline CTCAE grade, by laboratory variable and treatment group. Two separate tables will show results for the ITP (for the SS) and the initial and maintenance treatment period (combined) (for the AMS).
- By-study participant listings of all laboratory data (including urinalysis) will be provided. These listings will be presented by treatment group and will include: center, study participant identifier, age, sex, race, weight, visit, laboratory variable, result (with abnormal values flagged as “L” or “H” accordingly) and unit.
- A separate listing will be provided for laboratory results classified as Grade 3 or Grade 4 for the SS.

The table for markedly abnormal liver function tests (LFTs) will contain data beyond the CTCAE Grade 3 thresholds outlined in Section 6.10.1 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: >3xUpper Limit of Normal (ULN), >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

For any participant with at least one markedly abnormal LFT (AST >3xULN, ALT >3xULN, bilirubin >3xULN, or ALP >1.5xULN) the New Ratio (nR) will be calculated as the ratio of either maximum ALT or maximum AST (whichever is higher) to ALP, all expressed as multiples of their ULN as follows:

- nR = [maximum(ALT/ULN or AST/ULN)]/(ALP/ULN)

A plot displaying shift in liver function tests from baseline to maximum post-baseline result and a plot showing maximum post-baseline Total Bilirubin versus maximum post-baseline AST and ALT will be provided for the AMS if there are study participants with reported markedly abnormal LFT.

The following definition of potential drug induced liver injuries (pDILI) will be used (all criteria must be met at the same assessment):

- (AST or ALT ≥ 3xULN) and Total Bilirubin ≥ 1.5xULN
- (AST or ALT ≥ 3xULN) and Total Bilirubin ≥ 2xULN

A table for 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.

In addition, a table will be produced to summarize potential Hy's Law cases. The following two definitions will be used in that table (all criteria must be met at the same assessment):

- [AST ≥3xULN or ALT ≥3xULN] and Total Bilirubin ≥2xULN in the absence of ALP ≥2xULN

In case any study participants meeting the potential Hy's Law criteria, a plot displaying time course for serum LFTs will be provided on the AMS.

4.5.3.2 Vital signs

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

For summaries for the ITP and Initial and Maintenance Period (combined) where multiple measurements across different visits are considered (as of markedly abnormal values tables), the vital sign results will be attributed according to their collection date and time at risk for each period (see Section 4.5.1).

- A summary of the absolute and change from Baseline value for each vital sign variable by treatment group and visit for the SS displaying the Placebo/BKZ 320mg Q4W and BKZ 320mg Q4W/Q8W.

- A summary of the number and percentage of study participants experiencing at least one markedly abnormal value for a vital sign variable as defined in Section 6.10.2, by treatment group. Two separate tables will show results for the ITP (for the SS) and the initial and maintenance treatment period (combined) (for the AMS).
- A by-study participant listing of all vital signs data will be provided for the SS. This listing should be presented by treatment group and will include: center, study participant identifier, age, sex, race, weight, visit, vital sign variable and result.

4.5.3.3 Electrocardiograms

Electrocardiogram (ECG) data will be recorded at the Screening Visit. A by-study participant listing of all ECG data will be provided for the SS.

4.5.3.4 Other safety endpoints

4.5.3.4.1 Physical examination

A physical examination is performed at screening, Baseline, Week 16, Week 32/PEOT and SFU and may also be performed at unscheduled visits, although findings are only recorded on the CRF at screening visit. Abnormal results of the physical examination at screening visit together with details of abnormalities: abnormality clinically significant or not, will be listed by study participant for the SS. A by-study participant listing of body weight will also be provided for the SS.

4.5.3.4.2 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 results at all applicable visits will be presented for the Initial and Maintenance Treatment Period (combined) for the SS presenting Placebo/BKZ 320mg Q4W and BKZ 320mg Q4W/Q8W.

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

A by-study participant listing of the result of study related medical procedures (including chest x-ray and computed tomography) for tuberculosis will be provided by treatment group for the RS.

4.6 Other analyses

4.6.1 Other endpoints and/or parameters

4.6.1.1 Pharmacokinetics

PK variables will be analyzed for all study participants in the PK-PPS. Bimekizumab plasma concentrations will be summarized for each treatment group at each scheduled visit. All plasma concentration data will be reported in µg/mL in the tables, figures, and listings. For study participants randomized to placebo and switched to BKZ 320mg Q4W, the baseline corresponds to the Week 16 pre-dose observation.

PK summaries will be based on observed values. No imputation will be used. However, if plasma concentration measurements are below limit of quantification (BLQ), then for calculation of the derived statistics the result will be set to 0.125 µg/ml, which is ½ of the lower limit of

quantification (LLOQ). Descriptive statistics including number of values, geometric mean, geometric coefficient of variation, geometric mean 95% CI, mean, SD, median, minimum, and maximum if applicable will be calculated if at least ⅔ of the values of interest are above the LLOQ and n>=3. Otherwise, only number of values, median, minimum, and maximum will be presented.

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 the PK summary.

If the PK sampling date is >1 day after the dosing date, data points will be excluded from the PK summary tables and figures, but not from the listing.

However, all PK concentrations will be listed for the AMS.

If more than 10% of the PK concentration results have been excluded from the table summaries, the PK excluded results will be listed in a separate listing.

4.6.1.2 Pharmacodynamics

Not applicable.

4.6.1.3 Population pharmacokinetics

PK model-based analyses may be described in a separate analysis plan and reported independently.

4.6.1.4 Immunogenicity

4.6.1.4.1 Definitions

4.6.1.4.1.1 ADAb sample status (positive, negative, missing)

The ADAb sample results will be provided as "Positive Screen" (PS) or "Negative Screen" (NS). For samples presenting ADAb levels that are PS, a further confirmatory assay will be performed, and the result will be reported as either "Positive Immunodepletion" (PI) or "Negative Immunodepletion" (NI).

The ADAb status for each sample will be derived as follows:

- Sample values that are either NS, or PS and NI and where the bimekizumab concentration is less than the validated ADAb assay drug tolerance limit (200µg/mL) will be defined as ADAb-negative. Since the bimekizumab concentration is not collected at the SFU visit, the ADAb status will be defined as ADAb-negative if the ADAb sample values are either NS, or PS and NI at the SFU visit.
- Sample values that are either NS, or PS and NI and where the bimekizumab concentration exceeded the validated ADAb assay drug tolerance limit will be defined as inconclusive. Since the bimekizumab concentration is not collected at the SFU visit, the ADAb status will be defined as ADAb-negative if the ADAb sample values are either NS, or PS and NI at the SFU visit.
- Sample values that are PS and PI will be defined as ADAb-positive (regardless of availability of a titer value).
- Missing or non-evaluable samples will be defined as missing.

The PI samples will be titrated and the ADAb titer (reciprocal dilution factor including minimum required dilution) will be reported. The PI samples will also be analyzed in a neutralizing assay to evaluate the anti-bimekizumab antibody neutralized target binding of bimekizumab (IL-17AA or IL-17FF or both) in vitro.

4.6.1.4.1.2 Cumulative ADAb status

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

A study participant will be counted 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 1 missing/inconclusive sample with all negative ADAb samples up to that time point, the study participant will be classified as negative. An exception remains for the Baseline Visit where only 1 sample could be available. If the sample is missing/inconclusive, then the sample will be classified as being negative for the cumulative ADAb status.

Otherwise, the study participant will be classified in the missing ADAb category.

4.6.1.4.1.3 Overall ADAb status (Positive, Negative, Missing)

A participant's Overall ADAb Status will be derived for the following periods:

- Overall ADAb Status in the Initial and Maintenance Treatment Period (combined): Including any visit during the Initial and Maintenance Treatment Period (as defined in Section 4.1.1.2). Thus, this summary will exclude data obtained at the SFU visit and will include data obtained at Baseline. This summary will display the overall ADAb status up to Weeks 16 and 32 by treatment group (Placebo/BKZ 320mg Q4W, BKZ 320mg Q4W/Q8W).

For each time period, the participant will be classified as:

- Positive if the study participant has at least one positive sample up to the time point of interest (regardless of having missing/inconclusive data).
- Negative if the study participant has all the samples negative or only one missing/inconclusive sample with negative ADAb samples up to the timepoint of interest.
- Missing if the study participant has missed more than one ADAb result (or have more than one inconclusive sample) and all other available ADAb samples are negative up to the time point of interest.

4.6.1.4.1.4 ADAb categories

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

- **Pre ADAb negative – treatment emergent ADAb negative（Category 1）**: Includes study participants who are negative at Baseline and antibody negative at all sampling points (including SFU); one post-Baseline missing/inconclusive sample is allowed for study participants with pre-ADAb negative sample. This group also includes study participants

who have a missing/inconclusive pre-treatment sample (eg, either missing/inconclusive or insufficient volume) at Baseline with all post-Baseline samples as ADAb negative.

- **Pre ADAb negative – treatment emergent ADAb positive (Category 2)**: Includes study participants who are ADAb negative at Baseline and ADAb positive at any sampling point post treatment (including 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.
- **Pre ADAb positive – treatment emergent reduced ADAb (Category 3)**: Includes study participants who are ADAb positive at Baseline, and ADAb negative at all sampling points post treatment (including SFU).
- **Pre ADAb positive – treatment emergent unaffected ADAb positive (Category 4)**: Includes study participants who are positive at Baseline and are positive at any sampling point post treatment (including SFU) and all post-Baseline samples have titer values <2.07 times the Baseline titer (where 2.07 is Minimum Significant Ratio [MSR]).
- **Pre ADAb positive – treatment boosted ADAb positive (Category 5)**: Includes study participants who are positive at Baseline and have at least one post-treatment sample (including SFU) that has titer value ≥2.07 times the Baseline titer (where 2.07 is MSR).

  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 (ie, Category 5), assuming no other samples are available.
- **Inconclusive (Category 6)**: Includes study participants who have a positive pre-treatment sample and some post-treatment samples are missing/inconclusive, while other post-treatment samples are ADAb negative.
- **Total treatment-emergent (Category 7 [Categories 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).
- **Total prevalence of pre-ADAb positivity (Category 8 [Categories 3, 4, 5, and 6 combined]):** Study participants that are tested ADAb positive at Baseline.
- **Missing (Category 9):** Includes study participants who have a negative or missing/inconclusive pre-treatment sample at Baseline and more than one post-treatment samples that are missing/inconclusive, while other samples are ADAb negative. Also includes study participants who have a missing/inconclusive pre-treatment sample at Baseline, and only one missing post-Baseline sample with no ADAb-positive.

4.6.1.4.1.5 ADAb status groups for efficacy endpoint summaries

For the efficacy endpoint by ADAb summaries (described below), the following ADAb-efficacy status groups are defined:

- ADAb-positive - Defined as study participants having at least 2 ADAb-positive samples up to the time point of interest (ie, excluding Baseline, excluding SFU) regardless of other ADAb-negative samples and/or missing or inconclusive samples

- ADAb-negative - Defined as study participants for whom either
  1. all samples to the time point of interest are ADAb-negative and there are no missing or inconclusive samples,
  2. only one sample is ADAb-positive and all other to the time point of interest (including Baseline) are ADAb-negative or missing/inconclusive, or
  3. only one sample is missing/inconclusive and the remaining ADAb samples are negative.
- Missing - Defined as study participants who do not fulfil the criteria for one of the 2 groups listed above.

The ADAb data from Baseline up to the time point of interest will be used to derive the ADAb-efficacy status groups.

The rationale for requiring at least 2 time points in which the participant is confirmed positive is to exclude individuals who have only one occurrence of ADAb levels during the period of interest. Including such study participants would increase the number of ADAb-positive participants with potentially no impact on efficacy.

4.6.1.4.1.6 Neutralizing anti-bimekizumab antibodies (NAb) categories

The NAbs will be assessed using IL-17AA- and IL-17FF- specific assay methods, respectively. A NAb result will be positive or negative to each specific NAb assay or both.

Any NAb results derived from samples with drug concentrations higher than the drug tolerance limits of the NAb assays (100µg/mL) 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 from NAb assay:

- NAb negative:
  - ADAb positive / NAb negative: No NAb positive samples for IL-17AA and IL-17FF at Baseline or post-Baseline. This group also includes study participants who have only one missing sample and all other available samples during the period of interest are negative.
  - ADAb negative: negative samples (refer to Section 4.6.1.4.1.3) are not analyzed for NAb.
- 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 (and no samples are positive for IL-17FF).
  - Positive for IL-17FF only: one or more positive samples for IL-17 FF at Baseline or post-Baseline (and no samples are positive 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: more than one relevant NAb samples are missing/inconclusive and other available NAb samples during the period of interest are negative, eg, missing or insufficient sample left for NAb testing.

4.6.1.4.1.7 ADAb Sample Inclusion and Exclusion Rules

The following rules will be implemented for by-visit ADAb summaries if applicable:

- If the ADAb sample is collected within ±14 days (excluding the Week 32, PEOT, or SFU visit) relative to the visit date at which the IMP 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).

Samples collected outside the relevant windows described above will be excluded from the ADAb by-visit summaries and will be listed only.

For samples associated with the Week 32, PEOT, or SFU, all ADAb data obtained will be included in the by-visit summaries.

All other summaries of ADAb (as described in the following sections) will use all available (both scheduled and unscheduled) data.

The reason for exclusion will be assigned as one or more of the following:

- Sample collected out of window relative to current dose (or visit)
- More than one sample obtained at the same visit

4.6.1.4.2 Immunogenicity analyses

4.6.1.4.2.1 ADAb and NAb summaries

All analyses will be prepared on the AMS by treatment group, unless specified otherwise.

The following summaries of ADAb data will be prepared by treatment group:

- Summary table displaying the number and percentage of study participants with ADAb sample status (positive, negative, total of positive and negative, missing) at each visit, and overall ADAb status during the respective treatment periods of interest (overall up to Week 16 and Week 32 and separately overall up to Week 16 and Week 32 for the efficacy subgroup analysis). If ≥95% of study participants are in the nonmissing groups, the missing group will not be displayed.
- Number and percentage of study participants with first occurrence of ADAb-positive result by visit by ADAb category:
  - Any ADAb-positive: ADAb-positive sample regardless of category during the treatment period
  - Category 7: Total treatment-emergent ADAb positive (combination of categories 2 and 5 [PreADAb negative – treatment-emergent ADAb-positive; and PreADAb-positive – treatment emergent ADAb boosted positive, respectively])

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 the cumulative number and percentage of study participants with any ADAb-positive sample and treatment-emergent ADAb-positive and treatment boosted ADAb-positive results at each time point will be summarized.

- Number and percentage of study participants in each of the 9 ADAb categories (as defined in Section 4.6.1.4.1.4) up to Week 32 (repeated including SFU in the final analysis).
- All individual study participant-level ADAb results will be listed including the screening assay, confirmatory assay, ADAb sample status, and titers if applicable. Note that titer results will only be available if the confirmatory assay is positive. The listing will also include flags and reasons for exclusion for ADAb measurements that are excluded from the by-visit summaries, as well as information on whether the bimekizumab concentration exceeded the ADAb assay drug tolerance limit.

The following summaries of NAb data will be prepared by treatment group:

- Number and percentage of participants by the NAb categories (as defined in Section 4.6.1.4.1.6) during the respective treatment periods of interest (up to Week 16 and up to Week 32, repeated including SFU in the final analysis). These NAb summary tables will be repeated with percentages based on the total number of ADAb-positive participants in each treatment group (thus, the ADAb-negative group will not be displayed in this table).

4.6.1.4.2.2 Pharmacokinetics by ADAb and NAb summaries

The following summaries of ADAb data will be prepared by treatment group:

- Summary table displaying bimekizumab plasma concentrations by cumulative ADAb sample status (positive, negative, missing) and visit during the respective treatment periods of interest from Baseline up to Week 32.
- Figures displaying geometric mean bimekizumab plasma concentrations by cumulative ADAb status (ADAb-negative, ADAb-positive) over time during the respective treatment periods of interest from Baseline up to Week 32. SFU samples will not be included.

The following summaries of NAb data will be prepared by treatment group:

- Summary table displaying bimekizumab plasma concentrations by overall NAb status at Week 32 (ADAb-negative, ADAb-positive/NAb-negative, NAb-positive, and NAb missing) and visit during the respective treatment periods of interest from Baseline up to Week 32.

- Figures displaying geometric mean bimekizumab plasma concentrations and overall NAb status at Week 32 (ADAb-negative, ADAb-positive/NAb-negative, NAb-positive) over time during the respective treatment periods of interest from Baseline up to Week 32. SFU samples will not be included.

4.6.1.4.2.3 Efficacy endpoints by ADAb and NAb summaries

The following summaries of ADAb data will be prepared by treatment group:

- Number and percentage of PASI90 responders at Week 16 and at Week 32 by ADAb status. This will be repeated for IGA 0/1 responders at Week 16 and Week 32. These data will also be presented graphically.
- Number and percentage of PASI90 responders over time (up to Week 16 and Week 32) separated by overall ADAb status (up to Week 16 and Week 32, respectively). This will be repeated for IGA 0/1 responders (up to Week 16 and Week 32). These data will also be presented graphically.
- Number and percentage of PASI90 responders at Week 16 and Week 32 as a function of Week 16 and Week 32 ADAb titer categories (categorized as ≤100 [at or below the MRD of the assay], >100 – <median [of non-missing titer values >100], and ≥ median [of non-missing titer values >100]). This will be repeated for IGA 0/1 responders at Week 16 and at Week 32. These data will also be presented graphically (for the figure, any study participant with ADAb-positive/ADAb titer missing is included ≤100 group).
- Individual plots of bimekizumab concentrations, ADAb titer, and PASI90 response (based on NRI) will be created. All 3 endpoints will be plotted on the Y-axes by time (X-axis) for the full treatment period including SFU. Plots will be labeled and grouped into the 7 predefined ADAb categories (category 1, 2, 3, 4, 5, 6, and 9).

The following summaries of NAb data will be prepared by treatment group:

- Number and percentage of PASI90 responders at Week 16 and at Week 32, by NAb category (ADAb-negative, NAb-positive, ADAb-positive / NAb-negative). This will be repeated for IGA 0/1 responders. These data will also be presented graphically.
- Number and percentage of PASI90 responders over time (up to Week 16 and Week 32) separated by NAb category (ADAb-negative, NAb-positive, ADAb-positive/NAb negative). This will be repeated for IGA 0/1 responders (up to Week 16 and Week 32). These data will also be presented graphically.

4.6.1.4.2.4 Safety endpoints by ADAb and NAb summaries

Summaries include the number of TEAEs, number of study participants with TEAEs, percentage of study participants with TEAEs, EAIR with 95% CI, and EAER. TEAEs will be sorted by SOC, HLT and PT.

TEAEs by ADAb status and ADAb titer:

TEAEs of the study participants initially randomized to bimekizumab 320mg Q4W/Q8W treatment, or initially randomized to placebo and initiating bimekizumab 320mg Q4W treatment at Week 16, will be summarized by ADAb status based on all available data using the following categories:

- AEs starting before the first ADAb-positive result (study participants in Categories 2 and 5)
- AEs starting on or after the first ADAb-positive result (study participants in Categories 2, 3, 4, 5 and 6)
- AEs for study participants who are always ADAb-negative (study participants in Category 1)

For these summaries, a study participant's associated time at risk will be split into the time before the first positive result and on or after the first positive result. If a study participant has multiple reports of the same AE (ie, those which coded to the same PT) emerging both prior to first ADAb-positive result and after ADAb-positive result, both events will be summarized in the table in the appropriate column.

In addition, for ADAb-positive study participants, a table summary of TEAEs by tertiles of maximum ADAb titer value will be generated. The table will display the summary of TEAEs which start on or after the first ADAb-positive sample by subgroups based on the tertiles of ADAb titer. For this summary, a study participant's associated time at risk will be based on the time on or after the first positive result.

TEAEs by NAb status:

TEAEs will be summarized by NAb status based on all available data using the following categories:

- ADAb-negative
- ADAb-positive/NAb-negative
- NAb-positive

4.6.1.5 Genomics

Not applicable.

4.6.1.6 Biomarkers

Not applicable.

4.6.1.7 Pregnancy outcomes

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 for the SS.

4.6.1.8 Health care utilization related endpoints

Not applicable.

4.6.1.9 Health technology assessment related endpoints

Not applicable.

4.6.2 Subgroup analyses

No subgroup analyses will be conducted.

4.7 Interim analyses

A primary analysis will be performed after all randomized study participants have completed the Week 32 assessments or have been withdrawn from the study. A final analysis and CSR will be prepared once all data (through the SFU Visit) have been collected after study completion and database lock.

4.8 Changes to protocol-planned analyses

For key secondary efficacy endpoints, it's stated in protocol section 9.3.2.1 that missing data for these variables will also be imputed using multiple imputation (MI) similar to the sensitivity analyses for the co-primary endpoints. In addition, analyses will be repeated using the FAS and the NRI method. However, in SAP section 4.3.1.3 no sensitivity analyses based on MI or based on FAS with NRI method are provided.

4.9 Data Monitoring Committee (DMC) or other review board

No DMC will be conducted.

5 SAMPLE SIZE DETERMINATION

[redacted]

6 APPENDIX: SUPPORTING DOCUMENTATION

6.1 Appendix 1: List of Abbreviations

List of Abbreviations

antidrug antibody	ADAb
adverse event	AE
AE of special interest	AESI
Active Medication Set	AMS
Anatomical Therapeutic Chemical classification	ATC
below limit of quantification	BLQ
Body Mass Index	BMI
Body Surface Area	BSA
Cumulative distribution function	CDF
Confidence interval	CI
Cochran-Mantel-Haenszel	CMH
Coronavirus disease 2019	COVID-19
Case Report Form	CRF
clinical study report	CSR
Common Terminology Criteria for Adverse Events	CTCAE
coefficient of variation	CV
Cardiovascular Event Adjudication Committee	CV-CAC
drug-induced liver injury	DILI
Dermatology Life Quality Index	DLQI
Data Monitoring Committee	DMC
exposure-adjusted event rate	EAER
exposure-adjusted incidence rate	EAIR

Electrocardiogram	ECG
Enrolled Set	ES
Full Analysis Set	FAS
High level group term	HLGT
high level term	HLT
Inflammatory bowel disease	IBD
Inflammatory Bowel Disease Adjudication Committee	IBD-CAC
Informed Consent Form	ICF
Investigator's Global Assessment	IGA
Interferon-Gamma Release Assay	IGRA
investigational medicinal product	IMP
important protocol deviation	IPD
Initial Treatment Period	ITP
liver function test	LFT
lower limit of quantification	LLOQ
low level term	LLT
[redacted]	
latent TB infection	LTBI
missing at random	MAR
minimally clinical important difference	MCID
[redacted]	
Medical Dictionary for Regulatory Activities	MedDRA
Multiple imputation	MI
missing not at random	MNAR

Major adverse cardiac event	MACE
Maintenance Treatment Period	MTP
New Ratio	nR
Neutralizing anti-bimekizumab antibody	NAb
Negative Immunodepletion	NI
Non-responder imputation	NRI
Negative Screen	NS
observed case	OC
odds ratio	OR
Psoriasis Area and Severity Index	PASI
potential drug induced liver injury	pDILI
premature end of treatment	PEOT
Positive Immunodepletion	PI
pharmacokinetic(s)	PK
Pharmacokinetics Per Protocol Set	PK-PPS
Per Protocol Set	PPS
Positive Screen	PS
Patient Symptom Diary	PSD
Psoriasis Symptom and Impact Measure	P-SIM
psoriasis	PSO
Preferred term	PT
every 4 weeks	Q4W
every 8 weeks	Q8W
quality of life	QoL

Randomized Set	RS
Serious adverse event	SAE
statistical analysis plan	SAP
subcutaneous(ly)	sc
standard deviation	SD
Standard error	SE
safety follow-up	SFU
Suicidal Ideation and Behavior	SIB
Standard MedDRA Query	SMQ
Schedule of Activities	SoA
System Organ Class	SOC
Safety Set	SS
Tuberculosis	TB
treatment emergent adverse event	TEAE
treatment emergent markedly abnormal	TEMA
upper limit of normal	ULN
World Health Organization Drug Dictionary	WHO-DD

6.2 Appendix 2: Coding dictionaries

Medical history and AEs will be coded using the MedDRA® version 19.0. Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version Mar2021. Medical procedures will not be coded.

To maintain consistency across studies in the bimekizumab development program, the dictionary versions will be held constant to support consistency of coding in the regulatory submissions.

6.3 Appendix 3: Participant disposition

Summaries of reasons for screen failures (for all study participants screened), disposition of study participants (for all study participants screened), disposition of analysis sets (for RS), disposition and discontinuation reasons (for RS), as well as the study participants who discontinued due to AEs (for RS) will be produced. 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, AMS, MS, PPS, and PK-PPS) overall and by site.

The following listings for subject disposition will be provided: study participants who did not meet study eligibility criteria (ES), study participants disposition (ES), study discontinuation (RS), visit dates (RS), study participants analysis set (RS), rescreened study participants (ES).

6.4 Appendix 4: Baseline characteristics and demographics

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

6.4.1 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)
- Body Mass Index (BMI) (kg/m^2)

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

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

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, ≥100 kg)
- Body weight (≤120, ≥120 kg)
- Gender
- Race
- Ethnicity
- BMI (<25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2)

By-study participant listings on demographics and study participant's childbearing potential data will be provided for all screened study participants. A listing on lifestyle will be provided on the RS.

6.4.2 Baseline characteristics

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

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

- Psoriasis BSA (%)
- PASI score
- DLQI total score
- PSD item scores: Pain, Itch, Scaling
- Duration of disease (years)

  Duration of disease (years) will be calculated as:

$$\text{Disease Duration} = \frac{(\text{Date of randomization} - \text{Date of first diagnosis}^{1})}{365.25}$$

[1]If the date of first diagnosis 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). Partial dates of first diagnosis should not be imputed to a date later than the study participants' screening date. Note that if the date of randomization is missing then the duration of disease will be derived using the date of screening.

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

- Duration of disease (<median, ≥median)
- Baseline disease severity (PASI<20, PASI≥20)
- IGA score
- DLQI total score (=0, =1, >1)
- Baseline scalp involvement (yes, no)
- Baseline Scalp IGA score (0, 1, 2, 3, 4)
- Prior biologic therapy (yes, no)
- Prior primary failure to biologic (yes, no)
- Prior anti-TNF therapy (yes, no)
- Prior anti-IL-17 therapy (yes, no)
- Prior phototherapy or chemotherapy (yes, no)
- Any prior systemic therapy (yes, no)

The scalp IGA will only be assessed at post-Baseline visits for those study participants with scalp involvement (scalp IGA score >0) at Baseline. The categorization of whether or not study participants received prior psoriasis therapy will be based on the Psoriasis Treatment History CRF module.

Prior anti-TNFs include etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab (care should be taken in data cleaning to look for marketed names or biosimilars that should be categorized as anti-TNFs).

Prior anti-IL-17's include secukinumab, ixekizumab, and brodalumab.

The definition of prior systemic therapy is if a subject received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic chemotherapy or phototherapy. Subjects who never received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic chemotherapy or phototherapy will be classified as not receiving prior systemic treatment for psoriasis.

Finally, a by-participant listing will be presented on all baseline characteristics for the RS.

6.5 Appendix 5: Protocol deviations

A summary, using the RS, displaying the number and percentage of study participants with an IPD (including a summary of study participants excluded from the PPS or PK-PPS due to important protocol deviations) by treatment group and overall will be provided. The summary will be overall (any IPD) and by type of deviation (inclusion criteria deviation, exclusion criteria deviation, withdrawal criteria deviation, prohibited concomitant medication use, incorrect treatment or dose, treatment non-compliance, procedural non-compliance). This summary will be presented on the ITP and the MTP.

A by-study participant listing of important protocol deviations will be provided on the RS, a flag to mark COVID-19 related or not will be included in the listing.

To assess the impact of the COVID-19 pandemic on the study, a listing of 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 will be provided.

6.6 Appendix 6: Medical history

Previous and ongoing medical history will be summarized on the RS by treatment groups, SOC and PT using MedDRA®. Medical history summary will be ordered alphabetically for SOC and in terms of decreasing frequency for PT within SOC in all study participants group, and in the event of ties, PT will be sorted alphabetically.

The following listings for medical history will be provided on the RS: psoriasis history, medical history glossary, medical history conditions, infection history, concomitant medical procedure, and procedure history.

6.7 Appendix 7: 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.

Details of imputation methods for missing or partial dates are described in Section 6.8.1.2.

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.

Dosing period is defined as from first dose of study medication (including placebo) up to last dose of study medication + 28 days (The use of 28 days assumes a Q4W dosing interval. This will be adjusted based on the dosing interval [eg, for Q8W use last active dose of study medication + 56 days]).

For study participants who discontinue early, the dosing period ends at the last study medication date + 28 days (last active dose date + 56 in the case of Q8W dosing). For study participants who complete the study as planned, the dosing period ends at the later of the following two dates:

- Last study medication date + 28 days (last active dose date + 56 in the case of Q8W dosing)
- The last scheduled visit date not including SFU

The number and percentage of study participants taking prior medications (excluding past psoriasis 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 table summary will be ordered alphabetically for the Anatomical Main Group and in terms of decreasing frequency for PT within Anatomical Main Group in the all study participants group. In the event of ties, PT will be ordered alphabetically.

The number and percentage of study participants taking concomitant medications will be summarized similarly in separate tables. The summary will be presented on the SS.

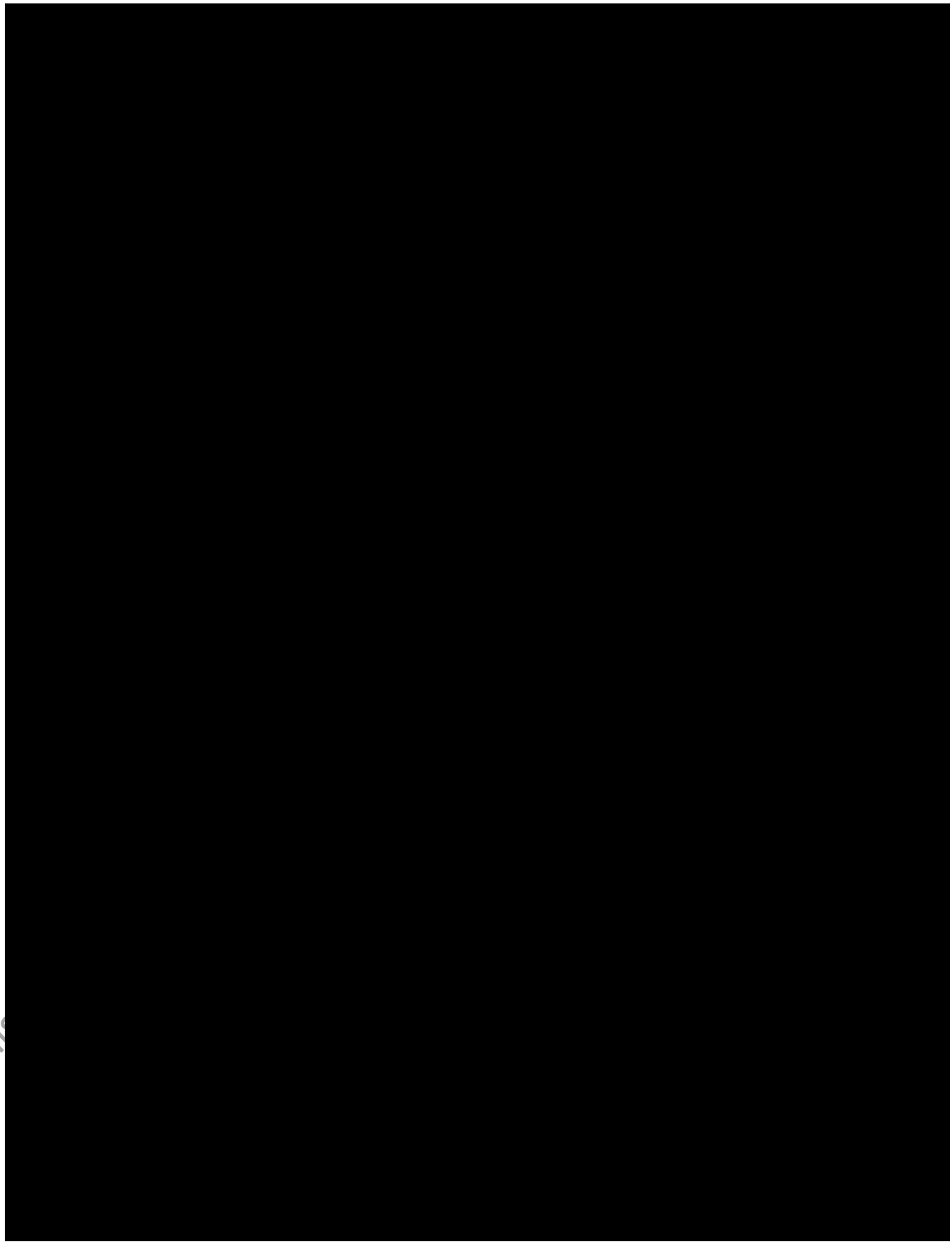
Past psoriasis medications will be captured separately and will also be summarized by treatment group. These medications are captured in a separate CRF module of Psoriasis Treatment History and are not subject to coding. In addition, study participants who failed past psoriasis biologic treatment will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

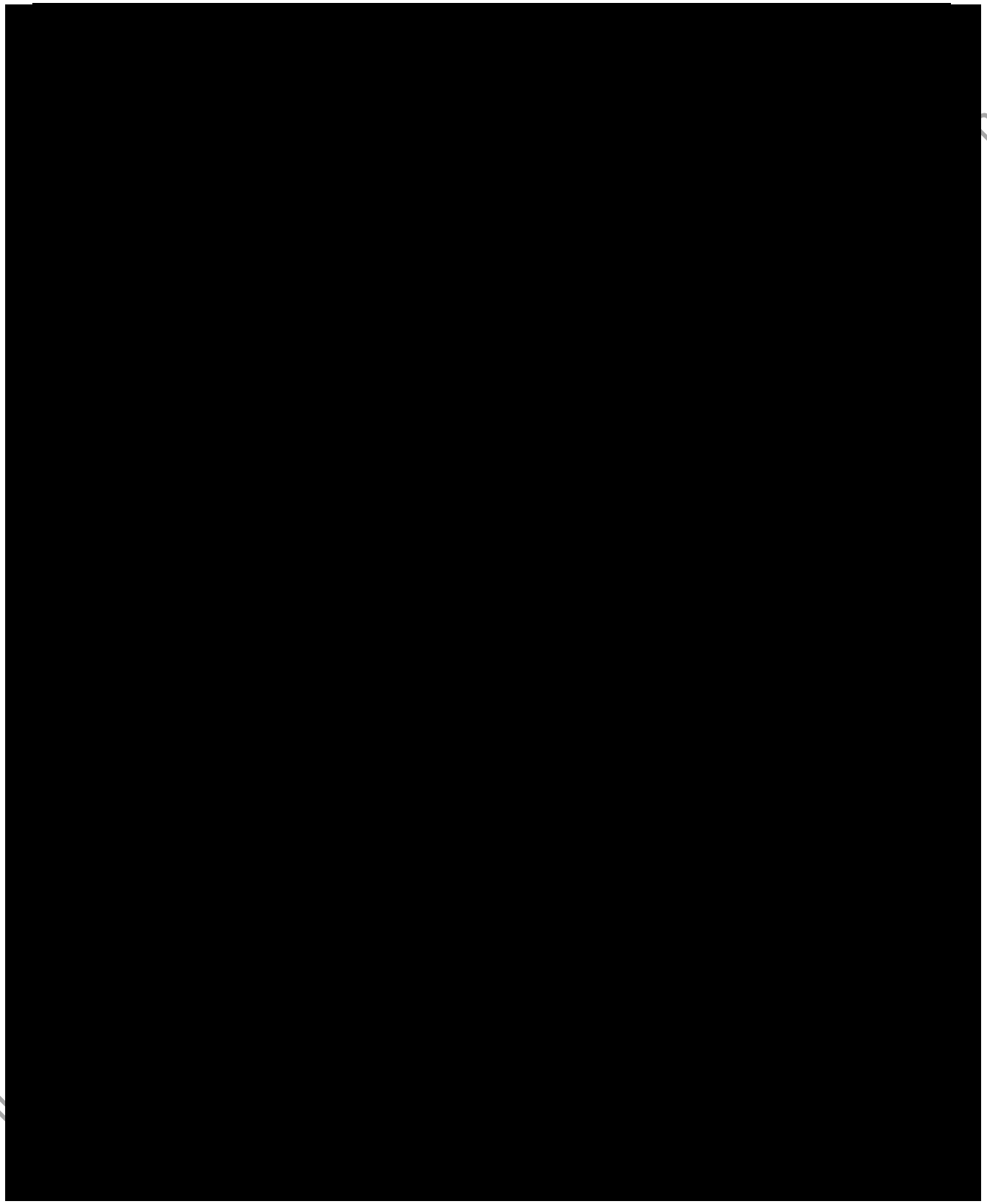
By-study participant listings of all prior and concomitant medications, prior and concomitant medications glossary, psoriasis treatment history, and prior and concomitant vaccines will be provided on the RS.

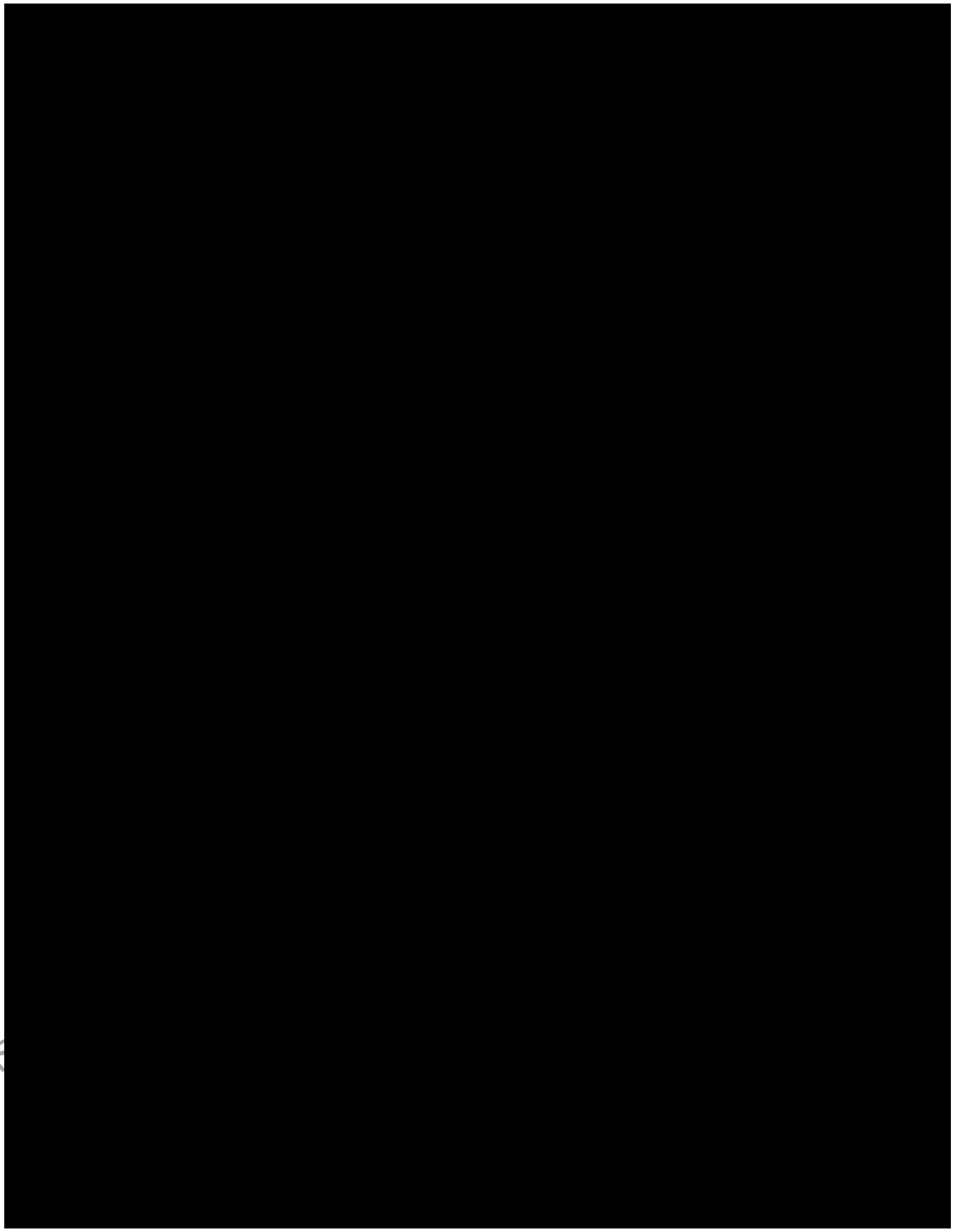
6.8 Appendix 8: Data derivation rules

[redacted]

[redacted]







6.8.2 PASI

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

The various body regions are weighted to reflect their respective proportion of BSA. The composite PASI score is then calculated by multiplying the sum of the individual-severity scores for each area by the weighted area-of-involvement score for that respective area, and then summing the four resulting quantities as follows (note for R, T, and S scores are as follows: 0 = none, 1 = slight, 2 = moderate, 3 = marked, and 4 = very marked):

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

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.

6.8.3 IGA

A static IGA for PSO will be used to assess disease severity in all study participants during the study. The Investigator will assess the overall severity of PSO using the 5-point scale presented in Table 6-3 .

Table 6-3 IGA

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

6.8.4 Scalp IGA

A static IGA for scalp PSO will be used to assess disease severity on the scalp. Scalp lesions will be assessed in terms of clinical signs of redness, thickness, and scaliness using the 5-point scale presented in Table 6-4.

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.

Table 6-4 Scalp IGA

Score	Short descriptor	Detailed descriptor
0	Clear	Scalp has no signs of PSO; post-inflammatory 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

IGA=Investigator's Global Assessment; PSO=psoriasis; scalp IGA=scalp-specific IGA

6.8.5 DLQI

The DLQI is a questionnaire designed for use in adult study participants with PSO. The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect study participants' health-related QoL. This instrument asks study participants about symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. It has been shown to be valid and reproducible in study participants with PSO. The DLQI score ranges from 0 to 30, with higher scores indicating lower health-related QoL. A 4-point change in the DLQI score (DLQI response) has been reported to be meaningful for the study participant (within-participant minimal important difference), while a DLQI absolute score of 0 or 1 indicates no effect on patient's life (Basra et al, 2015; Hongbo et al, 2005).

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

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 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 one 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.

6.9 Appendix 9: AEs of Special Interest

An AE of special interest (AESI) is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the

administration of a UCB product/compound. For bimekizumab, the following event requires immediate reporting (within 24 hours regardless of seriousness) to UCB:

- 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 summary will be provided as specified in Section 4.5.3.1.

6.10 Appendix 10: Potentially Clinically Significant Criteria for safety endpoints

6.10.1 Criteria for Markedly abnormality for laboratory data

Markedly abnormal values are defined as those with a severity of Grade 3 and above based on the CTCAE criteria (U.S. Department of Health and Human Services 2010). Definitions of markedly abnormal values using the Grade 3 cut points are given in the tables below for age ranges of ≥17 years (Table 6-5 for markedly abnormal liver function test values, Table 6-6 for markedly abnormal biochemistry values, and Table 6-7 for markedly abnormal hematology values).

Table 6-5: Definitions of Markedly Abnormal Liver Function Values

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

Table 6-6: Definitions of Markedly Abnormal Biochemistry Values

Parameter name	Conventional		Standard		Abnormal designation
	Unit	Criteria	Unit	Criteria	
Creatinine	mg/dL	>3.0 x ULN	mmol/L	>3.0 x ULN	AH
Glucose	mg/dL	<40 >250	mmol/L	<1.7 >13.9	AL AH
Calcium	mg/dL	>12.5 <7.0	mmol/L	>3.1 <1.75	AH AL
Potassium	mmol/L	>6.0 <3.0	mmol/L	>6.0 <3.0	AH AL

Parameter name	Conventional		Standard		Abnormal designation
	Unit	Criteria	Unit	Criteria	
Sodium	mmol/L	>155 <130	mmol/L	>155 <130	AH AL
Cholesterol	mg/dL	>400	mmol/L	>10.34	AH

Table 6-7: Definitions of Markedly Abnormal Hematology Values

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

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.

6.10.2 Criteria for Markedly abnormality for vital signs data

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

Table 6-8: 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

For this summary, Baseline values and values observed more than 119 days after the last administration of study medication are not considered.

6.11 Appendix 11: Compliance

Due to the method of administration of the treatments, compliance will be examined in terms of completed injections.

Treatment compliance will be calculated as:

$$\frac{\text{total number of completed injections}}{\text{total number of expected injections}} \times 100\%$$

where the total number of expected injections is derived relative to when the study participant finishes treatment. In this study, Baseline visit and Weeks 4, 8, 12, 16, 20, 24, 28 are dosing visits. Two injections are administered at each given visit either with active dosing or placebo injection. It is expected that a study participant should complete total 16 injections by the end of study. If a study participant discontinues early, then the number of expected injections is based on the time of early discontinuation relative to the dosing visits. For example, if a study participant discontinues after Week 8 visit and prior to Week 12 visit, the total number of expected injections will be 6.

A summary of percent treatment compliance categorized as <75% and ≥75% will be provided by treatment group and study periods (ITP for the SS, MTP for the MS, and the Initial and Maintenance Treatment Period (combined) for the AMS).

A by-study participant listing of treatment compliance will be provided on the SS.

6.12 Appendix 12: MedDRA algorithmic approach to anaphylaxis

The SMQ Anaphylactic reaction consists of three parts:

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

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)**

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)**

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)**

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)]

6.13 Appendix 13: Definition of CTCAE grades

Table 6-9: Definitions of CTCAE grades by biochemistry parameter

Parameter (unit)	Definition	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	High	mmol/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
Cholesterol	High	mmol/L	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92
Glucose	Low	mmol/L	<LLN – 3.0	<3.0 – 2.2	<2.2 – 1.7	<1.7
Glucose	High	mmol/L	>ULN – 8.9	>8.9 – 13.9	>13.9 – 27.8	>27.8

Note that high glucose values (hyperglycemia) are based on fasting glucose and in this study glucose is collected nonfasting.

Table 6-10: 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 ULN	>20-40 above ULN	>40 above ULN	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 subjects 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.

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