

STATISTICAL ANALYSIS PLAN

AMENDMENT 2

Study: PS0020

Product: Bimekizumab

**A MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY TO
ASSESS THE PHARMACOKINETICS, SAFETY, AND
EFFICACY OF TWO DOSES OF BIMEKIZUMAB IN
ADOLESCENT STUDY PARTICIPANTS WITH MODERATE TO
SEVERE PLAQUE PSORIASIS**

PHASE 2

SHORT TITLE:

An open-label, randomized study to evaluate the pharmacokinetics, safety, and efficacy of 2 doses of bimekizumab in adolescent study participants with moderate to severe plaque psoriasis

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study PS0020 is based on the protocol amendment 3 dated 08 Mar 2022.

SAP Version	Approval Date	Change	Rationale
1.0	18 Feb 2021	Not applicable	Original version
2.0	22 Oct 2021	Amendment	Protocol Amendment 2 and clarifying language throughout document.
3.0	09 Apr 2025	Amendment	Protocol Amendment 3 and Database Lock

Details about the changes in this SAP amendment can be found in Section [6.4.1](#).

LIST OF ABBREVIATIONS

List of Abbreviations

ADAb	antidrug antibody
ADaM	Analysis Data Model
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BKZ	bimekizumab
BMI	body mass index
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
EDV	early discontinuation visit
EMA	European Medicines Agency
E-R	exposure-response
ES	Enrolled Set
HLT	high level term
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IMP	investigational medicinal product
LLN	lower limit of normal
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities

List of Abbreviations

NAb	neutralizing antibodies
OC	observed case
OLE	open label extension
OLS	Open Label Set
PASI	Psoriasis Area and Severity Index
PBO	placebo
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PSO	psoriasis
PT	preferred term
Q4W	every 4 weeks
QOL	Quality of Life
RS	Randomized Set
SAP	statistical analysis plan
sc	subcutaneous(ly)
SFU	Safety Follow-up
SIB	suicidal ideation and behavior
SDG	Standardised Drug Grouping
SMQ	Standardized MedDRA Query
SOC	system organ class
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
ULN	upper limit of normal
WHO	World Health Organization
WHO-DD	WHO Drug Dictionary

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1 INTRODUCTION

PS0020 is an open-label, randomized study assessing the pharmacokinetics (PK), safety, and efficacy of 2 doses of bimekizumab in adolescents with moderate to severe plaque psoriasis (PSO). This Statistical Analysis Plan (SAP) prespecifies the analyses for endpoints in PS0020, including PK, safety, efficacy, quality of life (QOL), and immunogenicity. Results obtained from the analyses in this SAP will serve as the basis of the clinical study report (CSR) for PS0020.

1.1 Objectives and Endpoints

Table 1–1: Objectives and Endpoints

Objectives	Endpoints
Primary	
<ul style="list-style-type: none"> To assess the PK of bimekizumab administered subcutaneously (sc) in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> Bimekizumab plasma concentrations
Secondary	
<ul style="list-style-type: none"> To evaluate the safety of bimekizumab in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> Treatment Emergent Adverse Events (TEAEs) <ul style="list-style-type: none"> Serious TEAEs TEAEs leading to discontinuation of investigational medicinal product (IMP) TEAEs leading to withdrawal from the study Selected safety topics of interest (including infection [serious, opportunistic, fungal, and tuberculosis (TB)], inflammatory bowel disease [IBD], and injection site reactions) with onset occurring from day of first dose through 20 weeks after final dose of investigational medicinal product (IMP) adjusted by duration of participant exposure to IMP Change from Baseline in vital signs and physical examination findings Change from Baseline in laboratory analyses (chemistry and hematology) Growth assessment, as assessed by the change in height and weight

Objectives	Endpoints
<ul style="list-style-type: none"> To evaluate the efficacy of bimekizumab in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> Psoriasis Area and Severity Index (PASI) 90 (PASI90) response at Week 16 Investigator's Global Assessment (IGA) 0/1 response (Clear [0] / Almost Clear [1] with at least 2-category improvement from Baseline) at Week 16 PASI75 response at Week 4
<ul style="list-style-type: none"> To evaluate the immunogenicity of bimekizumab in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> Anti-bimekizumab antibody detection prior to and following IMP administration
<ul style="list-style-type: none"> To evaluate the change in quality of life in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> Change from Baseline in Children's Dermatology Life Quality Index (CDLQI) response (total score) at Week 16
Other	
<ul style="list-style-type: none"> To assess the efficacy of bimekizumab over time in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> PASI50 response over time PASI75 response over time PASI90 response over time PASI100 response over time Absolute and percent change from Baseline in PASI score over time IGA 0/1 response (with at least 2-category improvement from Baseline) over time IGA 0 response (with at least 2-category improvement from Baseline) over time Scalp-specific IGA (scalp IGA) response (Clear or Almost Clear with at least 2-category improvement from Baseline for participants with scalp PSO at Baseline) over time
<ul style="list-style-type: none"> To assess the exposure (PK)-response relationship with selected clinical outcomes in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> The relationship between plasma bimekizumab exposure and, though not limited to, the following clinical outcomes: PASI score over time, PASI change from Baseline, IGA score over time, IGA change from Baseline

Objectives	Endpoints
<ul style="list-style-type: none"> To assess the change in quality of life over time in adolescents with moderate to severe plaque PSO 	<ul style="list-style-type: none"> Change from Baseline in CDLQI response over time CDLQI 0/1 response over time

1.2 Study Design

In this Phase 2, multicenter, randomized, open-label study, the PK, safety, and efficacy of bimekizumab in male and female adolescents (from 12 to <18 years of age) with moderate to severe plaque PSO will be assessed.

The PK, safety, and efficacy of bimekizumab will be evaluated by treating at least 20 participants in each of 2 dose groups (for a total of at least 40 participants evaluable for PK). Both doses are expected to be efficacious based on exposure-response (E-R) predictions. Dose A (320mg every 4 weeks [Q4W] in participants ≥ 65 kg and 160mg Q4W in participants <65kg) is predicted to provide the same systemic bimekizumab exposure as the 320mg Q4W adult dose, and Dose B (64mg Q4W in participants ≥ 65 kg and 32mg Q4W in participants <65kg) is aimed at providing a lower systemic bimekizumab exposure. Weight-based dosing during the Initial Treatment Period will be based on the participant's weight at Baseline.

This study will consist of the following periods:

- Screening Period: up to 5 weeks
- Initial Treatment Period: 20 weeks (5 doses of bimekizumab; administered at Baseline, Week 4, 8, 12, and 16 followed by 4 weeks of observation)
- Open-label Extension (OLE) Period: 104 weeks (bimekizumab administration starts at Week 20 if participant is eligible)
- Safety Follow-up (SFU) Period: 20 weeks after the final dose of bimekizumab

After the Screening Period of up to 5 weeks, eligible participants will be randomized to 1 of the 2 dose groups. The randomization will be stratified by weight category. During the Initial Treatment Period, participants will receive 5 doses of open-label bimekizumab (at Weeks 0 [Baseline], 4, 8, 12, and 16). Participants who complete the Initial Treatment Period, tolerate the treatment, and achieve an IGA response ≤ 2 at Week 20 may continue bimekizumab treatment at the same dose level in the OLE Period.

All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information. Upon identification of the PS0021 dose, study participants in PS0020 may switch to the PS0021 dose at the Investigator's discretion during the 104-week OLE Period. Participants who do not tolerate the IMP or who have an IGA response ≥ 3 (on a scale from 0 to 4) at Week 20 will be withdrawn from the study. Each participant will complete the SFU Period of 20 weeks following his/her final dose of bimekizumab.

During the Initial Treatment Period, IMP will be administered by a health care professional at the study site. In the OLE Period, Dose A and Dose B may be administered at the study site or at

home, as indicated in the Schedule of Activities in the protocol. Home visits are encouraged during the OLE Period upon agreement of the Investigator, study participant, and his/her caregiver. Dose A of the IMP may be administered by a health care professional, caregiver, or the study participant (once he/she becomes 18 years of age). Administration of Dose A by the caregiver or study participant is optional and requires training. Dose B will be administered by a health care professional, whether at home or at the study site, to ensure accurate dosing of the lower volume of IMP.

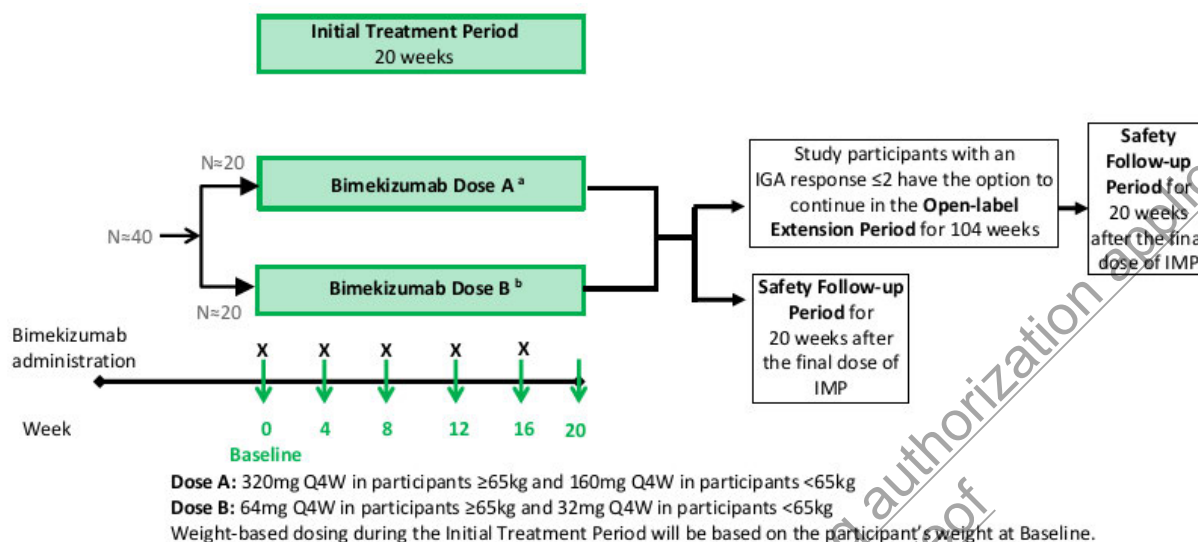
The end of the study is defined as the date of the last participant's last visit. The study design of PS0020 provides participants who are receiving benefit from bimekizumab therapy with the opportunity to receive active treatment for a total of 120 weeks.

Safety assessments will be made by ongoing monitoring and evaluation of adverse events (AEs) and other safety topics of interest specific to bimekizumab. Safety topics of interest for this study include infections (serious, opportunistic, fungal, and TB), IBD, injection site reactions, and neuropsychiatric AEs (including suicidal ideation/behavior [SIB]-related AEs). Additionally, in keeping with the adult bimekizumab program, the following topics will also be closely monitored: neutropenia, hypersensitivity (including anaphylaxis), major cardiovascular events, liver function test changes/enzyme elevations, and malignancies. Additional safety assessments will include physical examinations (including growth assessments) and pregnancy testing for female participants of childbearing potential.

An independent external Data Monitoring Committee (DMC) will periodically review and monitor safety data from this study. An IBD Adjudication Committee and a Neuropsychiatric Adjudication Committee will also periodically review data from this study. Details will be provided in separate IBD and Neuropsychiatric Adjudication Committee charters.

A schematic of the design of PS0020 is provided in [Figure 1-1](#).

Figure 1–1: Study Schematic



IGA=Investigator's Global Assessment; IMP=investigational medicinal product; OLE=Open-label Extension; PK=pharmacokinetics; Q4W=every 4 weeks
 Note: All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information. Upon identification of the PS0021 dose, study participants in PS0020 may switch to the PS0021 dose at the Investigator's discretion during the 104-week OLE Period.

Note: Participants who do not tolerate the IMP or who have an IGA response ≥ 3 (on a scale from 0 to 4) at Week 20 will be withdrawn from the study.

^a Dose A is predicted to provide the same systemic bimekizumab exposure as the 320mg Q4W adult dose.

^b Dose B is aimed at providing a lower systemic bimekizumab exposure than Dose A.

2 STATISTICAL HYPOTHESES

The primary variable of this study is bimekizumab plasma concentrations. The PK data will be subject to a population PK analysis which will be described in a separate analysis plan.

No formal hypothesis testing or statistical inference will be conducted for the secondary efficacy variables, including safety, efficacy, immunogenicity, and QOL variables. All analyses will be descriptive.

3 SAMPLE SIZE DETERMINATION

The number of study participants, at least 40 total participants randomized 1:1 across the 2 dose arms, is considered to be sufficient to assess bimekizumab population PK and E-R in adolescents. The sample size is based on simulations from an adult PASI E-R model, adjusted for body weight differences in PK for adolescents (ie, allometric scaling in clearance and distribution volume) and assuming the same efficacy response in adolescents as in adults (ie, same parameter estimates for simulation were assumed). A total of 40 participants allocated evenly to 2 dose arms was found in the modeling and simulation to be sufficient for the estimation of PK and pharmacodynamics (PD) parameters with precision in a combined adult-adolescent analysis. Approximately 58 participants will be screened to achieve the sample size of at least 40 participants.

4 POPULATIONS FOR ANALYSIS

4.1 Analysis Sets

4.1.1 Enrolled Set

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

4.1.2 Randomized Set

The Randomized Set (RS) will consist of all randomized participants. Unless otherwise stated, efficacy analyses will be based on the RS and as randomized for the Initial Treatment Period.

4.1.3 Safety Set

The Safety Set (SS) will consist of all participants that receive at least 1 dose of the IMP. Safety analyses will be based on the SS and as treated.

4.1.4 Pharmacokinetics Per-Protocol Set

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized participants who receive at least 1 dose of the IMP and provide at least 1 quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration. Pharmacokinetic variables will be analyzed for all participants in the PK-PPS and will be summarized as randomized.

4.1.5 Open-label Set

The Open-label Set (OLS) will consist of all study participants who receive at least 1 dose of study medication at or after Week 20 in the OLE Period (including the Week 20 dose). The OLS will be the basis for analysis of data from OLE Period. OLS analyses will be based on the SS and as treated.

For summaries using both PK-PPS and OLS, participants will be summarized as randomized.

Immunogenicity analyses will be based on SS or OLS, and participants will be summarized as randomized.

5 STATISTICAL ANALYSES

5.1 General Considerations

All available study PK data and clinical data (including selected efficacy and safety data) will be analyzed when all participants have completed the Initial Treatment Period and at the end of the study. The analysis performed when all participants have completed the Initial Treatment Period will be used for determination of PS0021 dose selection and will not be considered as an interim analysis or provided in an interim CSR.

For by-visit tables summarizing efficacy data, the SFU visit should not be included, but SFU efficacy data should be listed. By-visit tables summarizing safety data should include the SFU visit for the ITP + OLE and OLE summaries. However, SFU should not be included in by-visit safety tables for the ITP alone, due to low sample size.

Descriptive statistics will be displayed to provide an overview of the study results. Summary statistics will consist of frequency tables for categorical variables. The number and percentage of study participants in each category will be presented. The denominator for percentages will be

based on the number of participants appropriate for the purpose of analysis. For continuous variables, summary statistics will consist of the number of available observations, arithmetic mean, standard deviation (SD), median, minimum, and maximum, unless stated otherwise.

Study participants with missing data will be accounted for using the following approaches:

- All efficacy data collected later than 33 days—derived as 28 days allotted for the planned dosing interval plus 5 days allotted for the maximum allowable visit window during either study period—and all safety data that are collected later than 140 days after the last administration of study treatment will be treated as missing and subject to imputation as applicable.
- For summaries of demographics and Baseline characteristics: percentages will be based on all study participants in the relevant analysis set and a “Missing” category (corresponding to study participants with missing data for the variable being summarized) will be included as the last row in the list of categories being summarized, if at least one dose group has a value missing.
- All summaries of PK concentrations will be based on the observed values. No imputation of missing data will be used.
- For efficacy and safety variables, summaries will be typically based on the 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 will be displayed in the table. The general format for displaying this will be “n/Nsub (%)”. Selected efficacy variables will be imputed for their missing data as outlined in Section 5.1.1.7.3. Partial dates for AEs will be imputed as outlined in Section 5.1.1.7.5.
- For secondary efficacy variables of responses, 95% Clopper-Pearson confidence intervals (CIs) will be provided for responder rates (PASI90 at Week 16, PASI75 at Week 4, and IGA0/1 at Week 16) in each dose group. For Change from Baseline in CDLQI response at Week 16, 95% CIs will be provided for the mean change for each dose group.

Percentages will be presented to 1 decimal place. If the percentage is 100%, a decimal will not be presented. If the count is 0, the percentage will not be presented. For percentages representing proportions, for the purpose of the tabulations the lower and upper confidence limits for the percentages will be truncated at 0 and 100% respectively.

In order to avoid issues caused by inaccurate floating-point representation of numeric values, the ADaM (Analysis Data Model) variables AVAL (analysis value), CHG (change) or PCHG (percentage change) will be rounded to twelve decimal places prior to the comparison to the threshold. This should be applied exclusively during the derivation of new response parameters (subsequently retained in the dataset) or critical value variables and does not imply inherent rounding on AVAL, CHG or PCHG variables which are retained unrounded in the final ADaM dataset.

If the calculated lower bound for a confidence interval of a proportion is less than 0, the lower bound should be presented as 0. Similarly, if the upper bound of the confidence interval exceeds 100, the upper bound should be presented as 100. Decimal places for descriptive statistics will be subject to the following rounding rules:

- “n” will be an integer.
- Mean, SD, and median will use 1 additional decimal place compared to the original data.
- Coefficient of variation (CV) [%] will be presented with 1 decimal place.
- Minimum and maximum will have the same number of decimal places as the original value.

Per protocol, visit windows are ± 3 days from the date of first dose for the Initial Treatment Period and ± 5 days for the OLE Period. For by-visit presentations, data from unscheduled visits should generally not be included, since sample sizes for unscheduled visits are expected to be small and are often not representative of the whole sample. One exception is Baseline, where data from unscheduled visits are considered if this is the only value prior to the first administration of study medication. Another exception where data from unscheduled visits should be considered is any by-visit table which includes post-Baseline rows for minimum, maximum and/or last measurements. In case of repeated laboratory tests at a particular visit, the last measurement should generally be used for visit presentation in by-visit summaries.

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

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

5.1.1 General study level definitions

5.1.1.1 Analysis time points

5.1.1.1.1 Relative day

The relative study day will in general be calculated using the algorithm below:

- If the event occurred on or after the date of first study drug 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 study drug administration.

- If the event occurred before the date of first study drug 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 study drug administration will be preceded by a “-”, when presented in listings.

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

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

Date of last dose is the date of last study drug administration. Relative days that occur after the date of last study drug administration will be preceded by a “+”, when presented in listings.

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

5.1.1.1.2 End date of the Treatment Period

The end date of the Initial Treatment Period will be the last scheduled visit (Week 20 Visit) date for participants who complete the Initial Treatment Period or the Early Discontinuation Visit (EDV) date for participants who withdraw from the study during the Initial Treatment Period. Similarly, the end date of the OLE Period for participants who entered the OLE Period will be the Week 124 Visit date or the EDV date. The end date of the treatment period (the Initial Treatment Period and the OLE Period) is defined as the end date of the Initial Treatment Period if the participant does not continue into OLE Period or the end date of the OLE Period if the participant enters the OLE Period.

If a participant does not have a Week 20 / Week 124 Visit or EDV, then either the date of the last visit (scheduled or unscheduled) or the date of last known dose of study drug during the Treatment Period, whichever is later, will define the end date of the corresponding Treatment Period.

5.1.1.1.3 Study periods

The following study periods are defined for the classification by study period:

- Screening: visits with dates before randomization date
- Initial Treatment Period: from randomization date to Week 20 visit date
- OLE Period: From the date of Week 20 visit to the end of study. The Week 20 Visit date will serve as the start date of the OLE Period for participants who entered the OLE Period

The Week 20 Visit date serves, according to protocol, as both the end of the Initial Treatment Period and the beginning of OLE Period. Unless otherwise stated, any assessment or measurement made prior to or on the Week 20 visit will be attributed to the Initial Treatment Period (irrespective of time of collection), and adverse events related to dosing (see Section 5.6.2) and IMP administration will be attributed to the OLE Period.

5.1.1.1.4 Mapping of assessments performed at Early Discontinuation Visit

If the EDV occurs at a scheduled visit as outlined in the schedule of assessments, then no mapping is necessary, and any early withdrawal assessments should correspond to that scheduled visit. Premature study withdrawal visit assessments that occur on a date after a scheduled visit will be assigned to the next scheduled site visit per the protocol following the last visit where assessments were available. This approach means that there is a chance that data will be mapped to a visit where a given assessment was not actually collected per the protocol schedule of assessments. Such data would subsequently not be summarized in by-visit tables (though it would be available in the listings). This possibility is understood, but it is also potentially problematic to map to the next visit where the given assessment is collected. If an assessment is infrequently performed, then the mapping could cover an unreasonably long period. It also presents the challenge that different assessments collected on the same date could be mapped to a number of different visits. Bearing these considerations in mind, the approach of mapping to the next scheduled site visit, irrespective of the schedule for the given assessment, has been adopted for the bimekizumab program.

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

All by-visit data summaries will contain nominal visits only. Unscheduled visits will not be mapped to scheduled visits. Note that based on the early withdrawal mapping conventions described above, a mapped early withdrawal visit is considered as observed at that visit and should be summarized as such in the tables.

5.1.1.1.5 Definition of Baseline values

A Baseline value for clinical variables is defined as the latest measurement on or prior to the first dosing day of study medication, regardless of the time of the measurement, for the Initial Treatment Period and the OLE Period.

If Baseline plasma concentration is measured at a time after the first administration of study medication, then it should not be eligible to be considered as a Baseline plasma concentration. When the time of first dose is derived, it should be based on the first injection of study treatment.

5.1.1.2 Protocol deviations

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

5.1.1.3 Treatment assignment and treatment groups

For Initial Treatment Period, treatment assignment will use randomized dose groups (Dose A and Dose B) for efficacy analysis. For safety and PK/PD analysis, treatment assignment will use dosing group as treated and stratified by low/high dosing categories based on weight, ie, weight-categorized dose groups:

- Dose A (320mg Q4W), Dose A (160mg Q4W), Dose A (all)
- Dose B (64mg Q4W), Dose B (32mg Q4W), Dose B (all)

In the OLE Period, dose group assignment will follow the same approach taken for the Initial Treatment Period. However, participants are allowed to change to PS0021 dosing based on the PK interim results or change dosing based on their weight category changes in the OLE Period. The treatment assignment group therefore will reflect dosing changes with appropriate adjustments to tables and listings when necessary.

For PK and immunogenicity analyses, participants who change dose based on their weight category changes in the OLE will be summarized according to their Baseline weight-categorized dose group.

5.1.1.4 Center pooling strategy

No pooling of centers is planned for this study.

5.1.1.5 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). Lab data will also be coded using Common Terminology Criteria for Adverse Events (CTCAE) grade. Medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Medical procedures will not be coded.

For MedDRA, version 23.1 or greater will be used. For WHO-DD, version Mar/2021 B3 or greater will be used. For CTCAE, version 4.03 will be used.

5.1.1.6 Multicenter studies

Disposition data will be presented by center. Other data may be presented by center when necessary.

5.1.1.7 Handling of dropouts or missing data

Details about approaches to handle missing data are described in this section. An intercurrent event is defined as discontinuation of IMP prior to Week 16.

5.1.1.7.1 Rationale for estimand

Intercurrent events have been identified within the estimands for this study because of their potential to impact efficacy assessments linked with the secondary study objectives. In order to account for the effect of any observed post-randomization intercurrent events on the efficacy analyses, the following estimand strategies will be implemented when evaluating the secondary efficacy endpoints:

- A composite estimand strategy will be used for the analysis of secondary binary endpoints (PASI90 response at Week 16, PASI75 response at Week 4, IGA 0/1 response at Week 16).
- A hypothetical estimand will be used for the analysis of the continuous secondary endpoint (CDLQI total score change from Baseline at Week 16).

The assumptions and robustness of the secondary efficacy analyses involving binary endpoints and the composite estimand strategy will be assessed through the sensitivity analyses defined in Section 5.4.1.3.

5.1.1.7.1.1 Composite estimand

A composite estimand strategy as defined in Section 5.4.1.2 allows incorporation of the intercurrent event (eg, discontinuation of IMP on or before Week 4 or Week 16) within the definition of the secondary efficacy endpoint. This intercurrent event is considered meaningful to the efficacy outcomes following administration of IMP. For example, within the proposed composite estimand framework, a randomized study participant who discontinues from IMP prior to Week 16 will be considered a treatment failure at Week 16 in the analysis of the PASI90 response at IGA 0/1 response analyses regardless of the observed PASI or IGA data.

5.1.1.7.1.2 Hypothetical estimand

The hypothetical estimand strategy is defined in Section 5.4.1.2, and involves a data-driven approach to account for the potential impact of an intercurrent event (eg, discontinuation of IMP

on or before Week 16) on the analysis of continuous secondary efficacy data. Under this framework, outcomes for study participants without an intercurrent event are analyzed as observed. Conversely, outcomes for study participants with an intercurrent event are imputed via the LOCF method a, ie, data which are missing on or after the intercurrent event will be imputed via LOCF following the method described in Section 5.1.1.7.3.

5.1.1.7.2 PK and antibody missing data

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

5.1.1.7.3 Efficacy missing data

An intercurrent event is defined as discontinuation of IMP prior to the time point of interest. For secondary efficacy variables with binary responses, (eg, PASI90 at Week 16, PASI75 at Week 4, and IGA0/1 response at Week 16), study participants who have an intercurrent event will have their efficacy response variable at the timepoint of the intercurrent event and all subsequent timepoints (whether the data were observed or not) set to “nonresponse”. An observed case (OC) analysis will be performed as a sensitivity check.

For secondary continuous efficacy endpoints (CDLQI [total score] change from Baseline at Week 16), the last observation carried forward (LOCF) will be used for participants who have an intercurrent event. The observed cases (OC) method will also be performed. Definitions of intercurrent event and missing data handling specific to each secondary efficacy endpoint are provided in Section 5.4.1.2. Note, the same approach will be used for missing data not preceded by an intercurrent event, ie, LOCF for continuous endpoints and nonresponder imputation for binary endpoints. Baseline measurements are eligible to be carried forward in the event that this is the last available measurement for a participant who is missing post-Baseline data.

5.1.1.7.4 Safety missing data

For analyses of safety endpoints related to TEAEs, a complete date must be established to correctly identify the AE as occurring during treatment or not. For purposes of imputing missing components of partially reported start and stop dates for AEs, algorithms are defined in Section 5.1.1.7.5. If the intensity of an adverse event is unknown, it will be considered as severe. If the relationship to study drug is missing, it is considered as related. Note that if the seriousness of an adverse event is unknown, every attempt should be made to resolve this prior to a snapshot for an interim analysis or database lock; in the exceptional case that the seriousness of an adverse event is still missing then no imputation should be applied for this characteristic.

Vital signs, physical examination findings, growth assessments, laboratory analyses will be based on observed data; no imputation will be performed. Endpoints will be presented with descriptive statistics, as observed.

5.1.1.7.5 Missing dates and times

For PK analysis, observations with missing IMP time will be excluded and no imputation will be performed.

For analyses of AEs and concomitant medication usage, a complete date is required in order to correctly identify the AE or concomitant medication as occurring during treatment or not, and for correctly assigning an AE or concomitant medication to the ITP or OLE Period.

For purposes of imputing missing components of partially reported start and stop dates for AEs and for concomitant medication use, the algorithms listed below will be followed. Start and stop dates of AEs or concomitant medication will be displayed as reported in the participant data listings (ie, no imputed values will be displayed in data listings). Partial AE and concomitant medication start dates will be imputed as follows:

Imputation of Partial Start Dates

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

Imputation of Partial Stop Dates:

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

If the imputed stop date is prior to the imputed start date:

- For missing start day and start month:
 - If the year of start date is the same as the year of first dose and the imputed stop date is on or after the date of first dose, then set the start date to the date of first dose.
 - Otherwise set to the 1st January of the year of the start date.
- For missing start day only
 - If the month and year of the start date is the same as the month and year of first dose and the imputed stop date is on or after the date of first dose, then set the start date to the date of first dose.
 - If the month and year of the start date is the same as the month and year of first dose and the imputed stop date is before the date of first dose, then set the start date to the 1st of that month.

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

5.1.1.8 Adjustments for covariates

All analyses are descriptive and covariate adjustments are not planned.

5.1.1.9 Multiple comparisons/multiplicity

Not applicable.

5.1.1.10 Use of an efficacy subset of participants

The PK-PPS will be used to evaluate participants who have efficacy data during the treatment periods and are reasonably compliant with the conditions of the study, in addition to RS.

Two subgroup analyses are planned for efficacy endpoints: weight category and sex. Details are provided in Section 5.8.

5.2 Study Participant Dispositions

The number and percentage of participants who are screened, enrolled, and randomized will be summarized for each clinical site and overall. Number and percentages of screen failures will also be summarized in the ES, and summaries of reasons for screen failures will be produced. The participants who discontinued treatment, discontinued study, or completed the study, as well as the discontinuation reasons, will be summarized for study periods by dose group in the RS. The overall number and percentages will also be summarized.

In addition, the number and percentages of participants in each of the analysis sets (ES, RS, SS, PK-PPS, and OLS) will be summarized by treatment arm and overall.

For purposes of summarizing disposition, study participants will be considered to have completed a study period if they complete the last scheduled study visit during that study period, not including SFU visits. A participant will be considered to have completed the study as follows:

- Completion of Initial Treatment Period is defined as completing the Week 20 Visit and the completion date is the Week 20 Visit date.
- Completion of OLE Period: for participants who entered the OLE period, completion is defined as completing the Week 124 Visit, and the completion date is the Week 124 visit.
- Completion of Study: For all participants, completion of study is considered as completion of OLE Period. Participants who do not tolerate the IMP or who have an IGA response ≥ 3 (on a scale from 0 to 4) at Week 20 will be considered as withdrawn from the study due to lack of efficacy. Participants who are eligible for but elect not to enter the OLE period at Week 20 will be considered as withdrawn from the study due to consent withdrawn.

In parallel, the end date of the study for a participant will be defined considering SFU Visit: the later date of the last visit including SFU or the date of last known dose of study drug.

5.2.1 COVID-19 impact analysis

The World Health Organization (WHO) declared the novel COVID-19 outbreak a global pandemic on 11 Mar 2020. For the purposes of summarizing disposition with respect to COVID, post-COVID refers to an event or record reported after the date when WHO declares the global pandemic has ended. If the WHO has not declared an official end date, an alternative end date may be used at the discretion of study team. If no suitable end date exists, the global pandemic is considered ongoing.

To assess the impact of the COVID-19 pandemic on the study, the following summaries will be presented:

- A summary of study visits impacted by the COVID-19 pandemic, and associated listing

5.3 Primary Endpoint Analysis

The primary analysis for this study is the PK analysis, outlined in Section 5.7.1.1.

5.4 Secondary Endpoints Analysis

Secondary variables include safety variables, efficacy variables, QOL variables, and immunogenicity variables. This section will outline the analysis for the secondary efficacy and QOL variables. The analysis for safety and immunogenicity variables will be presented in Section 5.6 and Section 5.7.1.4.

5.4.1 Secondary endpoints

5.4.1.1 Definition of endpoints

5.4.1.1.1 PASI response

The PASI is the most used and validated assessment for grading the severity of PSO in clinical studies (Feldman, 2004) and will be completed by the Investigator.

The percent body surface area of PSO involvement (BSA%) is estimated across the 4 body areas, head, upper limbs, trunk, and lower limbs. The BSA% is then converted into a degree score on a scale of 0 to 6 (0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected). This degree score is used in the calculation of PASI score as shown in Table 5-1. The total percent body surface area (BSA) of PSO involvement will also be estimated as a number between 0 and 100.

Three aspects of the PSO lesion severity including erythema (redness), induration (thickness), and desquamation (scaling) are respectively rated on a 5-point scale (0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked) across four body areas (head, upper limbs, trunk, and lower limbs). The sum of the three severity scale scores is weighted by the BSA involvement degree for each body area and aggregated into the PASI with prefixed weights (10% for head, 20% for upper limbs, 30% for trunk, and 40% for lower limbs). The PASI score ranges from 0 to 72 with a higher score indicating increased disease severity.

Details of calculations of PASI is provided in Section 6.1.6.1.

Table 5–1: Body areas for calculation of percent BSA for PASI

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

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

The PASI response is a binary variable based on the percent improvement from Baseline for each assessed timepoint. The percent improvement from Baseline for PASI for a participant will be calculated as:

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

A participant will be classified as a PASI90 responder if his or her percent improvement at a timepoint is $\geq 90\%$. The PASI75, PASI50, and PASI100 response variables are defined in a similar fashion for PASI percent change from Baseline, ie, $\geq 75\%$, $\geq 50\%$, and $\geq 100\%$. The secondary PASI efficacy variables are PASI90 and PASI75 evaluated at Week 16 and Week 4:

- A PASI90 responder at Week 16 is a participant whose PASI percent improvement from Baseline is $\geq 90\%$ at Week 16.
- A PASI75 responder at Week 4 is a participant whose PASI percent improvement from Baseline is $\geq 75\%$ at Week 4.

5.4.1.1.2 IGA response

A static IGA will be used to assess PSO severity in all participants during the study. The IGA will be completed by the investigator on a 5-point scale as specified in [Table 5–2](#).

Table 5–2: Five-Point IGA

Score	Short Descriptor	Detailed Descriptor
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominately fine scaling

Score	Short Descriptor	Detailed Descriptor
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

The IGA response is a binary variable based on the improvement from Baseline of the IGA score at each assessed timepoint. A participant will be classified as an IGA 0/1 responder for each assessed timepoint if his or her IGA response at a timepoint is clear (0) or almost clear (1) with at least a 2-category improvement from Baseline.

A participant will be classified as an IGA 0 responder for each assessed timepoint if his or her IGA response at a timepoint is clear (0) with at least a 2-category improvement from Baseline.

5.4.1.1.3 CDLQI (total score) change from baseline

The CDLQI (Lewis-Jones and Finlay, 1995) is a questionnaire designed to measure the impact of skin diseases on the lives of children. The questionnaire consists of 10 questions based on the experiences of children with skin disease concerning symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The questions relate to the impact of the skin disease on the child over the last week (ie, over the last 7 days) and are rated using a 4-point scale score from 0 to 3 (CCI [REDACTED]) (Table 5–3).

Participants will be asked to complete the CDLQI via an app. Any CDLQI data collected on paper via electronic data capture and digitally in the app will be pooled together for analysis. The CDLQI data source (ie, paper, app) will be displayed in the listing. All study participants, including those whose ages reach ≥ 17 years during the study, will complete the CDLQI throughout the study.

Table 5–3: Children’s Dermatology Life Quality Index (CDLQI) Scoring

CCI

[REDACTED]

The CDLQI total score is a continuous variable and calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0; the higher the score, the greater impairment on quality of life.

If 1 question is left unanswered, the unanswered question will be 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 CDLQI total score will not be derived and will be missing. If responses are collected for both Q7A and Q7B, they will be displayed in the listing, however only the response corresponding to the answer given in Q7 will be tabulated.

5.4.1.2 Main analytical approach

5.4.1.2.1 PASI90 (Week 16) response

The estimand for the secondary efficacy endpoint PASI90 response at Week 16 is defined as follows:

- **Participant-level outcome:** PASI90 response at Week 16.
- **Treatment:** Bimekizumab high dose (Dose A) and low dose (Dose B).
- **Population:** Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
- **Intercurrent event handling:** An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving PASI90 response at Week 16 and not discontinuing IMP through Week 16.
- **Population-level summary:** Percentage of participants achieving PASI90 response at Week 16 in each dose group.

The number and percentages of PASI90 responders at Week 16 will be reported for each dose group with 95% CIs. Missing data not preceded by an intercurrent event will be imputed as nonresponse for this and other binary secondary efficacy variables. An OC method will also be implemented to assess the impact of the main method of handling missing data.

5.4.1.2.2 PASI75 (Week 4) response

The estimand for the secondary efficacy endpoint PASI75 response at Week 4 is defined as follows:

- **Participant-level outcome:** PASI75 response at Week 4.
- **Treatment:** Bimekizumab high dose (Dose A) and low dose (Dose B).
- **Population:** Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
- **Intercurrent event handling:** An intercurrent event is defined as discontinuation of IMP prior to Week 4. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving PASI75 response at Week 4 and not discontinuing IMP through Week 4.
- **Population-level summary:** Percentage of participants achieving PASI75 response at Week 4 in each dose group.

The PASI75 at Week 4 will be analyzed in the same manner as PASI90 at Week 16.

5.4.1.2.3 IGA 0/1 response (Week 16)

The estimand for the secondary efficacy endpoint IGA 0/1 response at Week 16 is defined as follows:

- **Participant-level outcome:** IGA 0/1 response at Week 16.
- **Treatment:** Bimekizumab high dose (Dose A) and low dose (Dose B).
- **Population:** Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
- **Intercurrent event handling:** An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving IGA 0/1 response at Week 16 and not discontinuing IMP through Week 16.
- **Population-level summary:** Percentage of participants achieving IGA 0/1 response at Week 16 in each dose group.

The number and percentages of IGA 0/1 responders at Week 16 will be reported for each dose group in the same manner as PASI90/PASI75 responder variables. Missing data and intercurrent events will be handled similar to the PASI response variables.

5.4.1.2.4 CDLQI (total score) change from baseline (Week 16)

The estimand of the secondary QOL endpoint CDLQI total score change from Baseline to Week 16 is defined as follows:

- **Participant-level outcome:** Change from Baseline to Week 16 in CDLQI total score.
- **Treatment:** Bimekizumab high dose (Dose A) and low dose (Dose B).
- **Population:** Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
- **Intercurrent event handling:** An intercurrent event is defined as discontinuation of IMP prior to Week 16. A hypothetical strategy will be implemented in which participants with an intercurrent event are treated as though they had completed the randomized IMP through Week 16.
- **Population-level summary:** Mean change from Baseline to Week 16 in CDLQI total score in each dose group.

The change from Baseline to Week 16 in CDLQI total score will be summarized descriptively including n, mean, median, SD, min/max, and lower/upper quartiles in each dose group. The 95% CIs for the mean change will also be provided.

The LOCF method will be used to impute the missing value. The OC method will also be used.

5.4.1.3 Sensitivity Analysis

The OC analysis will serve as the sensitivity analysis for the secondary efficacy endpoints (PASI90 response at Week 16, PASI75 response at Week 4, IGA0/1 response at Week 16, and CDLQI total score change from baseline to Week 16) to assess the impact of missing value on the main imputed analysis.

The following analysis will also be performed as a sensitivity check:

- Separate summary of the secondary efficacy endpoints based on the PK-PPS

5.5 Other Endpoints Analysis

5.5.1 PASI50 / PASI75 / PASI90 / PASI100 response over time

Other PASI response variables, including PASI50, PASI75, PASI90, and PASI100, will be derived and analyzed using the same methods outlined in Section 5.4.1.2. The number and percentage of PASI responders will be reported by dose group for each parameter at each assessed timepoint.

In addition, the number and percentage of participants who achieve the absolute scores of PASI ≤ 1 , ≤ 2 , ≤ 3 , and ≤ 5 at each time point will be summarized for the OC.

5.5.2 PASI change from baseline

The PASI score values and change from Baseline will be summarized descriptively for each timepoint for the OC.

In addition, the value, change, and percent change from Baseline of percent BSA involvement will be summarized descriptively for each timepoint by dose group in the OC.

5.5.3 IGA response over time

The number and percentages of IGA 0/1 and IGA 0 responders at each time point will be reported for each dose group using the same methods outlined in Section 5.4.1.2.3.

5.5.4 Scalp IGA response over time

A static IGA for scalp PSO (Table 5–4) will be completed by the investigator to assess disease severity on the scalp. Scalp lesions will be assessed in terms of clinical signs of redness, thickness, and scaling on a 5-point scale using Table 5–4. This is the same scale with corresponding descriptors used for the overall IGA but will be specific to the scalp. Only participants with a scalp IGA score > 0 at Baseline will have the scalp IGA evaluated.

Scalp IGA response variables will be defined and derived similar to IGA. Scalp IGA 0/1 response is defined as clear [0] or almost clear [1] with at least a 2-category improvement from Baseline. For analysis purposes, the evaluation of scalp IGA will be limited to study participants with a Baseline scalp IGA of at least 2.

Scalp IGA response will be summarized for number and percentages by dose group at each timepoint.

Table 5–4: 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

Score	Short Descriptor	Detailed Descriptor
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

5.5.5 CDLQI (total score) change from baseline over time

The absolute value, change and percent change from Baseline for CDLQI total score to each assessed post-Baseline timepoint will be summarized descriptively including n, mean, median, SD, min/max, and lower/upper quartiles in each dose group.

5.5.6 CDLQI 0/1 response over time

The number and percentage of participants who have a CDLQI total score of 0 or 1 will be reported for each time point and by dose group for OC only.

5.5.7 Efficacy and PK relationship

An analysis, based on the Initial Treatment Period, will be conducted to investigate the relationship between plasma bimekizumab exposure and the efficacy variables (PASI response, PASI75, PASI90, IGA 0/1).

This analysis will be described in a separate analysis plan and reported separately.

5.6 Safety Analysis

Safety variables will be analyzed for all study participants in the SS (for the Initial Treatment Period and combined Initial Treatment Period and OLE Period when needed), and in the OLS (for the OLE Period). In general, safety data that are collected within 140 days of the last study drug dose (covering the 20-week SFU Period) will be attributed to the period in which the participant was before initiating the SFU Period and will be analyzed according to the most recent dose prior to or at the time of the collection.

By-visit tables summarizing safety data should include the SFU visit for the ITP + OLE and OLE summaries. However, SFU should not be included in by-visit safety tables for the ITP alone, since only a few participants will not enter the OLE.

5.6.1 Extent of exposure

Descriptive statistics will be provided for the duration of exposure to the study treatment by weight-categorized dose group for the Initial Treatment Period and the entire study. For all exposure summaries, the “All Participants” column will be a summary of the time from date of first dose through the date of last dose of any treatment, regardless of dose level. Time at risk will be summarized descriptively in the same manner as the duration of exposure.

The cumulative study medication duration will be summarized for participants exposed for given durations of time, and the following categories for duration will be used:

CCI

CCI



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

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

5.6.1.1 Initial Treatment Period

Duration of exposure (days):

- $\text{Date of last dose (Initial Period)} - \text{Date of first dose (Initial Period)} + 28$

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

Note: If the date of last dose (Initial Period) + 28 extends to a date beyond the date of first dose of the OLE Period:

- $\text{Date of first dose (OLE Period)} - \text{Date of first dose (Initial Period)} + 1$

Note: For participants who die during the Initial Treatment Period: $\text{Date of death} - \text{Date of first dose (Initial Period)} + 1$

Time at risk (days):

For participants who complete the final visit of the Initial Treatment Period and continue to the OLE Period:

- $\text{Date of first dose (OLE Period)} - \text{Date of first dose (Initial Period)} + 1$

Note: For participants who die prior to the final visit of the Initial Period:

- $\text{Date of death} - \text{Date of first dose (Initial Period)} + 1$

Note: If a participant discontinues on or prior to the final visit of the Initial Treatment Period and does not continue to the OLE Period, use the minimum of the following:

- *Total number of days in the Initial Treatment Period (140 days)*

- *Date of last clinical contact – Date of first dose (Initial Period) + 1*

5.6.1.2 Open Label Extension (OLE) Period

Duration of exposure (days):

Study participants who are enrolled into OLE Period may be allowed dose modification from the Initial Treatment Period. The duration of exposure will be calculated by aggregating distinct dosing periods with respect to each dose level.

The exposure for the i -th dosing period P_i can be calculated as follows:

- *Exposure(P_i) = Last Dose Date of P_i – 1st Dose Date of P_i + min (28, Date of Death – Last Dose Date of P_i)*

Note: If *Last Dose Date of P_i + 28* extends to a date beyond the date of first dose of the next dosing period, then this calculation reverts to:

- *Exposure(P_i) = First Dose Date of P_{i+1} – 1st Dose Date of P_i + 1*

The aggregated exposure for dose level (say A) is the sum of the exposure over all the dosing periods of dose level A:

- *Dose A Exposure = $\sum_{\text{Dose A dosing periods}} \text{Exposure}(P_i)$*

Note: If days between the last dose of P_i and the first dose of P_{i+1} is more than 28 days, then there will be a gap in between the two periods.

Time at risk (days):

For any dosing period P_i before the last dosing period,

- *Time at Risk (P_i) = min (First Dose Date of P_{i+1} , Date of Death) – 1st Dose Date of P_i + 1*

For the last dosing period P_n ,

- *Time at Risk(P_i) = Last Dose Date of P_n – 1st Dose Date of P_n + min (141, Date of Death – Last Dose Date of P_n)*

The aggregated time at risk for dose level is calculated in a similar fashion as the aggregated exposure:

- *Dose A Time at Risk = $\sum_{\text{Dose A dosing periods}} \text{Time at Risk}(P_i)$*

5.6.1.3 Combined Initial Treatment Period and OLE Period

The combined duration of exposure will be the sum of exposure calculated from the Initial Treatment Period (as defined in Section 5.6.1.1) and OLE Period (as defined in Section 5.6.1.2) for each dose level, minus 1 day. Only the same dose level can be combined within a participant. The time at risk will be calculated similarly.

5.6.2 Adverse Events

Adverse events will be coded according to the MedDRA. Safety Topics of Interest (defined in Section 5.6.2.3) and Safety Topics Closely Monitored (defined in Section 5.6.2.4) will be given special attention in analysis.

Adverse events will be allocated to the respective weight-categorized dose group received. If an AE occurs on the date of a dose switch or on Week 20 dose date, the AE will be attributed to the original dose/period (the “preswitch” dose/period). The only exception to this is for the following type of events, which will be attributed to the new weight-categorized study dose/period:

- Events that fulfill the anaphylaxis criteria for acute events
- Events that fulfill the hypersensitivity reaction criteria
- Events with a high-level term (HLT) of “Administration site reactions NEC”
- Events with an HLT of “Injection site reactions” will be attributed to the dose received at onset

5.6.2.1 General data considerations for AEs

Treatment-emergent AEs are defined as those AEs that have a start date on or following the first dose of IMP through the final dose of study treatment +20 weeks (140 days).

The rules for imputing partial start or stop dates are outlined in Section 5.14.7.5. If it is not possible (due to partial dates) to determine whether an AE is treatment-emergent then it will be assumed to be a TEAE. If the intensity of an AE is unknown, it will be considered as severe. If the relationship to study drug is missing, it will be considered as related.

Treatment-emergent AEs will be summarized as participant incidence (number and percentage of participants experiencing the AE) and AE frequencies (number of AEs including repeat events) by weight-categorized dose group for the Initial Treatment Period, OLE Period, and the combined periods. Treatment-emergent AEs will be attributed to Initial Treatment Period and OLE Period based on duration of exposure definition in Section 5.6.1. For AEs that emerged after 140 days of first dosing but still within the 140 days after last dose window, those AEs will be classified as TEAE but will be excluded from the output based on the Initial Treatment Period. However, these AEs will be included in the AE summaries for Initial Treatment Period and OLE Treatment Period combined.

For AEs that emerged > 140 days after the last dose, these AEs will only be listed in an “All Adverse Events” listing and will not be summarized.

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

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

EAIR in ITP tables should be calculated based on the first occurrence of the AE within ITP. Similarly, EAIR in OLE tables should be calculated based on the first occurrence of the AE

within OLE. For a combined ITP + OLE table, EAIR should be calculated based on the first occurrence of the AE regardless of the period. EAER should include all repeat occurrences within ITP, OLE, or ITP + OLE, depending on the summary. Details of the calculations for exposure adjusted rates (EAIR and EAER) can be found in the Appendix 6.1.6.2.

5.6.2.2 AE summaries

The following AE summaries for participant incidence and event number will be provided by weight-categorized dose group for the Initial Treatment Period, OLE Period, and the combined periods. Selected summaries as noted will report exposure adjusted rates. An overall summary of the AEs will also be provided. AE tables will summarize Dose A (320mg, 160mg, Total), Dose B (all) and All Participants on one page; the subsequent page will contain Dose B (64mg, 32mg, Total), Dose A (all) and All Participants.

- Summary by system organ class (SOC), HLT, and preferred term (PT):
 - Any TEAE (with exposure-adjusted rates)
 - Serious TEAE (with exposure-adjusted rates)
 - TEAEs leading to withdrawal from the study (with exposure-adjusted rates)
 - TEAE leading to discontinuation of investigational medicinal product (IMP) (with exposure-adjusted rates)
 - TEAE leading to death
 - Related TEAE
 - Related serious TEAE
 - TEAE for safety topics of interest and safety topics closely monitored (with exposure-adjusted rates)
- Summary by relationship, SOC, HLT, and PT
 - Any TEAE
 - TEAE leading to death (for EudraCT reporting purposes)
- Summary by maximum relationship, SOC, HLT, and PT
 - Any TEAE
- Summary by severity, SOC, HLT, and PT
 - Any TEAE
- Summary by maximum severity, SOC, HLT, and PT
 - Any TEAE

Ordered and subset of AE summaries will be reported in a separate table to facilitate review when needed. Examples include:

- Serious TEAE by SOC and PT
- Nonserious TEAE by SOC and PT above reporting threshold of 5%

- Any TEAE by decreasing frequency of PT

The following summary will be provided for antibody data (Section 5.7.1.4.1.6 and Section 5.7.1.4.2.1):

- Incidence of TEAEs per 100 participant years by SOC, HLT, and PT and by time of onset relative to ADAb status. Note: Only presented for combined Initial Treatment Period and OLE Period.
- Incidence of TEAEs per 100 participant years by SOC, HLT, and PT and by time of onset relative to NAB status. Note: Only presented for combined Initial Treatment Period and OLE Period.

The following AEs will be listed separately:

- Any TEAE with onset at day 1
- Any TEAE related to TB including latent TB and IGRA tests

The following summaries will be produced for the Plain Language Summaries:

- Incidence of Drug-related TEAEs – Overview
- Incidence of Drug-related TEAEs by Preferred Term
- Incidence of Serious Drug-related TEAEs by Preferred Term

5.6.2.3 Safety topics of interest

Safety topics of interest for this study include infections (serious, opportunistic, fungal, and TB), IBD, and injection site reactions. Additionally, in keeping with the conduct of the adult bimekizumab program, the following topics will also be closely monitored: neutropenia, hypersensitivity (including anaphylaxis), major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and SIB (see Section 5.6.2.4). Safety topics of interest are defined as events for which special monitoring, additional data collection activities, and/or enhanced signal detection activities are applied.

The TEAEs of safety topics of interest and safety topics closely monitored will be presented in a combined table. The participant incidence, number of events, and exposure adjusted rates (incidence and event rate per 100 participant years) will be reported by SOC, HLT, and PT. Summaries will be provided for the Initial Treatment Period, OLE Period, and All Periods (Initial Treatment Period + OLE Period).

The details of each safety topics of interest are provided below.

5.6.2.3.1 Infections (serious, opportunistic, fungal and TB)

- Serious infections: The combined table will include serious infections identified based on MedDRA classification (SOC “Infections and infestations”) using the “Any SAE” table.
- Fungal infections: The combined table will include all TEAEs (serious and non-serious) which code into the High Level Group Term “Fungal infections disorders”.
- Opportunistic infections (including TB): The combined table will include all TEAEs identified using the SMQ “Opportunistic infections (SMQ)”. All TEAEs which code to a PT included in the Scope = Narrow search will be included in this table.

- TB: TB will be analyzed as part of opportunistic infections. Summary of the number and percentage of participants with negative, positive, and indeterminate interferon gamma release assay (IGRA) results at each visit will be presented. In addition, incidence of TB related TEAEs will be summarized (active TB, latent TB, and false positive TB testing). A by-participant listing of the “Evaluation of signs and symptoms of tuberculosis” questionnaire data, IGRA results, and chest x-ray results will be provided. A by-participant listing of “All Treatment-Emergent Adverse Events Related to TB including latent TB and IGRA tests” will be provided.

5.6.2.3.2 IBD

An external IBD adjudication committee will evaluate potential IBD events and will classify each one as follows:

- Event Type Code 1: Possible IBD – Crohn’s Disease
- Event Type Code 2: Probable IBD – Crohn’s Disease
- Event Type Code 3: Definite IBD – Crohn’s Disease
- Event Type Code 4: Possible IBD – Ulcerative Colitis
- Event Type Code 5: Probable IBD – Ulcerative Colitis
- Event Type Code 6: Definite IBD – Ulcerative Colitis
- Event Type Code 7: Possible IBD – Unclassified
- Event Type Code 8: Probable IBD – Unclassified
- Event Type Code 9: Definite IBD – Unclassified
- Event Type Code 10: Symptoms not consistent with IBD
- Event Type Code 11: Possible Inflammatory Bowel Disease – Microscopic Colitis
- Event Type Code 12: Probable Inflammatory Bowel Disease – Microscopic Colitis
- Event Type Code 13: Definite Inflammatory Bowel Disease – Microscopic Colitis
- Event Type Code 14: Possible Inflammatory Bowel Disease – no further differentiation possible
- Event Type Code 15: Probable Inflammatory Bowel Disease – no further differentiation possible
- Event Type Code 16: Definite Inflammatory Bowel Disease – no further differentiation possible
- Event Type Code 99: Not enough information to adjudicate

The combined safety topics of interest and safety topics closely monitored table will summarize events determined by the adjudication committee as definite IBD (event type codes 3, 6, 9, 13, and 16) and probable IBD (event type codes 2, 5, 8, 12, and 15).

A separate table will present the incidence and event rate of adjudicated gastrointestinal events by type for the combined ITP and OLE Period. For each gastrointestinal event type (17 total), the

individual PTs which fall within each event type will be summarized. It will include events determined by the adjudication committee as definite IBD, probable IBD, and possible IBD. It will also include events determined as Symptoms not consistent with IBD (event type code 10) and Not enough information to adjudicated (event type code 99).

A listing of all events identified for potential review by the IBD adjudication committee will be produced. This listing will indicate whether each event was escalated to the committee for formal review/adjudication.

A separate listing will present the adjudicated IBD events by type. For each IBD event type (event type codes 1 through 16 and 99; 17 total), the individual PTs which fall within each event type will be listed.

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

5.6.2.3.3 Injection site reactions

Injection site reactions will be evaluated in the combined table by looking under the following HLTs: “Administration site reactions NEC” and “Injection site reactions”

5.6.2.4 Safety topics closely monitored

The TEAEs of safety topics of interest and safety topics closely monitored will be presented in a combined table. The participant incidence, number of events, and exposure adjusted rates (incidence and event rate per 100 participant years) will be reported by SOC, HLT, and PT.

5.6.2.4.1 Hypersensitivity (including anaphylaxis)

The combined table will include acute anaphylactic events (reported on the same day as when an injection was administered or 1 day after) prepared based on the MedDRA anaphylaxis algorithm (see Section 6.1.8.1). All TEAEs which code to a PT included in the Scope=Narrow search will be included in the combined table. The combined table will also summarize serious hypersensitivity events, identified using the SMQ “Hypersensitivity (SMQ)”. All serious TEAEs which code to a PT included in the Scope=Narrow search will be included in the combined table. An AE glossary table will also be produced to summarize the MedDRA coding for these events. The glossary table will include the following fields: reported term, PT, LLT, HLT, and SOC.

5.6.2.4.2 Suicidal Ideation and Behaviour (SIB)

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

A separate table will present the incidence and event rate of adjudicated neuropsychiatric events by type. For each neuropsychiatric event type, the individual PTs which fall within each event type will be summarized. It will include events adjudicated as SIB and events adjudicated as non-suicidal. Note: that the event type “Suicidal ideation” can be classified as either SIB or non-suicidal.

Additionally, a listing of all events identified for potential review by the neuropsychiatric adjudication committee will be produced. This listing will indicate whether each event was

escalated to the committee for formal review/adjudication. A separate listing will also be produced to summarize the adjudicated results of all events escalated to the full committee.

5.6.2.4.3 Cardiovascular events

Cardiovascular events will be presented in the combined table only. Cardiovascular events will be identified by the following SMQs (regardless of seriousness).

- Level 1: “Ischaemic heart disease (SMQ)”
- Level 1: “Embolic and thrombotic events (SMQ)”
- Level 2: “Central nervous system haemorrhages and cerebrovascular conditions (SMQ)”

For each of the above SMQs, include all TEAEs which code to a PT included in the Scope=Narrow. Additionally, any TEAEs which code to the PT “Sudden death” will be included.

5.6.2.4.4 Hepatic events and PDILI

The combined table will include hepatic events, which will be created based on the SMQ of “Drug related hepatic disorders - comprehensive search (SMQ)”. However, these 2 sub-SMQs are to be excluded: “Liver neoplasms, benign (incl cysts and polyps) (SMQ)” and “Liver neoplasms, malignant and unspecified (SMQ)”. For each of the above SMQs, include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow. Note that all AEs meeting the above criteria are to be included. It should not be limited to events that the investigator determined to be related to study drug. Liver function test changes/enzyme elevations including cases of Hy’s Law will be reported separately in a liver function test table (refer to Section 5.6.3.1.1)

5.6.2.4.5 Malignancies

SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each SMQ. The combined table will include 2 different overall incidence rows:

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

5.6.2.4.6 Neutropenia

Neutropenia will be reported in the combined table based on PTs (regardless of seriousness) including:

- Autoimmune neutropenia
- Band neutrophil count decreased
- Cyclic neutropenia
- Febrile neutropenia

- Idiopathic neutropenia
- Neutropenia
- Neutropenic infection
- Neutropenic sepsis
- Neutrophil count decreased

5.6.3 Additional Safety Assessments

5.6.3.1 Clinical laboratory evaluations

Hematology, chemistry, urine laboratories, and liver function tests are assessed in this study. A by-participant listing of all laboratory data with the CTCAE grade and abnormality classifications will be provided.

5.6.3.1.1 Laboratory values over time

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. Additionally for tables where data are summarized by visit, summaries of the Initial Treatment Period will not include the SFU visit since sample sizes will be small, but these data will be included in listings. For tables where multiple measurements over a period of time are considered (as in shift tables), unscheduled and repeat visits will be considered as long as they were collected in the period being summarized (values observed more than 140 days after the last administration of study medication are not considered). All summaries will be presented in International System of Units and will be based on observed case values. In the case where laboratory values are below the LLQ, then these will be set to the midpoint between 0 and the lower limit of quantification for the purpose of summarizing the data. The following summaries will be presented:

- A summary of the absolute and change from Baseline values in each laboratory variable by weight-categorized dose group and visit will be presented.
- A summary of the number and percentage of participants with a given CTCAE grade (0, 1, 2, 3, or 4) based on minimum/maximum post-baseline value by laboratory variable and weight-categorized dose group will be presented. The criteria used for CTCAE grade classification is provided in Section 6.1.9.1.
- A shift table of the number and percentage of participants experiencing CTCAE grade 0, 1, 2, 3, or 4 values (as applicable) at Baseline to maximum post-Baseline CTCAE grade will be presented, by laboratory variable and weight-categorized dose group.
- A summary of the number and percentage of participants experiencing treatment-emergent markedly abnormal (TEMA) values will be presented for each weight-categorized dose group for the Initial Treatment Period, OLE Period, and the combined periods. The TEMA laboratory values are defined similarly to TEAE as those lab values assessed on or following the first dose of study treatment through the final dose of treatment +20 weeks (140 days) with a severity of CTCAE Grade 3 and above.
- A by-participant listing of all laboratory data (including urinalysis) will be provided. This listing will be presented by weight-categorized dose group and will include center,

participant identifier, age, sex, race, weight, visit, laboratory variable, result (with abnormal values flagged as “L” or “H” accordingly) and unit.

The table for markedly abnormal liver function tests (LFTs) will contain data beyond the CTCAE Grade 3 thresholds outlined 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 participants meeting the below criteria at any time during the study:

- AST (aspartate aminotransferase): >3xULN (upper limit of normal), >5xULN, >8xULN, >10xULN, >20xULN
- ALT (alanine aminotransferase): >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- AST or ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- Total 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:

- $nR = [\text{maximum}(\text{AST}/\text{ULN or AST}/\text{ULN})]/(\text{ALP}/\text{ULN})$

Potential drug induced liver injury (pDILI) will be summarized (all criteria must be met at the same assessment):

- (AST or ALT $\geq 3x\text{ULN}$) and Total Bilirubin $\geq 1.5x\text{ULN}$
- (AST or ALT $\geq 3x\text{ULN}$) and Total Bilirubin $\geq 2x\text{ULN}$

In addition, potential Hy's Law cases will be summarized with the LFT lab data. The following definition will be used:

- [AST $\geq 3x\text{ULN}$ or ALT $\geq 3x\text{ULN}$] and Total Bilirubin $\geq 2x\text{ULN}$ in the absence of ALP (Alkaline phosphatase) $\geq 2x\text{ULN}$

In order to meet the above potential Hy's Law laboratory criteria, a subject must experience the elevation in bilirubin and ALT or AST (and the absence of ALP elevation) at the same visit. For example, a subject who experiences a $\geq 2x$ ULN elevation of bilirubin at one visit and a $\geq 3x\text{ULN}$ elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria. Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.

Potential hepatotoxicity (meeting one of the pDILI or Hy's law laboratory criteria at least once) will be considered with and without symptoms potentially associated with hepatitis or hypersensitivity according to the investigator (reported on the Symptoms of Hepatitis and Hypersensitivity CRF page). To align with regulatory guidelines for PDILI assessment and reporting in CSRs, a table summarizing incidence of hepatotoxicity and lab criteria constituting a PDILI will be included.

5.6.3.1.2 Individual participant changes of laboratory values

A shift table will be provided for the number and percentage of participants experiencing CTCAE grade 0, 1, 2, 3, or 4 values (as applicable) at Baseline to minimum/maximum post-Baseline CTCAE grade.

5.6.3.2 Vital signs

Vital signs, including body temperature, heart rate (or pulse rate), systolic blood pressure, and diastolic blood pressure will be assessed and analyzed.

5.6.3.2.1 Vital sign values over time

Descriptive statistics for the absolute value and change from Baseline for each vital sign parameter will be provided by weight-categorized dose group at each timepoint.

5.6.3.2.2 Individual participant changes of vital sign values

The number and percentage of participants experiencing at least 1 markedly abnormal value (Appendix 6.1.9.2) for a vital sign variable will be summarized by weight-categorized dose group for the Initial Treatment period, OLE Period, and the combined periods.

5.6.3.3 Columbia suicide severity rating scale (C-SSRS)

The C-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior. The C-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent.

The incidence of study participants with suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior will be summarized by weight-categorized dose group through the Initial Treatment Period and through the Initial and OLE Treatment Periods combined. A listing of all C-SSRS questionnaire data will be provided. A listing of all participants who reported at least 1 suicidal ideation or behavior will also be provided.

5.6.3.4 PHQ-9

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

The number and percentage of participants with scores below 5, between 5 and 9, between 10 and 14, between 15 and 19, and greater than 20 in PHQ-9 will be summarized as a shift from Baseline by visit and weight-categorized dose group based on observed values. Descriptive statistics for the PHQ-9 scores will be summarized by weight-categorized dose group and visit. A by-study participant listing of the PHQ-9 questionnaire data will be provided by weight-categorized dose group including the change of PHQ-9 scores from the previous visit. The PHQ-9 data source will be displayed in the listing.

5.6.3.5 Electrocardiograms

Not applicable.

5.6.3.6 Other safety endpoints

5.6.3.6.1 Physical examinations

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

Clinically significant changes from Baseline in physical examination findings will be reported as AEs in the any TEAE table. Changes from Baseline in physical examination findings will therefore be summarized as part of the TEAE.

5.6.3.6.2 Growth assessment

Descriptive statistics for height and weight change from baseline will be reported by weight-categorized dose group over time. Growth percentiles will be calculated for height, weight, and body mass index (BMI) at Week 16, Week 64, and Week 124. A shift table of the number and percentage of participants falling in each percentile category from baseline to these post-baseline visits will be presented by weight-categorized dose group. The percentile categories are listed below.

- Height (percentile):
 - $<5^{\text{th}}$
 - $\geq 5^{\text{th}}$ to $<25^{\text{th}}$
 - $\geq 25^{\text{th}}$ to $<50^{\text{th}}$
 - $\geq 50^{\text{th}}$ to $<75^{\text{th}}$
 - $\geq 75^{\text{th}}$ to $<95^{\text{th}}$
 - ≥ 95
- Weight (percentile): the same percentile categories as height
- BMI (percentile):
 - $<5^{\text{th}}$ (underweight)
 - $\geq 5^{\text{th}}$ to $<85^{\text{th}}$ (normal or healthy weight)
 - $\geq 85^{\text{th}}$ to $<90^{\text{th}}$ (overweight)
 - $\geq 90^{\text{th}}$ to $<95^{\text{th}}$ (overweight)
 - $\geq 95^{\text{th}}$ to $<97^{\text{th}}$ (obese)
 - $\geq 97^{\text{th}}$ (obese)

Height and weight percentile reference levels are provided in Section 6.3.2.

5.6.3.6.3 Assessment and management of TB and TB risk factors

A summary of the number and percentage of participants with negative, positive, and indeterminate IGRA results at all applicable visits will be presented for the entire study.

A by-participant listing of the “Evaluation of signs and symptoms of tuberculosis” questionnaire data and IGRA results will be provided.

A by-participant listing of “All Treatment-Emergent Adverse Events Related to TB including latent TB and IGRA tests” will be provided. Please refer to Section 5.6.2.3.1 for additional information.

A by-participant listing of the result of chest x-ray for tuberculosis will be provided by weight-categorized dose group.

5.6.3.6.4 Pregnancy testing

A by-participant listing of the pregnancy test and outcome data will be provided by weight-categorized dose group at each timepoint for female participants.

5.7 Other Analyses

This section will outline PK and immunogenicity analyses.

5.7.1 Other endpoints and parameters

5.7.1.1 Pharmacokinetics

The primary variable of this study is plasma bimekizumab concentrations, assessed at Baseline, Week 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 40, Week 64, Week 88, Week 112, Week 124, EDV, and SFU Visit. Pharmacokinetic analyses will be performed in the PK-PPS. Summary tables will be created for the Initial Treatment Period for all participants in PK-PPS, and across All Periods (Initial Treatment Period + OLE Period) summaries for all participants that are in both the OLS and PK-PPS (i.e. all study participants who receive at least 1 dose of IMP at or after Week 20 in the OLE Period and who have at least 1 quantifiable plasma concentration without important protocol deviations that would affect the concentration in the OLE Period).

Bimekizumab plasma concentrations will be summarized with descriptive statistics and plotted for each weight-categorized dose group, at each scheduled visit. Summaries of bimekizumab plasma concentration over time will be reproduced with rounding to 1 decimal place and may be used for Plain Language Summaries. These tables and figures will be repeated by cumulative anti-bimekizumab antibody status (See Section 5.7.1.4.1.4) and by overall NAb status (See Section 5.7.1.4.2). Bimekizumab plasma concentrations summaries will be based on observed values, with each sample falling within the time window rules described below. No imputation will be used for missing data. If plasma concentration measurements are below the level of quantification (BLQ), then for calculation of the derived statistics the result will be set to $\frac{1}{2}$ of the LLOQ. Descriptive statistics including geometric mean, geometric coefficient of variation, and geometric mean 95% CI (if applicable) will be calculated if at least two-thirds of the values of interest are above the LLOQ and $n \geq 3$. If this is not the case, only median, minimum, and maximum will be presented.

All PK concentrations will be listed.

By-visit summaries and figures of plasma concentrations will exclude data points where protocol deviations and/or deviation from scheduled dose and sample collection window are expected to impact drug exposure. The protocol deviations will be reviewed by the Quantitative Clinical Pharmacology (QCP) representative and a decision about impacted data points will be made prior to generating summary statistics.

Out of window exclusion rules for bimekizumab plasma concentration summaries and figures:

- A sample will be considered out of window relative to the current dose and will be excluded from the summaries and graphs if the sample is collected >1 day after the dose administered at this visit. This excludes samples collected at an EDV visit, including Week 20 (if the participant did not enter the OLE Period) or Week 124 and Week 1, where a dose will not be administered at that visit.
- Alternatively, a sample will be considered out of window relative to the previous dose and will be excluded from the summaries and graphs if the sample is collected <14 days or >42 days after the previous dose, and the sample was collected prior to the dose at that visit (should a dose be scheduled). Week 1 will be excluded from this rule.

The PK data will be subject to a population PK analysis and will be described in a separate analysis plan and reported independently.

5.7.1.2 Pharmacodynamics

Pharmacodynamics are not evaluated in this study.

5.7.1.3 Genomics

Genomics is not evaluated in this study.

5.7.1.4 Immunological (Immunogenicity) Analysis

Immunogenicity variables are the anti-bimekizumab antibody status, anti-bimekizumab antibody titer and neutralizing anti-bimekizumab antibody status derived from anti-drug antibody assays. The analysis will be based on the SS.

Anti-bimekizumab antibodies will be measured using a 3-tiered assay approach: screening assay, confirmatory assay, and titration assay. Samples confirmed as positive within the confirmatory assay will be further evaluated. The samples will be titrated, and the ADA_b titer (reciprocal dilution factor, including the Minimum Required Dilution) will be reported. In addition, the sample will be assessed by a neutralizing antibody (NAb) assay to evaluate the potential of the ADA_b to neutralize the activity of bimekizumab (IL17A-specific or IL17F-specific, or both) in-vitro analysis details outlined in Section 5.7.1.4.2.

Samples were taken on the same schedule as PK assessments including Baseline, Week 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 40, Week 64, Week 88, Week 112, Week 124, EDV, and SFU.

Screening, confirmatory, and titer cut points of the respective assays will be determined by the bioanalytical laboratory based either on using commercially-available drug-naïve samples or on the predose samples obtained during the study.

Summary tables will be created for the Initial Treatment Period for all participants in the SS, and across the All Periods (Initial Treatment Period + OLE Period) summaries for all participants in the OLS.

5.7.1.4.1 Anti-bimekizumab antibody

5.7.1.4.1.1 ADAAb sample status

The following definitions will be applied regarding ADAAb status of each test sample:

- An ADAAb status will be confirmed as positive for any sample that is positive screen and positive immunodepletion (regardless of availability of a titer value).
- An ADAAb status of negative will be concluded for any sample that is either negative screen, or positive screen and negative immunodepletion, and where the bimekizumab concentration is less than or equal to the drug tolerance limit (200 µg/mL) of the validated ADAAb assay.
- Inconclusive - sample that is either negative screen or positive screen and negative immunodepletion and where the bimekizumab concentration exceeds the validated ADAAb assay drug tolerance limit. These samples will be regarded as missing.

If the titer for a sample that is positive screen and positive immunodepletion is missing, then a conservative approach will be used and ADAAb status will be considered as positive. No imputation rules apply for the missing titer. If a sample is positive screen but no confirmatory result could be determined, then a conservative approach will be used and ADAAb status will be considered as positive.

5.7.1.4.1.2 Overall ADAAb status

A participant's overall ADAAb status will be derived by dose (320 mg, 160 mg, Total for Dose A, 64 mg, 32 mg, Total for Dose B, and Total for all participants). For participants who undergo dose modifications in the OLE, their data will be summarized by the dose assigned at Baseline. The following periods will be summarized:

- Overall ADAAb status to Week 16 (SS) : Including all visits (including and excluding Baseline) up to Week 16, excluding the SFU sample.
- Overall ADAAb status to Week 20 (SS) : Including all visits (excluding Baseline) up to Week 20, excluding and including the SFU sample. If $\geq 95\%$ of participants in the Initial Treatment Period enter the OLE Period, overall ADAAb status to Week 20 including the SFU sample will not be summarized.
- Overall ADAAb status to Week 124 (OLS): Including all visits up (excluding Baseline) to Week 124, excluding the SFU sample.
- Overall ADAAb status to SFU (OLS): Including all visits up (including and excluding Baseline) to SFU.

Over each of the periods defined above:

- Overall positive is defined as having at least one value that is confirmed positive (regardless of missing data).

- Overall negative, if the study participant has all samples reported as negative or has only one missing/inconclusive sample.
- Overall missing, if the study participant has more than one missing ADA b sample for any reason (eg, insufficient sample, ADA b sample status is inconclusive, no result is available or a missed scheduled collection) and all other available ADA b samples are negative.

5.7.1.4.1.3 ADA b Subcategories

Furthermore, the following subcategories for each participant will be derived:

1. **Pre ADA b negative – treatment-emergent ADA b negative (category 1):** Includes participants who are negative at Baseline and ADA b negative at all sampling points posttreatment (excluding SFU) or has only one postbaseline missing/inconclusive sample. This includes study participants who have a missing/inconclusive sample at Baseline with all post-treatment samples reported as ADA b negative.
2. **Pre ADA b negative – treatment-emergent ADA b positive (category 2):** Includes participants who are negative at Baseline and ADA b positive at any sampling point posttreatment (excluding SFU). This group also includes participants who have a missing/inconclusive sample (either missing or insufficient volume) at Baseline with 1 or more ADA b positive posttreatment samples.
3. **Pre ADA b positive – treatment-emergent reduced ADA b (category 3):** Includes participants who are positive at Baseline, and ADA b negative at all sampling points posttreatment (excluding SFU) or has only one post-Baseline missing/inconclusive sample.
4. **Pre ADA b positive – treatment-emergent unaffected ADA b positive (category 4):** Includes participants who are positive at Baseline and are positive at any sampling point posttreatment (excluding SFU) with titer values of the same magnitude as Baseline (ie, < 2.07-fold difference from the Baseline value; 2.07 being the validated minimum significant ratio for this assay method).
5. **Pre ADA b positive – treatment-emergent ADA b boosted positive (category 5):** Includes participants who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with increased titer values compared to Baseline (≥ 2.07 -fold difference increase from Baseline).
6. **Inconclusive (category 6):** Includes participants who have a positive Baseline sample, and some posttreatment samples are missing/inconclusive, while other posttreatment samples are ADA b negative.
7. **Total treatment-emergent (category 7 [categories 2 and 5 combined]):** Includes study participants who are preADA b negative – treatment emergent ADA b positive (category 2) and preADA b positive – treatment boosted ADA b positive (category 5).
8. **Total prevalence of preADA b positivity (category 8 [categories 3, 4, 5, and 6 combined]):** Study participants that are tested ADA b positive at Baseline.
9. **Missing (category 9):** Includes participants who are antibody negative at Baseline and have more than 1 post-treatment scheduled assessments reported as missing/inconclusive, while other samples are ADA b negative. Note this is also applicable to participants who have a

missing Baseline sample, at least one missing/inconclusive postbaseline sample and have no ADAb positive samples.

Derivation for above classification will be different for the Initial Treatment Period (SS) and the combined Initial Treatment and OLE Periods (OLS). For the Initial Treatment Period, no OLE or SFU data will be considered. For the combined Initial Treatment and OLE Periods, data from the OLE and SFU visits be considered. That is, each instance of “excluding SFU” in the categories above, should be changed to “including SFU.”

In the case that a sample is collected 1 or more days following the scheduled visit date in which the drug was administered, the ADAb results for that sample will be associated with the scheduled visit and summarized accordingly. Such samples will also be considered when ADAb results are summarized over a given study period.

5.7.1.4.1.4 Cumulative ADAb status groups for PK summaries

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

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 one missing/inconclusive sample with all negative ADAb samples up to that timepoint, the study participant will be classified as negative. An exception remains for the Baseline Visit where only one 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.

5.7.1.4.1.5 ADAb status groups for Efficacy Endpoint Summaries

For purposes of efficacy subgroup analyses based on ADAb status, 3 categories will be used:

- ADAb positive – Defined as participants who have at least 2 ADAb positive samples up to the time point of interest (ie, excluding Baseline) regardless of other ADAb samples and/or missing or inconclusive samples.
- ADAb negative – Defined as study participants for whom either (1) all samples to the timepoint of interest are ADAb negative and there are no missing or inconclusive samples, (2) only 1 post-Baseline sample is ADAb positive and all others to the timepoint of interest 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.

ADAb status for efficacy subgroups will be derived at Week 16 (excluding SFU) for the Initial Treatment Period and Week 124 (including SFU) for the combined Initial Treatment and OLE Periods (OLS).

5.7.1.4.1.6 Analysis

Immunogenicity will be assessed through summary tables, figures, and listings of individual results by participant. Analyses will be run on the SS and OLS, unless specified otherwise. All individual participant-level ADA_b results will be listed. The listing will also include flags and reasons for exclusion for ADA_b measurements that were excluded from the by-visit summaries (as detailed below), as well as information on whether the BKZ concentration exceeds the ADA_b assay drug tolerance limit.

In the case that a ADA_b sample is collected within ± 21 days relative to the visit date at which BKZ was administered (or ± 21 days from a scheduled visit at which BKZ dosing was not planned eg, ET or SFU visits), the ADA_b result for that sample will be associated with the scheduled visit and summarized accordingly. Samples collected outside of this window will be excluded from the ADA_b by-visit summaries and will be listed only. All other summaries of ADA_b status (Section 5.7.1.4.1.2 to Section 5.7.1.4.1.5) will use all available (scheduled and unscheduled visit) data. Tables and figures listed below will be summarized by dose (320 mg, 160 mg, Total for Dose A, 64 mg, 32 mg, Total for Dose B, and Total for all participants). For participants who switch dose during the OLE, their data will be summarized by weight-categorized dose group at Baseline.

- Summary of ADA_b status overall and by each visit will be presented over the periods of interest (Section 5.7.1.4.1.2). This includes overall ADA_b status for the efficacy endpoint summaries (Section 5.7.1.4.1.5).
- Number and percentage of study participants with first occurrence of ADA_b positive result (on an ordinary and cumulative basis) by visit, for any ADA_b positive and Total treatment-emergent ADA_b positive (category 7 [categories 2 and 5 combined]) results over the study duration will be presented. Box-plots of the titer by time to first ADA_b positivity will be prepared.
- The number and percentage of participants in each of the 9 ADA_b subcategories (Section 5.7.1.4.1.3) over the study duration.
- Figure of PASI90 responders (based on NRI), separated by dose group (BKZ Dose A and BKZ Dose B), at Week 16 and Week 124 as a function of ADA_b titer group (categorized as ADA_b negative, titer < 100, and titer tertiles ≥ 100), will be presented graphically. If not supported by the data, the titer tertile groupings may be reduced eg ≥ 100 - <median [of the non-missing titer values ≥ 100], and ≥ 100 median [of the non-missing titer values ≥ 100]]. This will be repeated for IGA 0/1 (based on NRI).
- The number and percentage of PASI90 responders versus time for each dose group (BKZ Dose A and BKZ Dose B) will be summarized by overall ADA_b status (Section 5.7.1.4.1.5, ADA_b negative, ADA_b positive, missing). If $\geq 95\%$ of subjects are included in the non-missing ADA_b groups, the missing group will not be displayed in the figure. The data will be presented in a tabular (based on NRI and OC) and graphical (based on NRI only) format. The analyses will be repeated for IGA0/1.
- Individual plots of bimekizumab concentrations / ADA_b titer and PASI90 response (based on NRI) will be created. All three endpoints will be plotted on the Y-axes by visit (x-axis) for all participants for the full study duration. For interim analyses, the SFU visit and OLE period

will be excluded and for the final analyses, the SFU visit and OLE period will be included. Plots should be labeled and grouped into the 7 primary subcategories (excludes category 7 and category 8).

- Spaghetti plots of ADA_b titer (y-axis) by visit (x-axis), separated by weight-categorized dose group for all ADA_b positive participants in category 2 and category 5, may be provided.

Treatment emergent adverse events will be summarized by ADA_b status using the following categories:

- AEs starting before first ADA_b positive result
- AEs starting on or after first ADA_b positive result
- AEs for participants who were always ADA_b negative

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 code to the same preferred term) emerging both prior to first ADA_b positive result and after ADA_b positive result, both events will be summarized in the table in the appropriate column.

5.7.1.4.2 Neutralizing anti-bimekizumab antibody

For confirmed ADA_b positive samples, NAb will be assessed using IL-17AA-specific and IL-17FF-specific assay methods. NAb results will be positive or negative to each specific NAb assay or both.

Any NAb results derived from samples with drug concentrations higher than the drug tolerance limits of the IL-17AA-specific and the IL-17FF-specific NAb assays (100µg/mL) will be labeled 'inconclusive'. All inconclusive results will be regarded as missing.

In addition to the ADA_b classifications, participants may also receive an overall neutralizing (NAb) classification for each NAb assay separately, inclusive of Baseline and post-Baseline results, on the NAb assay results:

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

- Positive for IL-17FF only: one or more positive samples for IL-17 FF at baseline or post-baseline. No positive samples for IL-17AA.
- Positive for both IL-17AA and IL-17FF: one or more positive samples for both IL-17AA and IL-17FF at baseline or post-baseline.
- NAb Missing: >1 relevant NAb samples are missing/inconclusive and other available NAb samples during the period of interest are negative. Study participants who are NAb missing will be further classified as follows:
 - ADA b missing/NAb missing
 - ADA b positive/NAb missing (missing or insufficient sample left for NAb testing)

5.7.1.4.2.1 Analysis

The following table and listing will be produced, but may not be produced in the Final CSR.

The listing will be sorted by weight-categorized dose group and will summarize the following information for each participant assessed for NABs:

- Visit
- Study week since first bimekizumab dose
- Sampling date and time
- Time since previous dose (weeks)
- The corresponding bimekizumab plasma concentration level at each visit (µg/mL)
- ADA b titer at each visit
- IL-17AA NAb status and corresponding IL-17AA signal/negative control result
- IL-17FF NAb status and corresponding IL-17FF signal/negative control result
- Value excluded from PK summaries (Y/N)

The summary table will display the overall NAb categories, based on data from Baseline up to Week 16, Week 20, Week 124 and SFU. The data from weight-categorized dose groups that contain a low number of participants may be combined, presenting Dose A total, Dose B total and across all participants. The table would provide the following overall summary statistics by weight-categorized dose group:

- Total number and percentage of overall ADA b positive, ADA b negative and ADA b missing participants (including the baseline value)
- Number and percentage of NAb negative participants, as defined in Section 5.7.1.4.2.
- Number and percentage of NAb positive participants, as defined in Section 5.7.1.4.2.
- Number and percentage of NAb missing participants, as defined in Section 5.7.1.4.2.

In addition, two figures (side by side) summarizing efficacy response (PASI90) versus time for each dose group (BKZ Dose A and BKZ Dose B) by NAb status (ADA b negative, NAb positive, ADA b positive / NAb negative, missing) will be created. If ≥95% of subjects are included in the non-missing groups, the missing group will not be displayed in the figure. The analyses will be

repeated for IGA0/1. The data will also be presented in a tabular format. Both NRI and OC will be presented.

The analysis of treatment emergent adverse events will be summarized by NAb status using the following categories for the All Periods (Initial Treatment Period and OLE Period) summaries:

- ADA b negative
- NAb negative
- NAb positive

5.8 Subgroup Analyses

Two subgroups will be examined for the secondary efficacy endpoints:

- Body Weight ($\geq 65\text{kg}$ and $< 65\text{kg}$)
- Sex (male and female).

The analysis of secondary efficacy endpoints (Section 5.4.1.2.1 through to Section 5.4.1.2.4) will be stratified by baseline weight category and sex. If $\geq 95\%$ of study participants fall into one level of any subgroup, then the corresponding summary for that subgroup will not be presented.

5.9 Interim Analyses

There will be no formal interim analysis in this open-label study.

All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information.

The PK interim analyses will be conducted when 25%, 50%, 75%, and 100% participants reached Week 16 with PK data available for analysis. The ADA b analyses will be conducted when all participants have completed their Baseline visit and Week 16 visits. A final analysis for PK and ADA b will be conducted at the end of the study including SFU.

The PK interim analysis will include selected efficacy endpoints for relationship between the bimekizumab plasma concentration and the efficacy.

5.10 DMC or Other Review Board

An independent DMC will review and monitor safety data from this study and advise UCB periodically. Further details are provided in a separate DMC charter and DMC SAP. The DMC analysis will be a subset of the analysis outlined in this SAP.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: Non-key Analysis Specifications

6.1.1 Baseline characteristics and demographics

Baseline and demographic variables will be summarized by dose group (Dose A, Dose B) and overall, in the RS.

6.1.1.1 Demographics

The continuous demographics variables will be summarized using descriptive statistics including

- Age (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) = weight (kg) / height (m)²

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

- EudraCT age categories:
 - 12 - <18 years
- Gender
- Racial Group
- Ethnicity
- Region
- Country
- Weight category
 - < 65 kg
 - \geq 65 kg
- Height percentiles
 - <5th
 - \geq 5th to <25th
 - \geq 25th to <50th
 - \geq 50th to <75th
 - \geq 75th to <95th
 - \geq 95
- Weight percentiles: use the same percentile as height
- BMI percentiles (refer to Section 6.3)

- <5th (underweight)
- ≥5th to < 85th (normal or healthy weight)
- ≥85th to <90th (overweight)
- ≥90th to <95th (overweight)
- ≥95th to <97th (obese)
- ≥97th (obese)

6.1.1.2 Lifestyles

Lifestyle variables including alcohol use and smoking will be summarized for the RS. The continuous variables will be summarized descriptively, and the categorical variables will be reported for their frequencies and percentages. Missing values will be reported but not imputed.

6.1.1.3 Other baseline characteristics

Baseline characteristics will be summarized by dose group (Dose A, Dose B) and overall including but not limited to:

- PSO history parameters including duration of psoriasis disease, calculated as [date of randomization – date of PSO first diagnosis] / 365.25, psoriasis present and active at screening, physician's assessment of psoriasis severity, family history of psoriasis, received any prior psoriasis therapy
- Fungal skin infections, including any fungal skin infections in the past 12 months, and any required treatment for fungal skin infections
- Uveitis, including history and duration of uveitis
- IBD, including history and diagnosis
- Psoriatic arthritis, including history and duration of disease
- PSO BSA (%)
- PASI score
- CDLQI total score
- Duration of disease (<median, ≥median)
- IGA score
- Scalp IGA score
- Scalp involvement (yes, no)

The following will be summarized in a past psoriasis treatment and biologic treatment discontinuation reason summary:

- Prior biological treatments (yes, no)
- Prior phototherapy or chemotherapy (yes, no)
- Any prior systemic therapy (yes, no)

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

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

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

6.1.2 Protocol deviations

The number and percentages of participants with important protocol deviations (including a summary of participants excluded from the PK-PPS due to important protocol deviations) will be summarized in the enrolled set by dose group and overall.

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

Important PDs and the PDs that will result in the removal of participants from the PK-PPS are specified in the Protocol Deviation Assessment Plan.

6.1.3 Medical history

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

6.1.4 Prior/concomitant/follow-up medications

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 or with a start date greater than the last dose of study medication + 28 days. Any medication that started prior to the first dose of IMP and continued after will be classified as both prior and concomitant. Such medications will therefore be counted in the tabulations for both prior and concomitant medication.

The number and percentage of participants taking concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class for each dose group and overall, in the SS. Prior medications and prior antibiotic medications will be summarized similarly.

A by-study participant listing of all concomitant medications will be provided.

Concomitant medications will also be summarized for the Initial Treatment Period, OLE Period, and the combined periods. If participants have duplicate concomitant medication entries with the same date and time, the data will be listed with a flag to identify duplicates. Tables will count duplicates once, but listings will contain all occurrences.

6.1.4.1 Vaccines

Administration of inactivated vaccines and other types of non-live or non-attenuated vaccines is permissible during the study at the discretion of the Investigator and/or following discussion with the Medical Monitor. A prior vaccine refers to a vaccine administered to a participant within the 8 weeks prior to the start date of study medication, and a concomitant vaccine refers to a vaccine

administered with at least one day in common with the study medication dosing period. The vaccine data will be listed.

6.1.5 Past treatments for PSO

Past PSO medications will be summarized by treatment type and reported for each dose group and overall, in the RS. Note that past treatments are collected independently from the prior and concomitant medication data.

6.1.6 Data derivation rules

6.1.6.1 PASI

The PASI scoring of psoriatic plaques is based on 3 criteria: redness (R), thickness (T), and scaliness (S). Severity is rated for each index (R, S, T) on a 0 to 4 scale (0 for no involvement up to 4 for very marked involvement). The body is divided into 4 areas comprising the head (h), upper extremities (u), trunk (t), and lower extremities (l). In each of these areas, the fraction of total surface area affected is graded on a 0-6 scale (0 for no involvement, up to 6 for 90% - 100% involvement).

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

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

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:

$$\text{Percent improvement from Baseline} = 100 \times \frac{\text{Baseline PASI} - \text{Post Baseline PASI}}{\text{Baseline PASI}}$$

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. If the area of affected skin and/or all severity measurements for more than 2 regions is missing, but the BSA (Body Surface Area) is reported as 0 for the study participant, then the overall PASI score will be set to 0. Otherwise, the PASI will be set to missing.

6.1.6.2 Exposure-adjusted rates

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

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

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

If a participant has multiple events, the time of exposure is calculated to the first occurrence of the AE being considered. If a participant has no events, the total time at risk is used.

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

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

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

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

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

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

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

No confidence interval will be computed for EAER.

6.1.7 AEs of special interest

6.1.7.1 Hy's Law

Potential Hy's Law cases will be summarized with the LFT lab data. The following definition will be used:

- [AST $\geq 3 \times \text{ULN}$ or ALT $\geq 3 \times \text{ULN}$] and Total Bilirubin $\geq 2 \times \text{ULN}$ in the absence of ALP (Alkaline phosphatase) $\geq 2 \times \text{ULN}$

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST (and the absence of ALP elevation) at the same visit. For example, a subject who experiences a $\geq 2 \times \text{ULN}$ elevation of bilirubin at one visit and a $\geq 3 \times \text{ULN}$ elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria. Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.

6.1.8 Other AEs

6.1.8.1 Anaphylaxis

The SMQ *Anaphylactic reaction* consists of three parts:

1. 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
 - Procedural shock
 - Shock
 - Shock symptom
 - Type I hypersensitivity
2. 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

-
- Asthma
 - Bronchial oedema
 - Bronchospasm
 - Cardio-respiratory distress
 - Chest discomfort
 - Choking
 - Choking sensation
 - Circumoral oedema
 - Cough
 - Cough variant asthma
 - Cyanosis
 - Dyspnoea
 - Hyperventilation
 - Irregular breathing
 - Laryngeal dyspnoea
 - Laryngeal oedema
 - Laryngospasm
 - Laryngotracheal oedema
 - Mouth swelling
 - Nasal obstruction
 - Oedema mouth
 - Oropharyngeal oedema
 - Oropharyngeal spasm
 - Oropharyngeal swelling
 - Pharyngeal oedema
 - Pharyngeal swelling
 - Respiratory arrest
 - Respiratory distress
 - Respiratory failure
 - Reversible airways obstruction
 - Sensation of foreign body

-
- Sneezing
 - Stridor
 - Swollen tongue
 - Tachypnoea
 - Throat tightness
 - Tongue oedema
 - Tracheal obstruction
 - Tracheal oedema
 - Upper airway obstruction
 - Wheezing
 - Category C (Angioedema/Urticaria/Pruritus/Flush terms)
 - Acquired C1 inhibitor deficiency
 - Allergic oedema
 - Angioedema
 - Circumoral swelling
 - Erythema
 - Eye oedema
 - Eye pruritus
 - Eye swelling
 - Eyelid oedema
 - Face oedema
 - Flushing
 - Hereditary angioedema with C1 esterase inhibitor deficiency
 - Injection site urticaria
 - Lip oedema
 - Lip swelling
 - Nodular rash
 - Ocular hyperaemia
 - Oedema
 - Oedema blister
 - Periorbital oedema

-
- Periorbital swelling
 - Pruritus
 - Pruritus allergic
 - Rash
 - Rash erythematous
 - Rash pruritic
 - Skin swelling
 - Swelling
 - Swelling face
 - Swelling of eyelid
 - Urticaria
 - Urticaria papular
 - 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
 - Hypotensive crisis
 - Post procedural hypotension
 - 3. 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 must have been reported, both events must have occurred within one day of each other (as anaphylaxis is an acute event, imputed dates should not be used in the algorithmic approach):
 - A narrow term or a term from Category A
 - A term from Category B – (Upper Airway/Respiratory) AND a term from Category C – (Angioedema/Urticaria/Pruritus/Flush)

- A term from Category D – (Cardiovascular/Hypotension) AND [a term from Category B – (Upper Airway/Respiratory) OR a term from Category C – (Angioedema/Urticaria/Pruritus/Flush)]

6.1.9 Potentially clinically significant criteria for safety endpoints

6.1.9.1 Marked abnormality criteria for laboratory data

Markedly abnormal values are defined as those with a severity of Grade 3 and above based on the common terminology criteria for adverse events (CTCAE). Assessed labs and definitions of markedly abnormal values using the Grade 3 cut points are given below.

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

The following tables lists lab assessments and abnormal value cutoffs for this study.

Table 6–1: Laboratory Assessments

Laboratory assessments	Parameters			
Hematology	Platelet Count	<u>RBC Indices:</u> MCV MCH %Reticulocytes		<u>WBC Count with Differential:</u> Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count			
	Hemoglobin			
	Hematocrit			
Clinical Chemistry ^a	Blood Urea Nitrogen	Potassium	AST/serum glutamic-oxaloacetic transaminase	Total and direct bilirubin
	Creatinine	Sodium	ALT/serum glutamic-pyruvic transaminase	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	<ul style="list-style-type: none"> Specific gravity pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase by dipstick Microscopic examination (if blood or protein is abnormal) 			
Other Screening Tests	<ul style="list-style-type: none"> Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) by central laboratory at Screening and urine pregnancy test locally for all assessments after Screening (or at home during the OLE Period) IGRA testing Serology (HBsAg and hepatitis C virus antibody) Plasma sample for HIV antibody assessment The results of each test must be entered into the eCRF.			

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report Form; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell count; ULN=upper limit of normal; WBC=white blood cell count

^a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in protocol. All events of ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$ ($>35\%$ direct bilirubin) or ALT $\geq 3 \times \text{ULN}$ and INR >1.5 , if INR measured, may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

Table 6–2: Definitions of Markedly Abnormal Haematology Values

Parameter name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Hemoglobin	g/dL	<8.0 >4.0 above ULN or Baseline if Baseline > ULN	g/L	<80 >40 above ULN or Baseline if Baseline > 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

AH=abnormal high, AL=abnormal low, dL=deciliter, g=gram, L=liter, ULN=upper limit of normal, WBC=white blood cells. ULN will be sourced from lab.

Table 6–3: Definitions of Markedly Abnormal Biochemistry Values

Parameter name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Creatinine	mg/dL	>3.0 x ULN or Baseline if Baseline > ULN	µmol/L	>3.0 x ULN or Baseline if Baseline > 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
Magnesium	mg/dL	>3.0 <0.9	mmol/L	>1.23 <0.4	AH AL
Potassium	mmol/L	>6.0 <3.0	mmol/L	>6.0 <3.0	AH AL
Sodium	mmol/L	>155 <130	mmol/L	>155 <130	AH AL

AH=abnormal high, AL=abnormal low, dL=deciliter, L= liter, LLN=lower limit of normal, mg=milligram, mmol=millimole, ULN=upper limit of normal. ULN/LLN will be sourced from lab. Participants who meet the decreased potassium criterion of 3.0-<LLN, which is specified as the decreased potassium lab criterion for both CTCAE Grade 1 and Grade 2, will be counted as Grade 2.

Table 6–4: Definitions of Markedly Abnormal Liver Function Tests

Parameter name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
ALP	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH
ALT	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH
AST	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH
Total Bilirubin	mg/dL	>3.0 x ULN	μmol/L	>3.0 x ULN	AH
GGT	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH

AH=abnormal high, AL=abnormal low, ALT=alanine aminotransferase, ALP = alkaline phosphatase, AST=aspartate aminotransferase, dL=deciliter, GGT=gamma-glutamyl transferase, L=liter, mg=milligram; μmol=micromole, ULN=upper limit of normal. ULN will be sourced from lab.

6.1.9.2 Marked abnormality criteria for vital signs

The marked abnormality criteria for blood pressure are provided in the table below:

Table 6–5: Definitions of Markedly Abnormal Vital Signs

Parameter (unit)	Age group	Markedly Abnormal Low	Markedly Abnormal High
Systolic blood pressure (mmHg)	≤17	<90 or a decrease from Baseline of ≥30%	>5 above the 99 th percentile
	>17	<90 or a decrease from Baseline of ≥30%	>160 or an increase from Baseline of ≥30%
Diastolic blood pressure (mmHg)	≤17	<50 or decrease of ≥20% from Baseline	>5 above the 99 th percentile
	>17	<50 or decrease of ≥20% from Baseline	>105

The values of the 99th percentile of systolic and diastolic blood pressure values, by age, sex and height percentile are provided in Section 6.3.3 for participants aged 17 or less.

6.1.10 Compliance

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

Treatment compliance will be calculated as:

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

For participant who permanently discontinues IMP, the number of expected injections is based on the time of early discontinuation relative to the dosing visits.

Compliance will be summarized descriptively by weight-categorized dose group and overall, for each study periods separately and combined. The number and percentage of participants meeting certain compliance thresholds (<75% and ≥75%) will also be reported.

6.2 Appendix 2: Changes to Protocol-Planned Analyses

The following have been added to the SAP, but are not present in the Protocol:

- The COVID-19 impact analysis (Section 5.2.1) has been added.
- The definition of analysis sets has been changed (Section 4.1):
 - Immunogenicity analyses will be based on SS or OLS, and participants will be summarized as randomized.
 - Pharmacokinetic variables will be analyzed for all participants in the PK-PPS and will be summarized as randomized.
 - OLS analyses will be based on the SS and as treated.
 - For summaries using both PK-PPS and OLS, participants will be summarized as randomized.
- Multiple imputation is no longer being applied to missing continuous data. Instead, the LOCF method will be used to impute the missing value (Section 5.1.1.7.3).
- Shift tables for growth assessments for height and weight (Section 5.6.3.6.2) have been added.

6.3 Appendix 3: Percentiles Derivation and Growth Charts

This appendix describes the approach used to derive age and sex-specific percentiles for BMI, weight, and height from LMS parameters available in published growth charts. The LMS parameters are the smoothed skew (L), the median (M), and the coefficient of variation (S).

Additionally, this appendix provides the 99th percentile values for systolic and diastolic blood pressure by age, sex and height percentile. These values will be used to identify markedly abnormal values for participants aged ≤17 years.

6.3.1 Derivation of percentiles from LMS parameters

The L, M, and S parameters from growth charts for BMI, height, and weight, by age and sex, are provided in Section 6.3.2.

Deriving the percentile value of a given measurement, for a given participant is done in 3 steps (Cole, 1990):

1. From the growth chart of the measurement of interest (BMI, height, or weight), identify the L, M, and S parameters corresponding to the participant sex and age (at the time of the measurement).
2. Calculate the z-score for the measurement using the following formula:

$$z = \frac{\left[\left(\frac{X}{M}\right)^L - 1\right]}{L \times S}$$

Where X is the measurement value and L, M, and S are the parameters identified in step 1.

3. The calculated z-score is then converted to the percentile value using the cumulative distribution function from the standard normal distribution.

6.3.2 Growth charts

6.3.2.1 Growth chart for BMI by age and sex

The BMI growth chart (CDC, 2000) provides the L, M, and S parameters by age and sex, where the age is provided in months at the half-month point. For example, 78.5 months represents the interval [78.0, 79).

In this study, age is recorded in years at each visit where the weight and height are recorded. In the BMI growth chart, the L, M, and S parameters for each age in years were mapped to the chart values corresponding to the half-year time point for that year, with respect to sex. For example, LMS values for a 12 year-old correspond to the half-year timepoint of $12.5 \times 12 = 150$ months, that is the interval [150.0, 151.0) represented by 150.5 months in the chart.

Table 6–6: Growth Chart for BMI¹ (kg/m²) by Age and Sex

Sex	Age (years)	Month in the chart	L	M	S
Male	12	150.5	-2.385858029	18.1387275	0.132990575
Male	13	162.5	-2.277017201	18.81201584	0.134879611
Male	14	174.5	-2.179425674	19.50672885	0.135308594
Male	15	186.5	-2.085574403	20.20858236	0.134718085
Male	16	198.5	-1.993150137	20.90294449	0.1336202
Male	17	210.5	-1.908831065	21.57417053	0.132584784
Female	12	150.5	-1.959520079	18.42002284	0.149783482
Female	13	162.5	-1.9610997	19.04811118	0.151176355
Female	14	174.5	-2.002014224	19.64746266	0.151009595
Female	15	186.5	-2.074459502	20.19980767	0.14984254
Female	16	198.5	-2.167044578	20.6891237	0.148349348
Female	17	210.5	-2.26238209	21.10163241	0.147323144

BMI=body mass index

¹ Centers for Disease Control and Prevention (2000). https://www.cdc.gov/growthcharts/percentile_data_files.htm

6.3.2.2 Growth chart for height by age and sex

Similar to the BMI growth chart, the height growth chart (CDC, 2009) provides the L, M, and S parameters by age and sex, where the age is provided in months at the half-month point.

In the Growth Chart for Height, the L, M, and S parameters for each age in years were mapped to the chart values corresponding to the half-year time point for that year, with respect to sex.

Table 6–7: Growth Chart for Height¹ (cm) by Age and Sex

Sex	Age (years)	Month in the chart	L	M	S
Male	12	150.5	0.531951655	152.6623878	0.050273285
Male	13	162.5	1.232768816	160.3493168	0.049926861
Male	14	174.5	2.016781776	167.4641466	0.047506783
Male	15	186.5	2.2253265	172.1562865	0.044362674
Male	16	198.5	1.927320937	174.6309856	0.042107465
Male	17	210.5	1.543252982	175.8359757	0.040938463
Female	12	150.5	1.358162799	154.755501	0.046198356
Female	13	162.5	1.076970655	159.2074654	0.042114211
Female	14	174.5	0.902452436	161.3267744	0.040409354
Female	15	186.5	0.913397733	162.2908474	0.039913066
Female	16	198.5	0.971038162	162.7718741	0.03976685
Female	17	210.5	1.025142554	163.0401953	0.039706971

¹ Centers for Disease Control and Prevention (2009). https://www.cdc.gov/growthcharts/percentile_data_files.htm

6.3.2.3 Growth chart for weight by age and sex

In the Growth Chart for Weight, the L, M, and S parameters for each age in years were mapped to the chart values corresponding to the half-year time point for that year, with respect to sex.

Table 6–8: Growth Chart for Weight¹ (kg) by Age and Sex

Sex	Age (years)	Month in the chart	L	M	S
Male	12	150.5	-0.76027	43.18828	0.197464
Male	13	162.5	-0.65414	48.51113	0.194344
Male	14	174.5	-0.63492	53.91261	0.186442
Male	15	186.5	-0.72322	58.90293	0.176887
Male	16	198.5	-0.89044	63.03228	0.168655
Male	17	210.5	-1.0354	66.10749	0.163439
Female	12	150.5	-0.85031	43.96612	0.200419
Female	13	162.5	-1.00305	47.83661	0.19333
Female	14	174.5	-1.23801	50.92541	0.183328
Female	15	186.5	-1.51816	53.13327	0.172761
Female	16	198.5	-1.76224	54.61224	0.164368

Female	17	210.5	-1.86898	55.70624	0.160423
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¹ Centers for Disease Control and Prevention (2009). https://www.cdc.gov/growthcharts/percentile_data_files.htm

6.3.3 Blood pressure 99th percentile values by age, sex and height percentile

The Blood Pressure 99th Percentile Values table presents the values of the 99th percentile of systolic and diastolic blood pressure, by sex, age, and height percentile, for participants with age ≤17 years. Height percentile is calculated as described in Section 6.3.1 and should be rounded up or down to the nearest percentile in Table 6–9.

Table 6–9: Blood Pressure 99th Percentile Values¹ (mmHg) by Age, Sex and Height Percentile.

Sex	Age (years)	Height percentile	99 th percentile Systolic BP (mmHg)	99 th percentile Diastolic BP (mmHg)
Male	12	5	126	86
Male	12	10	127	87
Male	12	25	129	88
Male	12	50	131	89
Male	12	75	133	90
Male	12	90	134	90
Male	12	95	135	91
Male	13	5	128	87
Male	13	10	130	87
Male	13	25	131	88
Male	13	50	133	89
Male	13	75	135	90
Male	13	90	136	91
Male	13	95	137	91
Male	14	5	131	87
Male	14	10	132	88
Male	14	25	134	89
Male	14	50	136	90
Male	14	75	138	91
Male	14	90	139	92
Male	14	95	140	92
Male	15	5	134	88

Table 6–9: Blood Pressure 99th Percentile Values¹ (mmHg) by Age, Sex and Height Percentile.

Sex	Age (years)	Height percentile	99 th percentile Systolic BP (mmHg)	99 th percentile Diastolic BP (mmHg)
Male	15	10	135	89
Male	15	25	136	90
Male	15	50	138	91
Male	15	75	140	92
Male	15	90	142	93
Male	15	95	142	93
Male	16	5	136	90
Male	16	10	137	90
Male	16	25	139	91
Male	16	50	141	92
Male	16	75	143	93
Male	16	90	144	94
Male	16	95	145	94
Male	17	5	139	92
Male	17	10	140	93
Male	17	25	141	93
Male	17	50	143	94
Male	17	75	145	95
Male	17	90	146	96
Male	17	95	147	97
Female	12	5	127	86
Female	12	10	127	86
Female	12	25	128	87
Female	12	50	130	88
Female	12	75	131	88
Female	12	90	132	89
Female	12	95	133	90
Female	13	5	128	87
Female	13	10	129	87

Table 6–9: Blood Pressure 99th Percentile Values¹ (mmHg) by Age, Sex and Height Percentile.

Sex	Age (years)	Height percentile	99 th percentile Systolic BP (mmHg)	99 th percentile Diastolic BP (mmHg)
Female	13	25	130	88
Female	13	50	132	89
Female	13	75	133	89
Female	13	90	134	90
Female	13	95	135	91
Female	14	5	130	88
Female	14	10	131	88
Female	14	25	132	89
Female	14	50	133	90
Female	14	75	135	90
Female	14	90	136	91
Female	14	95	136	92
Female	15	5	131	89
Female	15	10	132	89
Female	15	25	133	90
Female	15	50	134	91
Female	15	75	136	91
Female	15	90	137	92
Female	15	95	138	93
Female	16	5	132	90
Female	16	10	133	90
Female	16	25	134	90
Female	16	50	135	91
Female	16	75	137	92
Female	16	90	138	93
Female	16	95	139	93
Female	17	5	133	90
Female	17	10	133	90
Female	17	25	134	91

Table 6–9: Blood Pressure 99th Percentile Values¹ (mmHg) by Age, Sex and Height Percentile.

Sex	Age (years)	Height percentile	99 th percentile Systolic BP (mmHg)	99 th percentile Diastolic BP (mmHg)
Female	17	50	136	91
Female	17	75	137	92
Female	17	90	138	93
Female	17	95	139	93

¹ US Department of Health and Human Services. “Diagnosis, evaluation, and treatment of high blood pressure in children and adolescents.” (2005).

6.4 Appendix 4: Details on amendments to the statistical analysis plan

6.4.1 Amendment 2

This statistical analysis plan has been amended to remove the COVID-19 TEAE and COVID-19 efficacy analyses, correct the PK and immunogenicity analyses, and clarify the missing data handling methods. In addition, other clarifications such as sections for safety topics of interest and safety topics closely monitored, and generic changes (eg. formatting or typos) have been incorporated.

Section # and Name	Description of Change	Brief Rationale
Global	Updated links to sections	Clarification
	Removed all COVID-19 specific analyses except “A summary of study visits impacted by the COVID-19 pandemic, and associated listing”.	Due to a sparsity of visits impacted with COVID-19, these analyses were removed.
	Correction of spelling, grammar, minor editorial, and typographical errors	Correction
1.2 Study Design	Removed “If Dose A is administered by a caregiver or a participant at home, the visit will be conducted via a telehealth system.”	Clarification; telehealth system will no longer be used.
4.1 Analysis Sets	Added that “Immunogenicity analyses will be based on SS or OLS, and participants will be summarized as randomized.”	Clarification
	Removed “Immunogenicity analyses will be based on the SS and as treated.”	Correction
	Added that Pharmacokinetic variables will be summarized as randomized.	Clarification
	Added that: <ul style="list-style-type: none"> • OLS analyses will be based on the SS and as treated. • For summaries using both PK-PPS and OLS, participants will be summarized as randomized. 	Clarification
	Removed COVID-19 Free Set.	Correction
5.1 General Considerations	Clarified that for efficacy, SFU is excluded from by-visit tables but included in listings. Clarified that for safety, SFU is included in by-visit tables for the OLE and All Periods summaries only (not ITP).	Clarification
	From second bulleted paragraph, clarified that if at least one dose group has a value missing, missing categories will be created in the summaries of demographics and baseline characteristics.	Clarification

	From fourth bulleted paragraph, updated link to Section for imputing partial AE dates.	Clarification
	From fifth bulleted paragraph, clarified CDLQI endpoint as “Change from Baseline in CDLQI response” and fixed a typo in CIs.	Clarification
	Added rounding of AVAL, CHG and PCHG to the 12 th decimal place in order to avoid inaccurate floating-point representation of numeric values. Added that 95% CIs cannot be below 0 or exceed 100.	Addition
5.1.1.1.3 Study Periods	Clarified that any assessment or measurement made prior to or on the Week 20 visit will be attributed to ITP regardless of time of collection, and adverse events related to dosing and IMP administration will be attributed to the OLE period.	Clarification
5.1.1.3 Treatment assignment and treatment groups (and all applicable sections thereafter)	Clarified that dose groups refer to Dose A and Dose B, whereas weight-categorized dose groups refer to dose group specific breakdowns: <ul style="list-style-type: none"> • Dose A (320mg Q4W), Dose A (160mg Q4W), Dose A (all) • Dose B (64mg Q4W), Dose B (32mg Q4W), Dose B (all) 	Clarification
	Clarified that for PK and immunogenicity analyses, all participants will be summarized according to Baseline weight-categorized dose group regardless of dose switching.	
5.1.1.7.4 Safety missing data	Separated this section’s language from Section 5.1.1.7.5.	Clarification
	Clarified that a complete date must be established for TEAEs for safety endpoints, and algorithms for start and stop date imputation have been described in Section 5.1.1.7.5.	Clarification

	Added that if the intensity of an adverse event is unknown, it will be considered as severe. If the relationship to study drug is missing, it is considered as related.	Addition
	Clarified that if the seriousness of an AE is unknown, no imputation will be made.	Clarification
	Clarified that vital signs, physical examinations, growth assessments, laboratory analyses will not be imputed and will be based on descriptive statistics only (observed case).	Clarification
5.1.1.7.5 Missing dates and times	Clarified language around assigning AEs and concomitant medications to ITP, OLE or both.	Correction
5.4.1.1.1 PASI response 5.4.1.1.2 IGA response 5.5.4 Scalp IGA response over time	Removed “electronically” from Investigator’s assessment.	Clarification
5.4.1.3 Sensitivity Analysis	Removed separate analysis on missingness of secondary endpoint data.	Correction
	Removed separate analysis on endpoints collected by different modalities, including data collected remotely vs. in-person.	
5.5.5 CDLQI (total score) change from baseline over time	Removed compliance analyses of CDLQI and by-visit analysis of CDLQI total score.	Correction
5.5.6 CDLQI 0/1 response over time	Replaced observed case with OC. Removed shift tables.	Correction
5.5.7 Efficacy and PK relationship	Removed specific language around efficacy-PK relationship analyses, and replaced with “An analysis, based on the Initial Treatment Period, will be conducted to investigate the relationship between plasma bimekizumab exposure and the efficacy variables (PASI response, PASI75, PASI90, IGA 0/1). This analysis will be described in a separate analysis plan and reported separately.”	Correction; specific analyses for efficacy-PK relationship will be reported in a separate analysis plan and are not appropriate in this SAP.

5.6 Safety Analysis	Clarified that SFU is not included in by-visit safety tables for the ITP alone, because few participants will not enter the OLE.	Clarification
5.6.1.1 Initial Treatment Period	Simplified algorithms to derive duration of exposure for ITP.	Clarification
5.6.1.2 Open Label Extension (OLE) Period	Removed the language around causing issues for attribution of AEs to doses occurring in the gap.	Correction; exposure should not be used for attributing AEs to periods. Time at risk is the relevant calculation.
5.6.2 Adverse Events	Clarified that on the AE on the date of a dose switch or on the Week 20 dose date, the AE will be attributed to the original dose/period (the “preswitch” dose/period).	Clarification
	Clarified that both Safety Topics of Interest and Safety Topics Closely Monitored will be given special attention in analysis.	Clarification
5.6.2.1 General data considerations for AEs	In the fourth paragraph, corrected AEs to be listed-only when occurring >140 days after the last dose (not 141).	Correction
	In the last paragraph, clarified that EAIR should be calculated to the first occurrence of the AE within ITP, and similarly for OLE. For combined tables, EAIR should be to the first occurrence regardless of period. EAER should include all repeat occurrences within the period of interest.	Clarification
5.6.2. Adverse events data considerations	Clarified that AE tables will summarize weight-categorized Dose A groups and All Participants on one page, and then the subsequent page will contain weight-categorized Dose B groups and All Participants.	Clarification

	<p>Summary by system organ class (SOC), HLT, and preferred term (PT):</p> <ul style="list-style-type: none"> Removed nonserious TEAEs Clarified that a combined table of safety topics of interest and safety topics closely monitored will be created. <p>Summary by relationship, SOC, HLT, and PT:</p> <ul style="list-style-type: none"> Removed serious TEAEs Removed nonserious TEAEs <p>Removed the following from ordered and subset of AE summaries:</p> <ul style="list-style-type: none"> Any TEAE by SOC and PT for above reporting threshold of 5% Related TEAEs by SOC and PT above reporting threshold of 5% TEAEs Identified as Safety Topics of Interest by SOC and PT <p>Antibody Data:</p> <ul style="list-style-type: none"> Added Incidence of TEAEs per 100 participant years by SOC, HLT, and PT and by time of onset relative to NAB status. Note: Only presented for combined Initial Treatment Period and OLE Period. <p>The following AEs will be listed only, and not summarized in the overall AE table:</p> <ul style="list-style-type: none"> Any TEAE with onset at Day 1 Any TEAE related to TB including latent TB and IGRA tests <p>The following Plain Language Summaries have been added:</p> <ul style="list-style-type: none"> Incidence of Drug-related TEAEs – Overview 	<p>Correction; changed safety outputs to be in-line with study objectives, added immunogenicity relevant outputs, and added Plain Language Summaries required by Disclosures.</p>
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	<ul style="list-style-type: none"> Incidence of Drug-related TEAEs by Preferred Term Incidence of Serious Drug-related TEAEs by Preferred Term 	
5.6.2.3 Safety topics of interest (and all applicable sub-sections)	Clarified that TEAEs of safety topics of interest and safety topics closely monitored will be presented in a combined table for ITP, OLE, and All Periods.	Clarification
5.6.2.3.1 Infections (serious, opportunistic, fungal and TB)	Clarified that opportunistic infections will be identified using the SMQ “Opportunistic Infections (SMQ)” and that all TEAEs which code to a PT included in the Scope = Narrow search will be included.	Clarification
	Added a by-participant listing of “All Treatment-Emergent Adverse Events Related to TB including latent TB and IGRA tests”.	Addition
5.6.2.3.2 IBD	<p>Clarified that the combined table will present definite IBD (event type codes 3, 6, 9, 13, and 16) and probable IBD (event type codes 2, 5, 8, 12, and 15).</p> <p>In the second paragraph after the bulleted list, clarified that incidence and event rate of adjudicated gastrointestinal events will be presented.</p>	Clarification
5.6.2.3.3 Injection site reactions	Moved the bulleted list of neutropenia events to the standalone Section 5.6.2.4.6.	Clarification
5.6.2.4 Safety topics closely monitored	Clarified that TEAEs of safety topics of interest and safety topics closely monitored will be presented in a combined table for ITP, OLE, and All Periods.	Clarification
	Added that, in this combined table, participant incidence, number of events, and exposure adjusted rates (incidence and event rate per 100 participant years) will be reported by SOC, HLT, and PT.	Addition

5.6.2.4.1 Hypersensitivity (including anaphylaxis)	Clarified that the combined table will include acute anaphylactic events (reported on the same day as when an injection was administered or 1 day after).	Clarification
	Removed AE glossary table, and any mention of standalone tables for hypersensitivity.	Correction; glossary was removed for Hypersensitivity due to sparsity of events.
5.6.2.4.2 Suicidal Ideation and Behaviour (SIB)	Clarified in the second paragraph that the combined table of safety topics of interest and safety topics closely monitored will include only the events adjudicated as suicidal by the committee.	Clarification
	Clarified that a stand-alone SIB table will present the incidence and event rate of adjudicated neuropsychiatric events by type.	
5.6.2.4.3 Cardiovascular events	Removed “potential” from potential cardiovascular events. Revised this section to correctly capture SMOs for cardiovascular events.	Correction; in line with updated algorithms .
5.6.2.4.5 Malignancies	Revised this section to use the correct strategy for capturing malignancies. The first incidence row will summarize “Any Malignancy” and the second row will summarize “Any Malignancy excluding melanomic skin cancers HLT”.	Correction; in line with updated algorithms .
5.6.2.4.6 Neutropenia	Created this section by moving the bulleted list of neutropenia events from Section 5.6.2.3.3 to this section.	Addition
5.6.3.1.1 Laboratory values over time	Corrected the criteria for potential drug induced liver injury (PDILI) summaries to use “>=” instead of “>” for ALT, AST, and Total Bilirubin.	Correction
5.6.3.3 Columbia suicide severity rating scale (C-SSRS)	Added a listing of all participants reporting at least 1 suicidal ideation or behavior.	Addition
5.6.3.6.3 Assessment and management of TB and TB risk factors	Added a listing of “All TEAEs related to TB including latent TB and IGRA tests”, with a relevant link to Section 5.6.2.3.1.	Addition

5.7.1.1 Pharmacokinetics	<p>In the first paragraph, added language that summaries will be created for ITP using PK-PPS and All Periods using OLS and PK-PPS combined.</p> <p>In the second paragraph, added that a summary of bimekizumab plasma concentration over time will be reproduced to 1 decimal place for the Plain Language Summaries. Also added that that bimekizumab plasma concentration over time summaries will be repeated for anti-bimekizumab antibody status and by overall NAb status.</p> <p>In the fourth paragraph, clarified that both by-visit summaries and figures of plasma concentrations will exclude data points with PDs expected to impact drug exposure.</p> <p>In the bulleted list, out of window rules have been added to exclude pharmacokinetic samples based on their relative time to the current or previous dose.</p>	Addition and clarification
5.7.1.4 Immunological (Immunogenicity) Analysis	Added that Immunogenicity variables are the anti-bimekizumab antibody status, anti-bimekizumab antibody titer and neutralizing anti-bimekizumab antibody status derived from anti-drug antibody assays.	Addition
	Added that the samples will be titrated, and the ADA _b titer (reciprocal dilution factor, including the Minimum Required Dilution) will be reported.	
	Removed the definition of neutralizing assays.	Correction
	Added that the summary tables will be created for ITP using SS, and the All Periods using OLS.	Addition
5.7.1.4.1.1 ADA _b sample status	In the first bullet, added that ADA _b status can be confirmed regardless of availability of a titer value.	Addition

	In the second bullet, clarified that an ADAb status of negative can be confirmed where the bimekizumab concentration is less than or equal to the drug tolerance limit (200 µg/mL) of the validated ADAb assay.	Clarification
	Replaced ADAb level with “sample”. Removed language around anomalous values being excluded from summaries and being flagged by a pharmacokinetic expert.	Correction; values will be excluded as per PK-PPS.
5.7.1.4.1.2 Overall ADAb status	Clarified that overall ADAb status must also be summarized by Total for Dose A, Total for Dose B, and All Participants in addition to the weight-categorized dose groups.	Clarification
	Added to the bulleted list of ADAb status: <ul style="list-style-type: none"> Overall ADAb status to Week 16 (SS) should be summarized by including and excluding baseline. Overall ADAb status to Week 20 (SS) should exclude baseline, and summarized by including and excluding SFU. Overall ADAb status to Week 124 (OLS) should exclude baseline and SFU. Overall ADAb status to SFU (OLS) should include all visits up (including and excluding Baseline) to SFU.	Addition; ADAb status summaries must be created for both the ITP (Week 16, Week 20) and OLS (Week 124).
5.7.1.4.1.3 ADAb Subcategories	Removed “pretreatment” from Category 1, 2, 5, 6, 8, 9.	Correction
	Clarified that categories will be derived for ITP (without OLE or SFU data), and for All Periods (with ITP, OLE, and SFU data).	Clarification

	<p>Added the following categories:</p> <ul style="list-style-type: none"> • Total treatment-emergent (category 7 [categories 2 and 5 combined]): Includes study participants who are preADAb negative – treatment emergent ADAb positive (category 2) and preADAb positive – treatment boosted ADAb positive (category 5). • Total prevalence of preADAb positivity (category 8 [categories 3, 4, 5, and 6 combined]): Study participants that are tested ADAb positive at Baseline. • Missing (category 9): Includes participants who are antibody negative at Baseline, and have more than 1 post-treatment scheduled assessments reported as missing/inconclusive, while other samples are ADAb negative. Note this is also applicable to participants who have a missing Baseline sample, at least one missing/inconclusive postbaseline sample and have no ADAb positive samples. 	<p>Addition; ADAb categories 7, 8 and 9 have to be summarized.</p>
5.7.1.4.1.4 Cumulative ADAb status groups for PK summaries	Clarified the derivation of ADAb status by period and up to the timepoint of interest.	Clarification
5.7.1.4.1.5 ADAb status groups for Efficacy Endpoint Summaries	Clarified that ADAb positive must exclude Baseline only (not SFU).	Clarification
	Clarified that ADAb negative can contain 1 post-baseline positive sample given all others are ADAb negative or missing/inconclusive.	Clarification
	Added that ADAb status for efficacy subgroups will be derived at Week 16 (excluding SFU) for the Initial	Addition; ADAb status for efficacy summaries must be created for both

	Treatment Period and Week 124 (including SFU) for the combined Initial Treatment and OLE Periods (OLS).	the ITP (Week 16) and OLS (Week 124).
5.7.1.4.1.6 Analysis	Added that analyses must be run on OLS, in addition to SS.	Addition
	<p>Clarified language around immunogenicity analyses.</p> <p>In the first bullet, clarified that summaries of ADA_b status by periods of interest will be presented, along with the overall ADA_b status for efficacy endpoint summaries.</p> <p>In the second bullet, clarified that the number and percentage of first ADA_b positivity (Category 7) participants will be summarized. Box plots of the titer will also be presented for time to first ADA_b positivity.</p>	Clarification
	The individual participant level ADA _b standalone listing was removed.	Correction; ADA _b values are presented in the PK listings, therefore standalone ADA _b listing was removed.
	<p>In the fourth bullet, clarified that PASI90 and IGA 0/1 responders (NRI) will be summarized by ADA_b titer (negative, titer <100 and titer tertiles > 100) and by dose group at Week 16 and Week 124. PASI75 and PASI100 will not be summarized.</p> <p>In the fifth bullet, clarified that the number and percentage of PASI90 and IGA 0/1 responders will be summarized by overall ADA_b status. The data will be summarized graphically (NRI) and in a tabular format (NRI and OC). PASI75 and PASI100 will not be summarized.</p>	Clarification

	<p>In the sixth bullet, clarified that individual plots of BKZ concentration / ADAb titer will be based on PASI90 and IGA 0/1 (NRI). Plots will be grouped in the main ADAb categories, excluding category 7 and 8.</p> <p>In the seventh bullet, clarified that the spaghetti plots will be for all ADAb positive participants (category 2 and 5).</p> <p>Clarified the time at risk derivation for the TEAE tables by ADAb status, and the summarization of TEAEs prior to and after ADAb positivity.</p>	
5.7.1.4.2 Neutralizing anti-bimekizumab antibody	Clarified that NAb will be assessed using IL-17AA-specific and IL-17FF-specific assay methods.	Clarification
	Added that any NAb results derived from samples with drug concentrations higher than the drug tolerance limits of the IL-17AA-specific and the IL-17FF-specific NAb assays (100µg/mL) will be labeled 'inconclusive'. All inconclusive results will be regarded as missing.	Addition
	Revised the NAb negative definition to be "NAb Missing: >1 relevant NAb samples are missing/inconclusive and other available NAb samples during the period of interest are negative. Study participants who are Nab missing will be further classified as either ADAb missing/NAb missing or ADAb positive/NAb missing (missing or insufficient sample left for NAb testing)."	Correction
5.7.1.4.2.1 Analysis	Created a separate header for NAb analysis.	Addition

	<p>Simplified language around NAb outputs being created for the Final CSR.</p> <p>Aligned columns presented in NAb listing to be in-line with BKZ program.</p>	Clarification
	<p>Added that the table must also present “Total number and percentage of overall ADAb positive, ADAb negative and ADAb missing participants (including the baseline value)”.</p>	Addition
5.8 Subgroups	<p>Added that “If $\geq 95\%$ of study participants fall into one level of any subgroup, then the corresponding summary for that subgroup will not be presented.”</p>	Addition
6.1.1.1 Demographics	<p>Moved region and country to demographics table from 6.1.1.3.</p>	Clarification
	<p>Removed all age categories except EUDRACT 12-18 years.</p>	Correction; the study only enrolled participants from 12-18 years.
6.1.1.3 Other baseline characteristics	<p>Added the following other baseline characteristics for summaries:</p> <ul style="list-style-type: none"> • PSO history parameters including duration of psoriasis disease, calculated as [date of randomization – date of PSO first diagnosis] / 365.25, psoriasis present and active at screening, physician’s assessment of psoriasis severity, family history of psoriasis, received any prior psoriasis therapy. • Fungal skin infections, including any fungal skin infections in the past 12 months, and any required treatment for fungal skin infections 	Addition

	<ul style="list-style-type: none"> • Uveitis, including history and duration of uveitis • IBD, including history and diagnosis • Psoriatic arthritis, including history and duration of disease • Scalp IGA score 	
	Clarified that the same duration of psoriasis disease algorithm will be applied to duration of uveitis, duration of IBD, and duration of psoriatic arthritis.	Clarification
	<p>Clarified that the following will be summarized in a past psoriasis treatment and biologic treatment discontinuation reason summary:</p> <ul style="list-style-type: none"> • Prior biological treatments (yes, no) • Prior phototherapy or chemotherapy (yes, no) • Any prior systemic therapy (yes, no) 	Clarification
6.1.4 Prior/concomitant/follow-up medications	Clarified that tables will count duplicates once, but listings will contain all occurrences.	Clarification
6.1.6.1 PASI	Revised derivation to set overall PASI score to 0 when BSA is 0 and the participant is missing area and/or severity measurements for more than 2 regions.	Addition
6.1.6.2 Exposure-adjusted rates	Corrected the formula for LCL and UCL.	Correction; formula was incorrect.
6.1.7.1 Hy's Law	Added the definition for Hy's Law.	Addition
6.1.8.1 Anaphylaxis	Clarified that imputed dates should not be used in the algorithmic approach for anaphylaxis.	Clarification

6.4.2 Amendment 1

Rationale for the amendment

This statistical analysis plan has been amended to modify the endpoints related to vital signs, physical examinations, laboratory analyses, and growth assessments to align with the agreed EU Paediatric Investigation implemented in the protocol amendment 2 dated 15 Mar 2021. In addition, other clarifications, updates to secondary and other endpoints analysis, and specific changes (eg. formats or typos) have been incorporated.

Modifications and changes

Change #1

List of Abbreviations

Added NAb and updated ALT/AST to align with protocol.

Original text:

ALT	serum glutamic-pyruvic transaminase
AST	serum glutamic-oxaloacetic transaminase

Has been changed to:

ALT	alanine aminotransferase
AST	aspartate aminotransferase
NAb	neutralizing antibodies

Change #2

1.1 Synopsis and 3 Objectives and Endpoints

Modified endpoints for vital signs, physical examinations, laboratory analyses, and growth assessments to clarify that these safety endpoints cover the whole duration of the study.

Original text:

- Change from Baseline in vital signs (systolic and diastolic blood pressure) at Week 16
- Change from Baseline in vital signs (heart rate) at Week 16
- Change from Baseline in physical examination findings reported as TEAEs with onset occurring from day of first dose through 20 weeks after final dose of IMP
- Change from Baseline in laboratory analyses (chemistry) at Week 16
- Change from Baseline in laboratory analyses (hematology) at Week 16
- Growth assessment, as assessed by the change in height from Baseline to Week 16
- Growth assessment, as assessed by the change in weight from Baseline to Week 16

Has been changed to:

- Change from Baseline in vital signs and physical examination findings
- Change from Baseline in laboratory analyses (chemistry and hematology)
- Growth assessment as assessed by the change in height and weight

Change #3

1.2 Study Design

Added text to include Neuropsychiatric Adjudication Committee language within the overall Study Design.

Original text:

An IBD Adjudication Committee will also periodically review data from this study. Details will be provided in the IBD Adjudication Committee charters.

Has been changed to:

An IBD Adjudication Committee and a Neuropsychiatric Adjudication Committee will also periodically review data from this study. Details will be provided in separate IBD and Neuropsychiatric Adjudication Committee charters.

Change #4

5.1 General Considerations

Added language “All efficacy data collected later than 33 days—derived as 28 days allotted for the planned dosing interval plus 5 days allotted for the maximum allowable visit window during either study period—and, all safety data that are collected later than 140 days after the last administration of study treatment will be treated as missing and subject to imputation as applicable.” to clarify how to summarize efficacy and safety data for study participants who discontinue study treatment but continue the study. Added Section cross reference for partial dates for AEs.

Change #5

5.1.1.1.2 End date of the Treatment Period

Updated to align with study with drawl text in protocol amendment 2 dated 15 Mar 2021.

Original text:

The end date of the Initial Treatment Period will be the last scheduled visit (Week 20 Visit) date for participants who complete the Initial Treatment Period or the Early Discontinuation Visit (EDV) date for participants who discontinue the study during the Initial Treatment Period.

Has been changed to:

The end date of the Initial Treatment Period will be the last scheduled visit (Week 20 Visit) date for participants who complete the Initial Treatment Period or the Early Discontinuation Visit (EDV) date for participants who withdraw from the study during the Initial Treatment Period.

Change #6

5.1.1.1.4 Mapping of assessments performed at Early Discontinuation Visit

Updated to correct abbreviation for antidrug antibody abbreviation from ADAB to ADAb.

Change #7

5.1.1.1.5 Definition of Baseline values

Updated definition of Baseline value for clinical variables to include both the Initial Treatment Period and the OLE Period.

Original text:

A Baseline value for clinical variables is defined as the latest measurement on or prior to the first dosing day of study medication, regardless of the time of the measurement, for the Initial Treatment Period.

Has been changed to:

A Baseline value for clinical variables is defined as the latest measurement on or prior to the first dosing day of study medication, regardless of the time of the measurement, for the Initial Treatment Period and the OLE Period.

Change #8

5.1.1.5 Coding Dictionaries

Accounted for the most current MedDRA and WHO-DD coding dictionary available throughout the course of the study.

Original text:

For MedDRA, version 23.1 will be used. For WHO-DD, version Mar/2021 B3 or greater will be used.

Has been changed to:

For MedDRA, version 23.1 or greater will be used. For WHO-DD, version Mar/2021 B3 or greater will be used.

Change #9

5.1.1.7.1 Rational for estimand

Added section to expand on rational for estimand to align with recent FDA guidance.

Change #10

5.1.1.7.4 Missing dates and times

Removed references to start and stop times for Adverse Events and Concomitant Medications to align with the most recent version of the CRF that does not include Adverse Events and Concomitant Medications start and stop times.

Concatenated paragraphs 2 and 3 to clarify imputation rules for Adverse Events and Concomitant Medications partially reported start and stop dates.

Change #11

5.2 Study Participant Dispositions

Updated Completion of Study Definition to align with protocol amendment 2 dated 15 Mar 2021.

Original text:

Completion of Study: For participants who enter the OLE period, completion of study is considered as completion of OLE Period. For participants who do not enter OLE period, completion of study is considered as completion of the Initial Treatment period.

Has been changed to:

Completion of Study: For all participants, completion of study is considered as completion of OLE Period. Participants who do not tolerate the IMP or who have an IGA response ≥ 3 (on a scale from 0 to 4) at Week 20 will be considered as withdrawn from the study due to lack of efficacy. Participants who are eligible for but elect not to enter the OLE period at Week 20 will be considered as withdrawn from the study due to consent withdrawn.

Change #12

5.2.1 COVID-19 impact analysis

Updated COVID-19 impact analysis to remove references to pre-COVID and COVID-19 AE analysis, summarized in Section 5.6.2.2.

Original text:

For the purposes of summarizing disposition with respect to COVID, pre-COVID refers to an event or record reported prior to this date, post-COVID refers to an event or record reported after the date when WHO declares the global pandemic has ended.

Has been changed to:

For the purposes of summarizing disposition with respect to COVID. Post-COVID refers to an event or record reported after the date when WHO declares the global pandemic has ended.

Removed language: The selected AE data will also be analyzed during and post COVID-19 pandemic, and details can be found in Section 5.6.2.2.

Change #13

5.4.1.1.3 CDLQI (total score) change from baseline

Added language “Any CDLQI data collected on paper via electronic data capture and digitally in the app will be pooled together for analysis. The CDLQI data source (ie, paper, app) will be displayed in the listing” to denote that these data will be pooled (paper via electronic data capture and digitally in the app) for presentation in the analyses.” Added language “If responses are collected for both Q7A and Q7B, they will be displayed in the listing, however only the response corresponding to the answer given in Q7 will be tabulated.”

Change #14

5.4.1.2.1 PASI90 (Week 16) response, 5.4.1.2.2 PASI75 (Week 4) response, 5.4.1.2.3 IGA 0/1 response (Week 16), and 5.4.1.2.4 CDLQI (total score) change from baseline (Week 16)

Global update to estimand population definitions to align with the most recent version of the BZK Program Conventions.

Original text:

- **Population:** Adolescents meeting the protocol-specified inclusion/exclusion criteria and randomized to IMP.

Has been changed to:

- **Population:** Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.

Change #15

5.4.1.3 Sensitivity Analysis

Updated CDLQI to CDLQI total score to accurately describe the secondary efficacy endpoint.

Original text:

The OC analysis will serve as the sensitivity analysis for the secondary efficacy endpoints (PASI90 response at Week16, PASI75 response at Week 4, IGA0/1 response at Week 16, and CDLQI change from baseline to Week 16) to assess the impact of missing value on the main imputed analysis.

Has been changed to:

The OC analysis will serve as the sensitivity analysis for the secondary efficacy endpoints (PASI90 response at Week16, PASI75 response at Week 4, IGA0/1 response at Week 16, and CDLQI total score change from baseline to Week 16) to assess the impact of missing value on the main imputed analysis.

Change #16

5.6 Safety Analysis

Updated text to clarify period attribution for safety data.

Original text:

Safety variables will be analyzed for all study participants in the SS (for the Initial Treatment Period and combined Initial Treatment Period and OLE Period when needed), and in the OLS (for the OLE Period). Safety events that occur within 140 days of the last study drug dose (covering the 20-week SFU Period) in general will be attributed to the period in which the participant was before initiating the SFU Period. In general, safety events will be analyzed according to the most recent dose prior to or at the time of the safety event.

Has been changed to:

Safety variables will be analyzed for all study participants in the SS (for the Initial Treatment Period and combined Initial Treatment Period and OLE Period when needed), and in the OLS (for the OLE Period). In general, safety data that are collected within 140 days of the last study drug dose (covering the 20-week SFU Period) will be attributed to the period in which the participant was before initiating the SFU Period and will be analyzed according to the most recent dose prior to or at the time of the collection.

Change #17

5.6.1 Extent of exposure

Updated to correct verb tense. Added clarification language “For all exposure summaries, the “All Participants” column will be a summary of the time from date of first dose through the date of last dose of any treatment, regardless of dose level” to denote meaning of All Participants column in exposure summaries.

Original text:

Time at risk will be summarize descriptively in the same manner as the duration of exposure.

Has been changed to:

Time at risk will be summarized descriptively in the same manner as the duration of exposure.

Change #18

5.6.1.1 Initial Treatment Period and 5.6.1.2 Open Label Extension (OLE) Period

Added language to extend time at risk definition for participants who continue into the OLE Period but who are missing final visit in the ITP. Updated time at risk definitions to more accurately describe time at risk period as well as to align with program conventions.

Original text:

5.6.1.1 Initial Treatment Period:

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

- $\text{Date of last dose (Initial period)} - \text{Date of first dose (Initial Period)} + 140$

5.6.1.2 Open Label Extension (OLE) Period: If there is an interval of more than 140 days between consecutive doses, then the number of days in excess of 140 days should be subtracted from the study medication duration and time at risk.

&

For the last dosing period P_n ,

- $\text{Exposure}(P_i) = \text{Last Dose Date of } P_n - 1\text{st Dose Date of } P_n + \min(28, \text{Date of Death} - \text{Last Dose Date of } P_n)$

Has been changed to:

5.6.1.1 Initial Treatment Period:

Note: If a participant does not complete the final visit of the Initial Treatment Period and continues to the OLE Period:

- $\text{Time at Risk} = \max\{\max(\text{Date of last visit [Initial Period]}, \text{Date of last dose [Initial Period]}) - \text{Date of first dose (Initial Period)} + 28, \text{Date of first dose (OLE Period)} - \text{Date of first dose (Initial Period)} + 1\}$

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

- *Date of last dose (Initial period) – Date of first dose (Initial Period) + 141*
- *Total number of days in the Initial Treatment Period (140 days)*
- *Date of last clinical contact – Date of first dose (Initial Period) + 1*

5.6.1.2 Open Label Extension (OLE) Period:

For the last dosing period P_n ,

- *Time at Risk(P_i) = Last Dose Date of P_n – 1st Dose Date of P_n + min (141, Date of Death – Last Dose Date of P_n)*

Change #19

5.6.1.3 Combined Initial Treatment Period and OLE Period

Clarified definition of combined duration of exposure.

Original text:

The combined duration of exposure will be the sum of exposure calculated from the Initial Treatment Period (as defined in Section 5.6.1.1) and OLE Period (as defined in Section 5.6.1.2) for each dose level. Only the same dose level can be combined within a participant. The time at risk will be calculated similarly.

Has been changed to:

The combined duration of exposure will be the sum of exposure calculated from the Initial Treatment Period (as defined in Section 5.6.1.1) and OLE Period (as defined in Section 5.6.1.2) for each dose level, minus 1 day. Only the same dose level can be combined within a participant. The time at risk will be calculated similarly.

Change #20

5.6.2.1 General data considerations for AEs and Global

Removed all references to risk differences.

Change #21

5.6.2.2 AE summaries

Updated formatting, AE discontinuation analysis, AE analysis preformed, and language for COVID-19 AE analysis.

Original text:

The following AE summaries for participant incidence and event number will be provided by dose group for the Initial Treatment Period, OLE Period, and the combined periods. Selected summaries as noted will report exposure adjusted rates and risk differences. An overall summary of the AEs will also be provided.

- Summary by system organ class (SOC), HLT, and preferred term (PT):
 - Any TEAE (with exposure-adjusted rates)
 - Serious TEAE (with exposure-adjusted rates)
 - TEAE leading to study discontinuation (with exposure-adjusted rates)
 - TEAE leading to study treatment discontinuation (with exposure-adjusted rates)
 - TEAE leading to death
 - Related TEAE
 - Related serious TEAE
 - Nonserious TEAE
 - TEAE for safety topics of interest (with exposure-adjusted rates)
- Summary by relationship, SOC, HLT, and PT
 - Any TEAE
 - Serious TEAEs (for European Union Drug Regulating Authorities Clinical Trials [EudraCT] reporting purposes)
 - TEAE leading to death (for EudraCT reporting purposes)
 - Nonserious TEAE
- Summary by maximum relationship, SOC, HLT, and PT
 - Any TEAE
 - Serious TEAE
 - Nonserious TEAE
- Summary by severity, SOC, HLT, and PT
 - Any TEAE
- Summary by maximum severity, SOC, HLT, and PT
 - Any TEAEs

Ordered and subset of AE summaries will be reported in a separate table to facilitate review when needed. Examples include:

- Any TEAE by SOC and PT for above reporting threshold of 5% (with risk difference)
- Related TEAEs by SOC and PT above reporting threshold of 5% (with risk differences)
- Serious TEAE by SOC and PT (with risk difference)
- TEAE for Safety topics of Interest by SOC and PT (with risk difference)
- Nonserious TEAE by SOC and PT for above reporting threshold of 5%
- Nonserious TEAE by SOC and PT and relationship for above reporting threshold of 5%;

- Any TEAE by decreasing frequency of PT
- Any TEAE for confirmed or suspected COVID-19 cases by SOC, HLT and PT
- Any TEAE by during and post COVID-19 pandemic by SOC, HLT, and PT

The following summary will be provided for antibody data:

- Incidence of TEAEs per 100 participant years by SOC, HLT, and PT and by time of onset relative to ADAb status.

The following AEs will be listed separately, and their incidences will be reported in the AE overall summary table.

- Any TEAE with onset at day 1
- Any TEAE related to TB including latent TB and IGRA tests
- Any TEAE for confirmed or suspected COVID-19 cases

Has been changed to:

The following AE summaries for participant incidence and event number will be provided by dose group for the Initial Treatment Period, OLE Period, and the combined periods. Selected summaries as noted will report exposure adjusted rates. An overall summary of the AEs will also be provided.

- Summary by system organ class (SOC), HLT, and preferred term (PT):
 - Any TEAE (with exposure-adjusted rates)
 - Serious TEAE (with exposure-adjusted rates)
 - TEAEs leading to withdrawal from the study (with exposure-adjusted rates)
 - TEAE leading to discontinuation of investigational medicinal product (IMP) (with exposure-adjusted rates)
 - TEAE leading to death
 - Related TEAE
 - Related serious TEAE
 - Nonserious TEAE
 - TEAE for safety topics of interest (with exposure-adjusted rates)
- Summary by relationship, SOC, HLT, and PT
 - Any TEAE
 - Serious TEAEs (for European Union Drug Regulating Authorities Clinical Trials [EudraCT] reporting purposes)
 - TEAE leading to death (for EudraCT reporting purposes)
 - Nonserious TEAE

- Summary by maximum relationship, SOC, HLT, and PT
 - Any TEAE
- Summary by severity, SOC, HLT, and PT
 - Any TEAE
- Summary by maximum severity, SOC, HLT, and PT
 - Any TEAEs

Ordered and subset of AE summaries will be reported in a separate table to facilitate review when needed. Examples include:

- Any TEAE by SOC and PT for above reporting threshold of 5%
- Related TEAEs by SOC and PT above reporting threshold of 5%
- Serious TEAE by SOC and PT
- TEAEs Identified as Safety Topics of Interest by SOC and PT
- Nonserious TEAE by SOC and PT for above reporting threshold of 5%
- Any TEAE by decreasing frequency of PT
- Any COVID-19 TEAEs by SOC, HLT and PT
- Any TEAE by during and post COVID-19 pandemic by SOC, HLT, and PT

The following summary will be provided for antibody data:

- Incidence of TEAEs per 100 participant years by SOC, HLT, and PT and by time of onset relative to ADAb status. Note: Only presented for combined Initial Treatment Period and OLE Period.

The following AEs will be listed separately, and their incidences will be reported in the AE overall summary table.

- Any TEAE with onset at day 1
- Any TEAE related to TB including latent TB and IGRA tests
- Any COVID-19 TEAEs

Change #22

5.6.2.4 Safety topics of interest

Updated language to clarify analysis for TB and adjudicated IBD and neuropsychiatric events.

Original text:

- TB. TB will be analyzed as part of opportunistic infections. In addition, summary of the number and percentage of participants with negative, positive, and indeterminate

interferon gamma release assay (IGRA) results at each visit will be presented. A by-participant listing of the “Evaluation of signs and symptoms of tuberculosis” questionnaire data, IGRA results, and chest x-ray results will be provided.

Has been updated to:

- TB. TB will be analyzed as part of opportunistic infections. Summary of the number and percentage of participants with negative, positive, and indeterminate interferon gamma release assay (IGRA) results at each visit will be presented. In addition, incidence of TB related TEAEs will be summarized (active TB, latent TB, and false positive TB testing). A by-participant listing of the “Evaluation of signs and symptoms of tuberculosis” questionnaire data, IGRA results, and chest x-ray results will be provided.

Original text:

Tables for adjudicated definite IBD events (event type codes 3, 6, 9, 13, and 16), probable IBD events (event type codes 2, 5, 8, 12, and 15), and possible IBD events (event type codes 1, 4, 7, 11, and 14) as determined by the IBD adjudication committee will be produced. A listing of all events identified for potential review by the IBD adjudication committee will be produced. This listing will indicate whether each event was escalated to the committee for formal review/adjudication. A separate table and listing will present the adjudicated IBD events by type. For each IBD event type (event type codes 1 through 16 and 99; 17 total), the individual PTs which fall within each event type will be summarized. A third listing will present the individual diagnostic criteria met for each adjudicated IBD event.

Has been changed to:

A table for combined ITP and OLE Period adjudicated IBD events (event type codes 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15 and 16) as determined by the adjudication committee will be produced. It will summarize events determined by the adjudication committee as definite IBD (event type codes 3, 6, 9, 13, and 16), probable IBD (event type codes 2, 5, 8, 12, and 15) and possible IBD (event type codes 1, 4, 7, 11, and 14). Definite and probable IBD will also be aggregated and summarized.

A separate table will present the adjudicated gastrointestinal events by type for combined ITP and OLE Period. For each gastrointestinal event type (17 total), the individual PTs which fall within each event type will be summarized. It will include events determined by the adjudication committee as definite IBD probable IBD and possible IBD. It will also include events determined as Symptoms not consistent with IBD (event type code 10) and Not enough information to adjudicated (event type code 99).

A listing of all events identified for potential review by the IBD adjudication committee will be produced. This listing will indicate whether each event was escalated to the committee for formal review/adjudication.

A separate listing will present the adjudicated IBD events by type. For each IBD event type (event type codes 1 through 16 and 99; 17 total), the individual PTs which fall within each event type will be listed.

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

Original text:

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

Has been changed to:

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

A separate table will present the adjudicated neuropsychiatric events by type. For each neuropsychiatric event type (6 total), the individual PTs which fall within each event type will be summarized. It will include events adjudicated as SIB and events adjudicated as non-suicidal. Note that the event type Suicidal ideation can be classified as either SIB or non-suicidal.

Change #23

5.6.3.1.1 Laboratory values over time

Updated text to align with most recent version of BKZ Program Conventions, corrected abbreviations of criteria, and added language “To align with regulatory guidelines for PDILI assessment and reporting in CSRs, a table summarizing incidence of hepatotoxicity and lab criteria constituting a PDILI will be included” to clarify PDILI analysis.

Original text:

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

- A summary of the absolute and change from Baseline values in each laboratory variable by dose group and visit will be presented.
- A summary of the number and percentage of participants with a given CTCAE grade (0, 1, 2, 3, or 4) based on minimum/maximum post-baseline value by laboratory variable and dose group will be presented. The criteria used for CTCAE grade classification is provided in Section 6.1.9.1.
- A shift table of the number and percentage of participants experiencing CTCAE grade 0, 1, 2, 3, or 4 values (as applicable) at Baseline to maximum post-Baseline CTCAE grade will be presented, by laboratory variable and dose group.
- A summary of the number and percentage of participants experiencing treatment-emergent markedly abnormal (TEMA) values will be presented for each dose group for the Initial Treatment Period, OLE Period, and the combined periods. The TEMA laboratory values are

defined similarly to TEAE as those lab values assessed on or following the first dose of study treatment through the final dose of treatment +20 weeks (140 days) with a severity of CTCAE Grade 3 and above.

- A by-participant listing of all laboratory data (including urinalysis) will be provided. This listing will be presented by treatment group and will include center, participant identifier, age, sex, race, weight, visit, laboratory variable, result (with abnormal values flagged as “L” or “H” accordingly) and unit.

The table for markedly abnormal liver function tests (LFTs) will contain data beyond the CTCAE Grade 3 thresholds outlined 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 participants meeting the below criteria at any time during the study:

- AST (aspartate aminotransferase): >3xULN (upper limit of normal), >5xULN, >8xULN, >10xULN, >20xULN
- ALT (alanine aminotransferase): >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- AST or ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- Bilirubin: >1.5xULN, >2xULN

In addition, potential Hy's Law cases will be summarized with the LFT lab data. The following definition will be used:

- [AST \geq 3xULN or ALT \geq 3xULN] and Total Bilirubin \geq 2xULN in the absence of ALP (Alkaline phosphatase) \geq 2xULN

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST (and the absence of ALP elevation) at the same visit. For example, a subject who experiences a \geq 2 x ULN elevation of bilirubin at one visit and a \geq 3xULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria. Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.

Has been changed to:

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. Additionally for tables where data are summarized by visit, summaries of the Initial Period will not include the SFU visit since sample sizes will be small, but these data will be included in listings. For tables where multiple measurements over a period of time are considered (as in shift tables), unscheduled and repeat visits will be considered as long as they were collected in the period being summarized (values observed more than 140 days after the last administration of study medication are not considered). All summaries will be presented in International System of Units and will be based on observed case values. In the case where laboratory values are below the LLQ, then these will be set to the midpoint between 0 and the lower limit of quantification for the purpose of summarizing the data. The following summaries will be presented:

- A summary of the absolute and change from Baseline values in each laboratory variable by dose group and visit will be presented.

- A summary of the number and percentage of participants with a given CTCAE grade (0, 1, 2, 3, or 4) based on minimum/maximum post-baseline value by laboratory variable and dose group will be presented. The criteria used for CTCAE grade classification is provided in Section 6.1.9.1.
- A shift table of the number and percentage of participants experiencing CTCAE grade 0, 1, 2, 3, or 4 values (as applicable) at Baseline to maximum post-Baseline CTCAE grade will be presented, by laboratory variable and dose group.
- A summary of the number and percentage of participants experiencing treatment-emergent markedly abnormal (TEMA) values will be presented for each dose group for the Initial Treatment Period, OLE Period, and the combined periods. The TEMA laboratory values are defined similarly to TEAE as those lab values assessed on or following the first dose of study treatment through the final dose of treatment +20 weeks (140 days) with a severity of CTCAE Grade 3 and above.
- A by-participant listing of all laboratory data (including urinalysis) will be provided. This listing will be presented by treatment group and will include center, participant identifier, age, sex, race, weight, visit, laboratory variable, result (with abnormal values flagged as “L” or “H” accordingly) and unit.

The table for markedly abnormal liver function tests (LFTs) will contain data beyond the CTCAE Grade 3 thresholds outlined 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 participants meeting the below criteria at any time during the study:

- AST (aspartate aminotransferase): >3xULN (upper limit of normal), >5xULN, >8xULN, >10xULN, >20xULN
- ALT (alanine aminotransferase): >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- AST or ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- Total 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:

- $nR = [\text{maximum}(\text{AST}/\text{ULN or AST}/\text{ULN})]/(\text{ALP}/\text{ULN})$

Potential drug induced liver injury (pDILI) will be summarized (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

In addition, potential Hy's Law cases will be summarized with the LFT lab data. The following definition will be used:

- [AST $\geq 3 \times \text{ULN}$ or ALT $\geq 3 \times \text{ULN}$] and Total Bilirubin $\geq 2 \times \text{ULN}$ in the absence of ALP (Alkaline phosphatase) $\geq 2 \times \text{ULN}$

In order to meet the above potential Hy's Law laboratory criteria, a subject must experience the elevation in bilirubin and ALT or AST (and the absence of ALP elevation) at the same visit. For example, a subject who experiences a $\geq 2 \times \text{ULN}$ elevation of bilirubin at one visit and a $\geq 3 \times \text{ULN}$ elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria. Follow-up information should be reported if an alternative etiology is identified during investigation and monitoring of the participant.

Potential hepatotoxicity (meeting one of the pDILI or Hy's law laboratory criteria at least once) will be considered with and without symptoms potentially associated with hepatitis or hypersensitivity according to the investigator (reported on the Symptoms of Hepatitis and Hypersensitivity CRF page).

To align with regulatory guidelines for PDILI assessment and reporting in CSRs, a table summarizing incidence of hepatotoxicity and lab criteria constituting a PDILI will be included.

Change #24

5.6.3.4 PHQ-9

Added language "Descriptive statistics for the PHQ-9 scores will be summarized by dose group and visit" to add additional summary table for PHQ-9 scores and "The PHQ-9 data source will be displayed in the listing" to denote source of collection on PHQ-9 listing.

Change #25

5.7.1.1 Pharmacokinetics

Updated visits to align with protocol amendment 2 dated 15 Mar 2021 Schedule of Assessments and most recent BKZ Program Conventions.

Original text:

The primary variable of this study is plasma bimekizumab concentrations, assessed at Baseline, Week 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 40, Week 64, Week 88, Week 112, Week 124, termination visit, and SFU Visit. Pharmacokinetic analyses will be performed in the PK-PPS. Separate summary tables will be created for the OLE Period for participants that are in both the PK-PPS and the OLS.

Pharmacokinetic variables will be analyzed for all participants in the PK-PPS. Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit. The PK summaries will be based on observed values. No imputation will be used for missing data. If plasma concentration measurements are below the level of quantification (BLQ), then for calculation of the derived statistics the result will be set to $\frac{1}{2}$ of the LLOQ. Descriptive statistics including geometric mean, geometric coefficient of variation, and geometric mean 95% CI (if applicable) will be calculated if at least two-thirds of the values of interest are above the LLOQ. If this is not the case, only median, minimum, and maximum will be presented. All PK concentrations will be listed.

The PK data will be subject to a population PK analysis and will be described in a separate analysis plan and reported independently.

Has been changed to:

The primary variable of this study is plasma bimekizumab concentrations, assessed at Baseline, Week 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 40, Week 64, Week 88, Week 112, Week 124, EDV, and SFU Visit. Pharmacokinetic analyses will be performed in the PK-PPS. Separate summary tables will be created for the OLE Period for participants that are in both the PK-PPS and the OLS.

Pharmacokinetic variables will be analyzed for all participants in the PK-PPS. Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit. The PK summaries will be based on observed values. No imputation will be used for missing data. If plasma concentration measurements are below the level of quantification (BLQ), then for calculation of the derived statistics the result will be set to $\frac{1}{2}$ of the LLOQ. Descriptive statistics including geometric mean, geometric coefficient of variation, and geometric mean 95% CI (if applicable) will be calculated if at least two-thirds of the values of interest are above the LLOQ and $n \geq 3$. If this is not the case, only median, minimum, and maximum will be presented. All PK concentrations will be listed.

By-visit summaries of plasma concentrations will exclude data points where protocol deviations and/or deviation from scheduled dose and sample collection window are expected to impact drug exposure. The protocol deviations will be reviewed by the Quantitative Clinical Pharmacology (QCP) representative and a decision about impacted data points will be made prior to generating summary statistics. Further details regarding deviations from scheduled dose and sample collection that can be identified programmatically should be added to SAPs in collaboration with the QCP representative.

The PK data will be subject to a population PK analysis and will be described in a separate analysis plan and reported independently.

Change #26

5.7.1.4 Immunogenicity

Updated section to align with Immunological (Immunogenicity) Analysis in program conventions. Section now includes additional tables, listings, and figures to include effects on BKZ concentrations.

Original text:

Has been changed to:

5.7.1.4 Immunological (Immunogenicity) Analysis

5.7.1.4.1 Anti-bimekizumab antibody

The analysis of immunogenicity includes ADA_{Ab} evaluations. The analysis will be based on the SS.

Anti-bimekizumab antibodies will be measured using a 3-tiered assay approach: screening assay, confirmatory assay, and titration assay. Samples confirmed as positive within the confirmatory

assay will be further evaluated in a neutralizing antibody (NAb) assay to evaluate the potential of the ADAb to neutralize the activity of bimekizumab (IL17A-specific or IL17F-specific, or both) in-vitro analysis details outlined in Section □.

Samples were taken on the same schedule as PK assessments including Baseline, Week 1, Week 4, Week 8, Week 12, Week 16, Week 20, Week 40, Week 64, Week 88, Week 112, Week 124, EDV, and SFU.

Screening, confirmatory, and titer cut points of the respective assays will be determined by the bioanalytical laboratory based either on using commercially-available drug-naïve samples or on the predose samples obtained during the study. The samples (or a subset) will also be subject to a neutralizing assay to evaluate whether the ADAb neutralizes the activity of bimekizumab (IL17A-specific or IL17F-specific or both) in-vitro.

The following definitions will be applied regarding ADAb status of each test samples:

- An ADAb status will be confirmed as positive for any sample with an ADAb level that is positive screen and positive immunodepletion.
- An ADAb status of negative will be concluded for any sample with an ADAb level that is either negative screen or (positive screen and negative immunodepletion).
- Inconclusive - sample values that are either negative screen or positive screen and negative immunodepletion and where the bimekizumab concentration exceeds the validated ADAb assay drug tolerance limit. These samples will be regarded as missing.

If the titer for an ADAb level that is positive screen and positive immunodepletion is missing, then a conservative approach will be used and ADAb status will be consider as positive. No imputation rules apply for the missing titer. If the ADAb level is positive screen but no confirmatory result could be determined, then a conservative approach will be used and ADAb status will be consider as positive.

Anomalous values will not be included in summaries/analysis and will be reviewed and flagged by pharmacokinetic expert.

For each participant an overall ADAb status will be derived:

- Overall positive is defined as having at least one value that is confirmed positive during the treatment period.
- Overall negative is defined as having no values that are confirmed positive at any time in the treatment period.
- The treatment period does not include Baseline/pretreatment samples or SFU samples.

Furthermore, the following subcategories for each participant will be derived:

10. **Pre ADAb negative – treatment-emergent ADAb negative:** Includes participants who are negative at Baseline and ADAb negative at all sampling points posttreatment (excluding SFU).
11. **Pre ADAb negative – treatment-emergent ADAb positive:** Includes participants who are negative at Baseline and ADAb positive at any sampling point posttreatment (excluding SFU). This group also includes participants who have a missing pretreatment sample (either

missing or insufficient volume) at Baseline with 1 or more ADA_b positive posttreatment samples.

12. **Pre ADA_b positive – treatment-emergent reduced ADA_b:** Includes participants who are positive at Baseline, and ADA_b negative at all sampling points posttreatment (excluding SFU).
13. **Pre ADA_b positive – treatment-emergent unaffected ADA_b positive:** Includes participants who are positive at Baseline and are positive at any sampling point posttreatment (excluding SFU) with titer values of the same magnitude as Baseline (ie, less than a 2.07-fold difference from the Baseline value; 2.07 being the validated minimum significant ratio for this assay method).
14. **Pre ADA_b positive – treatment-emergent ADA_b boosted positive:** Includes participants who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with increased titer values compared to Baseline (equal to or greater than a 2.07-fold difference increase from Baseline value).
15. **Inconclusive:** Includes participants who have a positive pretreatment sample and some posttreatment samples are missing, while other posttreatment samples are ADA_b negative.
16. **Missing:** Includes participants who are antibody negative at Baseline, are not positive at any post-Baseline visit, and have at least 1 missing posttreatment scheduled assessment. Note this is also applicable to participants who have missing Baseline.

Derivation for above classification will be different for the PK interim analysis and the final analysis. For the PK interim analysis, no OLE or SFU data will be considered. Only for the final analysis, when all OLE and SFU data will be available, will data from the OLE and SFU visits be considered. That is, each instance of “excluding SFU” in the categories above, should be changed to “including SFU.”

In the case that a sample is collected 1 or more days following the scheduled visit date in which the drug was administered, the ADA_b results for that sample will be associated with the scheduled visit and summarized accordingly. Such samples will also be considered when ADA_b results are summarized over a given study period.

ADA_b will be assessed through summary tables, figures, and listings of individual results by participant. All analyses will be run on the SS, unless specified otherwise.

- Summary of ADA_b status overall and by each visit separated by dose group will be presented.
- Summary of the time-point of the first occurrence of ADA_b positivity during the treatment period will be presented by dose group. A plot of the titer by time to first ADA_b positivity will be prepared.
- All individual participant-level ADA_b results will be listed.
- The number and percentage of participant in each of the 7 ADA_b categories during the treatment period by dose group, with an additional category combining participants in categories 2 and 5, summarized as total treatment-emergent. In addition, the count and percentage of participants who are pre ADA_b positive will be calculated (this is the sum of categories 3, 4, and 5).

- The prevalence of immunogenicity, separated by dose group, and defined subcategory, will be reported by visit, defined as (cumulative) proportion of participants having confirmed positive ADA_b samples at any visit up to and including that visit. Missing samples will not be included in the denominator.
- The time to achieving treatment-emergent ADA_b positivity, separated by dose group and defined sub-category, will be analyzed based on Kaplan-Meier methods. Participants will be considered to have an event at the time point at which treatment-emergent ADA_b positive is first achieved. Participants classified as treatment-emergent ADA_b negative will be censored at the time of the last available ADA_b result.
- Summary of PASI75, PASI90, PASI100 and IGA01 by Visit, Treatment Group and Anti-Bimekizumab Antibody Status.
- A summary of PASI100 responders, separated by dose group and defined subcategory, at week 16 as a function of ADA_b titer will be presented graphically. This will be repeated for PASI75 and 90 responders.
- Two figures (side by side) of PASI75 versus time for each treatment group (BKZ Dose A and BKZ Dose B) by ADA_b status (ADA_b negative, ADA_b positive, missing) will be created. If $\geq 95\%$ of subjects are included in the non-missing groups, the missing group will not be displayed in the figure. The data will also be presented in a tabular format. The analyses will be repeated for PASI90, PASI100, and IGA01. The data will be also presented in a tabular format.
- Individual plots of bimekizumab concentrations / ADA_b titer and PASI score will be plotted on the Y-axes by visit (x-axis) for the full treatment period (excluding SFU and OLE period for interim analyses and including SFU and OLE period for final analyses), where a participant has not progressed into the OLE. Plots should be labeled and grouped into the 7 subcategories.
- Spaghetti plots of ADA_b titer (y-axis) by visit (x-axis), separated by dose group for all ADA_b positive participants, including Baseline positive participants, will be provided.
- Box plots of ADA_b titer (logscale) by time to first ADA_b positivity will be reported by dose group.

For purposes of efficacy subgroup analyses based on ADA_b status, 3 categories will be used:

- ADA_b positive – This is defined as participants who have ADA_b levels above the specified cut point on at least 2 time points during the study (ie, including Baseline, and SFU).
- ADA_b negative – Participants who are not defined as ADA_b positive (as described above) will be defined as ADA_b negative.
- Missing.

The groups for defining ADA_b status for safety subgroup analyses are as follows:

- AEs starting before first ADA_b positive result
- AEs starting on or after first ADA_b positive result
- AEs for participants who were always ADA_b negative

5.7.1.4.2 Neutralizing antibodies

In addition to the ADA b classifications, participants may also receive an overall neutralizing (NAb) classification for each NAb assay separately, inclusive of Baseline and post-Baseline results, on the NAb assay results:

- NAb negative: No NAb positive samples for IL-17AA and IL-17FF at Baseline or post-Baseline. This group will also include subjects who have only 1 missing sample and all other available samples during the period of interest are negative. Study participants who are NAb negative will be classified as follows:
 - ADA b positive / NAb negative: ADA b positive subjects who are 1) NAb negative for all available ADA b positive samples or 2) with only one missing NAb sample and all other evaluated ADA b positive samples are NAb negative.
 - ADA b negative: if the subject has all the samples as ADA b negative or only one missing/inconclusive sample with all other available samples as negative ADA b.
- NAb positive: One or more positive samples (IL-17AA positive, IL-17FF positive, or both) at Baseline or post-Baseline (regardless of missing samples). Study participants who are NAb positive will be further classified as follows:
 - Positive for IL-17AA only: one or more positive samples for IL-17AA at baseline or post-baseline. No positive samples for IL-17FF.
 - Positive for IL-17FF only: one or more positive samples for IL-17 FF at baseline or post-baseline. No positive samples for IL-17AA.
 - Positive for both IL-17AA and IL-17FF: one or more positive samples for both IL-17AA and IL-17FF at baseline or post-baseline.
- NAb Missing:
 - >1 relevant NAb samples are missing and other available NAb samples during the period of interest are negative, eg, missing or insufficient sample left for NAb testing.

The NAb data will not be summarized for the analysis conducted for PS0021 dosing determination. It may be summarized in the final CSR or subsequent to the final CSR, based on the team's decision. If these data are reported, a table and listing will be prepared.

The listing will be sorted by treatment group and will summarize the following information for each participant assessed for NAb:

- Week of highest (most elevated) observed ADA b level
- The corresponding bimekizumab plasma concentration level at this week (µg/mL)
- The ADA b level at this week
- The highest ADA b level at which NAb were observed
- NAb status

The table would provide the following overall summary statistics by treatment group:

- Total number of ADA b positive participants

- Number (%) of NAb negative participants
- Number (%) of NAb positive participants
- Number (%) of missing participants

In addition, two figures (side by side) summarizing efficacy response (PASI75) versus time for each treatment group (BKZ Dose A and BKZ Dose B) by NAb status (ADAb negative, NAb positive, ADAb positive / NAb negative, missing) will be created. If $\geq 95\%$ of subjects are included in the non-missing groups, the missing group will not be displayed in the figure. The data will also be presented in a tabular format. The analyses will be repeated for PASI90, PASI100, and IGA01. The data will be also presented in a tabular format.

Change #27

6.1.1.1 Demographics

Added EudraCT and clinicaltrials.gov age categories:

- EudraCT age categories
 - 12 - <18 years
- clinicaltrials.gov age categories
 - ≤ 18 years
 - $19 < 65$ years
 - ≥ 65 years

to categorical variables summarized in Demographics to account for age grouping for relevant regulatory agencies.

Change #28

6.1.1.3 Other baseline characteristics

Updated duration of psoriasis disease calculation for it is reported in years.

Original text:

PSO history parameters including duration of disease, calculated as date of randomization – date of PSO first diagnosis

Has been changed to:

PSO history parameters including duration of psoriasis disease, calculated as [date of randomization – date of PSO first diagnosis] / 365.25

Change #29

6.1.2 Protocol deviations

Updated protocol deviations to include important and non-important protocol deviations in specified listing. In addition, added text to reference protocol deviations related to COVID-19.

Original text:

The number and percentages of participants with important protocol deviations will be summarized in the enrolled set by dose group and overall.

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

Important PDs and the PDs that will result in the removal of participants from the PK-PPS are specified in the Protocol Deviation Specification document.

Has been changed to:

The number and percentages of participants with important protocol deviations (including a summary of participants excluded from the PK-PPS due to important protocol deviations) will be summarized in the enrolled set by dose group and overall.

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

Important PDs and the PDs that will result in the removal of participants from the PK-PPS are specified in the Protocol Deviation Specification document.

Summaries of protocol deviations related to COVID-19 are described in Section 5.2.1.

Change #30

6.1.4 Prior/concomitant/follow-up medications

Updated definition of concomitant medications to account for concomitant medications started following the last dose of study medication taken (eg. time when the study drug was still in the subject).

Original text:

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. Any medication that started prior to the first dose of IMP and continued after will be classified as both prior and concomitant. Such medications will therefore be counted in the tabulations for both prior and concomitant medication.

The number and percentage of participants taking concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class for each dose group and overall, in the SS. Prior medications and prior antibiotic medications will be summarized similarly.

The concomitant medications will also be summarized for the Initial Treatment Period, OLE Period, and the combined periods.

Has been changed to:

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 or with a start date greater than the last dose of study medication + 28 days. Any medication that started prior to the first dose of IMP and continued after will be classified as both prior and concomitant. Such medications will therefore be counted in the tabulations for both prior and concomitant medication.

The number and percentage of participants taking concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) class for each dose group and overall, in the SS. Prior medications and prior antibiotic medications will be summarized similarly.

A by-study participant listing of all concomitant medications will be provided.

Concomitant medications will also be summarized for the Initial Treatment Period, OLE Period, and the combined periods.

Change #31

6.1.8.1 Marked abnormality criteria for laboratory data

Updated Tables 6-2 and 6-3 units and footnotes to ensure consistent and standard units are reported.

Change #32

6.1.9 Compliance

Updated treatment with IMP to align with protocol amendment 2 dated 15 Mar 2021.

Original text:

For participant who permanently discontinues treatment, the number of expected injections is based on the time of early discontinuation relative to the dosing visits.

Has been changed to:

For participant who permanently discontinues IMP, the number of expected injections is based on the time of early discontinuation relative to the dosing visits.

Change #33

6.3.2.3 Growth chart for weight by age and sex

Updated table in Sex column from 1/2 to Male/Female, respectively, to clarify chart values corresponding to the half-year time point for that year, with respect to sex.

Original text:

Table 6–10: Growth Chart for Weight¹ (kg) by Age and Sex

Sex	Age (years)	Month in the chart	L	M	S
1	12	150.5	-0.76027	43.18828	0.197464
2	13	162.5	-0.65414	48.51113	0.194344
2	14	174.5	-0.63492	53.91261	0.186442
2	15	186.5	-0.72322	58.90293	0.176887
2	16	198.5	-0.89044	63.03228	0.168655
2	17	210.5	-1.0354	66.10749	0.163439
2	12	150.5	-0.85031	43.96612	0.200419
2	13	162.5	-1.00305	47.83661	0.19333

2	14	174.5	-1.23801	50.92541	0.183328
2	15	186.5	-1.51816	53.13327	0.172761
2	16	198.5	-1.76224	54.61224	0.164368
2	17	210.5	-1.86898	55.70624	0.160423

Has been changed to:

Table 6–11: Growth Chart for Weight¹ (kg) by Age and Sex

Sex	Age (years)	Month in the chart	L	M	S
Male	12	150.5	-0.76027	43.18828	0.197464
Male	13	162.5	-0.65414	48.51113	0.194344
Male	14	174.5	-0.63492	53.91261	0.186442
Male	15	186.5	-0.72322	58.90293	0.176887
Male	16	198.5	-0.89044	63.03228	0.168655
Male	17	210.5	-1.0354	66.10749	0.163439
Female	12	150.5	-0.85031	43.96612	0.200419
Female	13	162.5	-1.00305	47.83661	0.19333
Female	14	174.5	-1.23801	50.92541	0.183328
Female	15	186.5	-1.51816	53.13327	0.172761
Female	16	198.5	-1.76224	54.61224	0.164368
Female	17	210.5	-1.86898	55.70624	0.160423

7 REFERENCES

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

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