STATISTICAL ANALYSIS PLAN

AMENDMENT 1

Study: UP0119

Product: Bimekizumab

PHASE 1

AN OPEN-LABEL, RANDOMIZED, PARALLEL-GROUP, SINGLE-DOSE BIOEQUIVALENCE STUDY OF BIMEKIZUMAB GIVEN AS 1X2ML OR 2X1ML SUBCUTANEOUS INJECTION USING AN AUTOINJECTOR IN HEALTHY STUDY PARTICIPANTS

SHORT TITLE:

A bioequivalence study of bimekizumab administered as 1x2mL or 2x1mL subcutaneously in healthy study participants

Sponsor Name: UCB Biopharma SRL

Legal Registered Address: Allée de la Recherche 60, 1070 Brussels, BELGIUM

Regulatory Agency Identifier Number(s):

Registry	**ID**
Eudra CT Number:	2021-005334-41
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Confidentiality Statement

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for study UP0119 is based on the Protocol Amendment 1 dated 21Mar2022.

SAP Version	Approval Date	Change	Rationale
1.0	29 Apr 2022	Not Applicable	Original version
2.0	02 Feb 2023	1. Update the rules in Section 5.4.1.1 Concentration Summary Tables 2. Update the guidelines in Section 5.4.1.2 Pharmacokinetics Parameters 3. Add a sensitivity analysis in Section 5.4.2.3 to include all excluded and available PK parameters in primary analysis model	1. To exclude PK concentration data from summary statistics if the blood samples for BKZ plasma concentrations collected -/+7 days from the scheduled study assessment 2. To clarify if participants withdrew early from the study the PK scientist's best knowledge will determine which PK parameters from these study participants shall be included in the statistical analysis, and the impact of any excluded values will be assessed in the sensitivity analysis. 3. To check the impact of any excluded PK parameters on the statistical analysis of bioequivalence

LIST OF ABBREVIATIONS

List of Abbreviations

$\%AUC_{extr}$	Percentage of the AUC Extrapolated from C_{last}
ADAb	Anti-Drug Antibody
ADE	Adverse Device Effect
AE	Adverse Event
AI	Auto-Injector
ALP	Alkaline Phosphatase
ALQ	Above the Limit of Quantification
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance

List of Abbreviations

aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Plasma Concentration-Time Curve from Time Zero to Infinity
AUC_{0-t}	Area Under the Plasma Concentration-Time Curve from Time Zero to Last Quantifiable Concentration
BE	Bioequivalence
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CF	Correction Factor
CI	Confidence Interval
CL/F	Apparent Total Body Clearance
C_{max}	Maximum Observed Plasma Drug Concentration
COVID-19	Coronavirus Disease 2019
CRO	Contract Research Organization
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
CV%	Between Subject Variability
DCP	Data Cleaning Plan
DEM	Data Evaluation Meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
geoCV	Geometric Coefficient of Variation
geoMean	Geometric Mean
GMR	Geometric Mean Ratio
GGT	Gamma Glutamyl Transferase
HbA1c	Glycosylated Hemoglobin
HBc-Ab	Hepatitis B Core Antibody

List of Abbreviations

HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin
HCV- Ab	Hepatitis C Virus Antibody
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HIV1/2-Ab	HIV1/2 Antibody
HIV1-Ag	HIV1 Antigen
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
IPD	Important Protocol Deviation
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
LLOQ	Lower Limit of Quantification
LSM	Least Squares Mean
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
MRD	Minimum Required Dilution
n	number of participants with available measurements
NCA	Non-Compartmental Analysis
NI	Negative Immunodepletion
NS	Negative Screen
NV	No Value
PDILI	Potential Drug-Induced Liver Injury
PI	Positive Immunodepletion
PK	Pharmacokinetic
PKS	Pharmacokinetic set
PS	Positive Screen
PT	Preferred Term
QTcF	QT Corrected for Heart Rate Using Fridericia's Formula
RBC	Red Blood Cell

List of Abbreviations

RS	Randomized Set
RT-PCR	Real-Time Reverse Transcriptase Polymerase Chain Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sc	Subcutaneous
SD	Standard Deviation
SFU	Safety Follow-Up
SOC	System Organ Class
SS	Safety Set
t½	Apparent Terminal Half-Life
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures and Listings
t_{max}	Time of Occurrence of Cmax
TMF	Trial Master File
ULN	Upper Limit of Normal
V_z/F	Apparent Volume of Distribution
WBC	White Blood Cell
WHO-DD	World Health Organization Drug Dictionary
λ_z	Apparent Terminal Elimination Rate Constant

1 INTRODUCTION

The bimekizumab (BKZ) 320mg dose was assessed in Phase 3 psoriasis [PSO] studies and was approved in the EU on 20 Aug 2021 for the treatment of moderate to severe PSO. After protocol approval, bimekizumab (BKZ) 320mg has also been approved in GB by MHRA on 25 Aug 2021, valid in England, Scotland, and Wales, in Japan by PMDA on 20 Jan 2022 (for the treatment of plaque psoriasis, generalized pustular psoriasis and psoriatic erythroderma) , in Canada by Health Canada on 14 Feb 2022, and in Australia by TGA on 17 Mar 2022. Currently, the dose is administered as 2x1mL subcutaneous (sc) injections of 160mg. To provide additional options to healthcare professionals and patients, it is considered of benefit by UCB to develop bimekizumab 320mg device presentations (ie, functional secondary packaging) where the dose can be delivered as a single 2mL sc injection. Study UP0119 aims to compare the pharmacokinetics (PK) of bimekizumab 320mg when administered sc using a 2mL auto-injector (AI; bimekizumab-AI-2mL, test) versus 2x1mL AI (bimekizumab-AI-2x1mL, reference) to support the development of the 2mL AI device presentations.

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required statistical analyses of study UP0119. It also defines the summary Tables, Figures and listings (TFLs) to be included in the final Clinical Study Report (CSR) according to the study protocol.

This SAP is based on and assumes familiarity with Protocol Amendment 1, dated 21 Mar 2022.

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

The content of this SAP is compatible with:

- The International Council for Harmonisation (ICH) and E9 Guidance documents[1]
- Food and Drug Administration (FDA) guidance[2]
- European Medicines Agency (EMA) guidelines[3,4]
- Canada Health ministry guidance[5,6]

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

1.1 Objectives and Estimands/Endpoints

1.1.1 Study objectives

1.1.1.1 Primary objective

The primary objective of the study is:

- To compare the PK of single sc dose of bimekizumab 320mg when administered using the bimekizumab-AI-2mL presentation (test) versus the bimekizumab-AI-2x1mL presentation (reference) in healthy study participants

1.1.1.2 Secondary objectives

The secondary objectives of the study are:

- To assess the safety and tolerability of a single sc dose of bimekizumab 320mg when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants
- To assess additional PK parameters of a single sc dose of bimekizumab 320mg when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants

1.1.1.3 Other/Exploratory objectives

The other/exploratory objectives of the study are:

- To assess additional PK parameters of a single sc dose of bimekizumab 320mg when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants
- To assess immunogenicity of a single sc dose of bimekizumab 320mg when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants
- To assess additional safety and tolerability of a single sc dose of bimekizumab 320mg when administered using the bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants

1.1.2 Study endpoints

1.1.2.1 Pharmacokinetic endpoints

Pharmacokinetic concentration data will be obtained at the following nominal time points, as described in the protocol: predose (within a maximum of 60 minutes prior to dosing), 1.5h, 5h, 24h, 48h postdose, and from Day 4 onwards at every visit (ie, Days 4 to 10, 13, 16, 19, 22, 25, 28, 56, 84, 112, and 140). The PK parameters provided in this section will be derived from the plasma concentration data. If calculable, the following PK parameters listed in Table 1–1 will be determined for bimekizumab in plasma for each presentation of a single sc injection dose administration

Table 1–1: Plasma Pharmacokinetic Parameters After Single Dose Administration

PK Parameter		WNL[1] Name	CDISC Name	Definition
Primary	C_{max}	Cmax	CMAX	Maximum observed concentration
	AUC_{0-t}	AUClast	AUCLST	AUC from time zero to the last quantifiable concentration

PK Parameter		WNL[1] Name	CDISC Name	Definition
	AUC	AUCINF_obs	AUCIFO	AUC from time zero extrapolated to infinity
Secondary	t_{max}	Tmax	TMAX	Time corresponding to occurrence of C_{max}
	$t_{½}$	HL_Lambda_z	LAMZHL	Apparent terminal elimination half-life
Exploratory	$\%AUC_{extr}$	AUC_%Extrap_obs	AUCPEO	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation beyond t_{last}
	CL/F	Cl_F_obs	CLFO	Apparent clearance following sc administration
	V_z/F	Vz_F_obs	VZFO	Apparent volume of distribution during terminal phase

[1] WNL: WinNonlin

1.1.2.2 Safety endpoints

1.1.2.2.1 Secondary safety endpoints

The secondary safety and tolerability endpoints are:

- Treatment-emergent adverse events (TEAEs)
- Treatment-emergent serious adverse events (SAEs)

1.1.2.2.2 Other/Exploratory safety endpoints

The other/exploratory safety and tolerability endpoints are:

- Vital signs (pulse rate, blood pressure, and tympanic body temperature)
- Safety laboratory data (hematology [including coagulation/hemostasis tests], clinical chemistry, and urinalysis)
- 12-lead electrocardiogram (ECG) assessments

1.1.2.3 Immunogenicity endpoints

1.1.2.3.1 Other/Exploratory immunogenicity endpoint

The other/exploratory immunogenicity endpoint is:

- Incidence of bimekizumab antidrug antibodies (ADAbs)

1.2 Study Design

This is a Phase 1, open label, randomized, parallel-group, single dose, 2-arm bioequivalence (BE) study to compare the PK of bimekizumab 320mg when administered as either a 1x2mL or 2x1mL sc injection in healthy male and female study participants using an AI presentation. The 2 arms will be:

1. bimekizumab-AI-2mL (test)
2. bimekizumab-AI-2x1mL (reference)

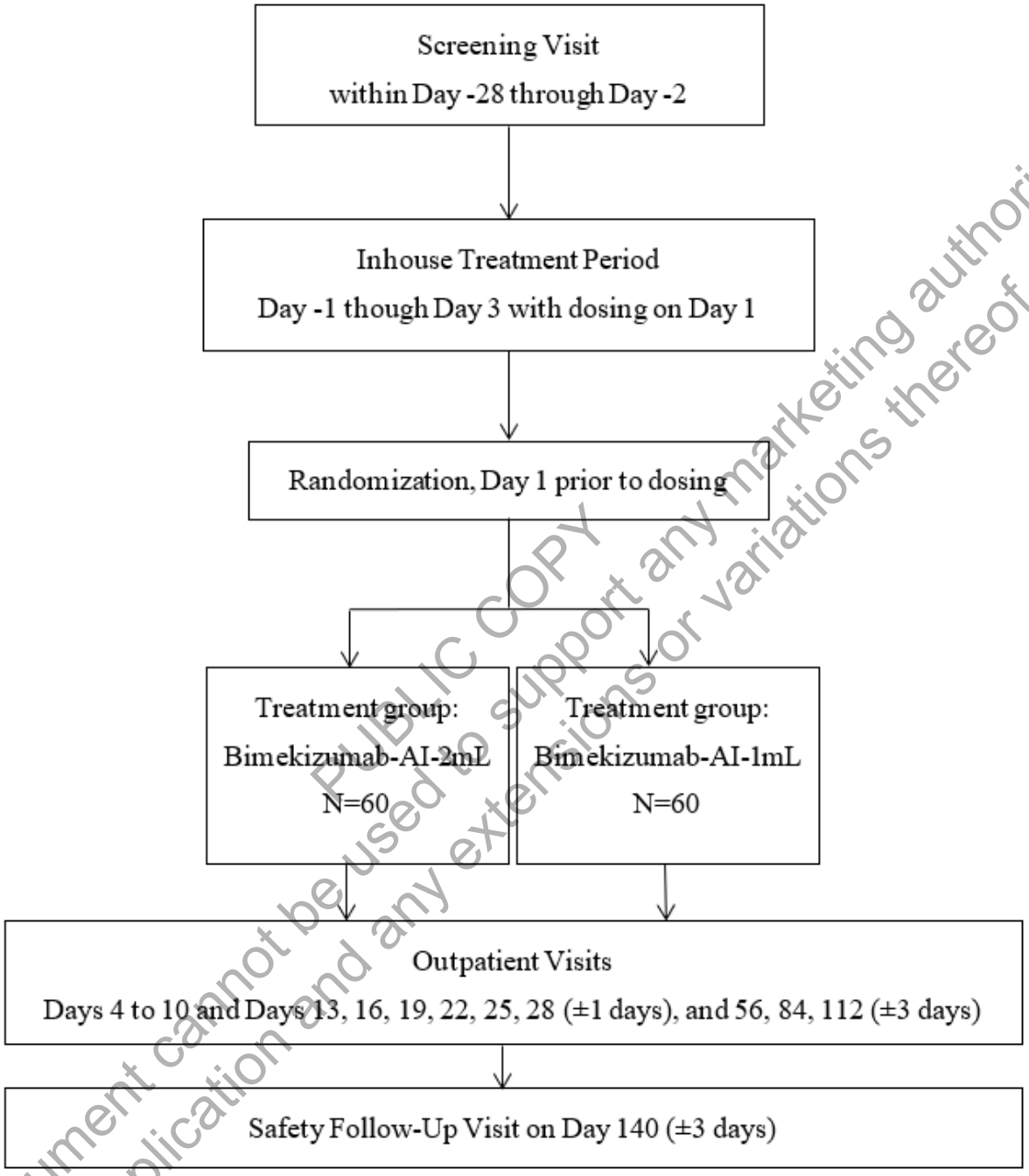
The aim of this study is to demonstrate the BE of bimekizumab administered as either 1x2mL or 2x1mL sc injections using the bimekizumab-AI presentation in healthy study participants.

Approximately 120 healthy male and female study participants will participate at a maximum of 2 sites in the study (approximately 60 study participants in each of 2 arms). Enrollment between the 2 sites will be balanced and treatments will be assigned using an approximate 1:1 ratio within each site, resulting in an approximate 1:1 ratio in the study. Each study participant will receive a single dose administration of bimekizumab 320mg, as either 1x2mL or 2x1mL sc injections.

Each eligible study participant will be matched with another participant for gender and body weight prior to randomization. The intention is that the body weights in each pair should differ by ≤10kg. Ideally, the participant's body weight at admission (Day -1) should be used for pairing. One participant within each pair will be randomly allocated to receive 1 of the 2 treatments; the other participant will be automatically allocated to the other treatment.

The duration of the study will be approximately 168 days, including 27 days of Screening, admission on Day -1, an inhouse Treatment Period from Day 1 to Day 3, Outpatients Visits until Day 112, and a Safety Follow-Up (SFU) Visit on Day 140. Randomization will occur on Day 1 prior to dosing. The schematic diagram of the study is presented in Figure 1–1.

Figure 1–1: Study Schematic



AI=auto-injector
Note: Approximately 120 study participants will participate at 2 sites in the study, 60 study participants per each site. Within each site the 60 study participants will be assigned to treatment groups in a 1:1 ratio: 30 study participants will receive bimekizumab-AI-2mL and 30 study participants will receive bimekizumab-AI-2x1mL. In addition, when assigning treatment only the first member of each pair will be randomly assigned. The treatment assignment of second member will depend on that of the first member.

The study design is deemed appropriate for conduct in healthy study participants during the COVID-19 pandemic.

2 STATISTICAL HYPOTHESES

The primary endpoint will be AUC, $AUC_{(0-t)}$, and C_{max}, and the key comparison will be for bimekizumab-AI-2mL presentation (test) versus bimekizumab-AI-2x1mL presentation. Bioequivalence will be concluded if the 90% CIs for the geometric mean ratio of the comparison is fully included in the acceptance range from 0.8 to 1.25. Please refer to Section 5.4.2.1 for details.

3 SAMPLE SIZE DETERMINATION

This is a BE study to compare the PK of bimekizumab-AI-2mL (test) versus bimekizumab-AI-2x1mL (reference).

The sample size estimation was based upon variability observed in studies UP0033 and UP0068. These were the 2 most recent studies which included the AI device with a single administration of bimekizumab in healthy study participants. The respective inter-participant variabilities (coefficient of variation [CV%]) observed in these studies were up to 32%, 33% for AUC and up to 31%, 25% for Cmax. The geometric mean ratios (GMRs) for all primary PK parameters were between 0.97 and 1.02 (UP0033) and between 1.03 and 1.15 (UP0068). The individual study CV% and GMRs are presented in Appendix 11 of the protocol.

Assuming a GMR of 1.08 (or 0.93) and inter-participant variability (CV%) of 32%, 54 study participants per group are required to assess BE with 80% power assuming that BE will be declared if the 90% CI for the GMR is contained entirely within the acceptance range (0.8, 1.25).

Sample size estimation was performed using SAS software (version 9.4).

Assuming a dropout rate and non-evaluable study participants of approximately 10%, 60 study participants per group for a total of approximately 120 study participants are to be enrolled in the study.

4 POPULATIONS FOR ANALYSIS

4.1 All Study Participants Set

The All Study Participants Set will consist of all study participants who signed the informed consent form (ICF).

4.2 Randomized Set

The Randomized Set (RS) will consist of all randomized study participants. Note: This set will only be produced if it differs from the Safety Set (SS). If RS is the same as SS then all analyses mentioned in this Statistical Analysis Plan to be performed based on the RS will be performed based on the SS.

4.3 Safety Set

The Safety Set will consist of all study participants who are randomized and receive full or partial IMP according to the treatment the participants actually received. The Safety Set will be used for summaries of demographics, medical history, prior and concomitant medications, IMP exposure, and general safety outcomes such as AEs, laboratory parameters, vital signs, and ECGs.

4.4 Pharmacokinetic Set

The Pharmacokinetic Set (PKS) will be a subset of the Safety Set, consisting of those study participants that received at least 1 total dose of IMP and have at least 1 observable concentration measurement and who have no important protocol deviations affecting the PK during the whole study phase. Partial data exclusion for PKS will be defined during the data evaluation meeting.

5 STATISTICAL ANALYSES

5.1 General Considerations

Statistical analysis and generation of tables, figures, participant data listings, and statistical output will be performed using Statistical Analysis System® (SAS®) version 9.4 or later (SAS Institute, Cary, NC, USA). All tables and listings will use Courier New font size 9.

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

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

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

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

For PK parameters other than t_{max}, summary statistics will include geometric mean (geoMean), geometric coefficient of variation (geoCV), 95% confidence intervals (CIs) for the geoMean, arithmetic mean, SD, median, min and max.

For t_{max}, summary statistics will include median, min and max.

All summaries of PK parameters will be based on the observed values. No imputation of missing data will be used. Imputation rules for PK concentration are provided in Section 5.4.1.

All results, regardless of local or central laboratory or repeated or unscheduled values, will be listed. However, only scheduled results from the central laboratory will be used in the summary statistics. In addition, if data from central laboratory is missing and meant to be presented, and a

local value is available, the local value will not be included in the summary statistics as it may be biased.

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

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

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

If participants have more than one observation for a given time point, the observation closest to the intended time point will be used. If both observations are equidistant from the intended time point, then the later value will be used.

Data listings containing all documented data and all derived data will be generated.

5.1.1 General study level definitions

5.1.1.1 Analysis Time Points

5.1.1.1.1 Relative day

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

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

Relative Day = [(Event Date – Date of sc injection)] *[1]*

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

Relative Day = [(Event Date – Date of sc injection) + 1] *[2]*

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

5.1.1.1.2 Study periods

The duration of the study for a study participant will be approximately 168 days; consisting of the following periods:

- Screening Period (Day -28 to Day -2)
- Inhouse Treatment Period (Day -1 to Day 3). Study participants will be dosed on Day 1.
- Outpatient Period (Day 4 to Day 112)
- Safety follow-up (Day 140)

A study participant is considered to have completed the study if he/she has completed all phases of the study including the Day 140 SFU Visit or the last scheduled procedure.

5.1.1.1.3 Definition of Baseline values

Baseline will be the last assessment prior to the sc injection of IMP, or if missing, the Screening value. Scheduled or unscheduled measurements can be used as the Baseline value. Expected measurement-specific Baseline time points are presented in Table 5–1. If an unscheduled measurement occurs after the planned baseline measurement time point but before injection, then the unscheduled measurement will be used.

Table 5–1: Expected Baseline Visits

Measurement	Definition of Baseline
Vital signs	Day 1, Predose value or, if missing, Day -1 value or, if both are missing, the screening value.
Body weight	Day -1 value or, if missing, the screening value.
Single 12-lead ECG	Day 1, Predose value or, if missing, Day -1 value or, if both are missing, the screening value.
Hematology (including coagulation/hemostasis)	Day -1 value or, if missing, the screening value.
Clinical Chemistry	Day -1 value or, if missing, the screening value.
Urinalysis	Day -1 value or, if missing, the screening value.
ADAb status	Day 1 Predose value

ADAb=anti-drug antibody; ECG=electrocardiogram

5.1.1.2 Handling of dropouts or missing data

In general, there will be no imputation of missing data unless stated otherwise below.

5.1.1.2.1 Pharmacokinetic concentration data

Detailed rules for PK data reporting and summaries are provided in Section 5.4.1.

Pharmacokinetic concentration data will not be available to the study team until after the last scheduled procedure for the last study participant in the study, so the decision to replace participants who dropped out or are missing PK visits can be made in an unbiased manner.

5.1.1.2.2 Safety laboratory data

Measurements BLQ will be imputed with half of the LLOQ for the purpose of calculating change and percentage change from Baseline for summaries and figures. Measurements above the limit of quantification (ALQ), if applicable, will be imputed to the upper limit of quantification.

Descriptive statistics will be calculated if at most 33% of the individual data points at a time point are missing or are either not quantifiable (<LLOQ) or ALQ. If no participants have data at a given time point, then only n=0 will be presented. If n<3, then only the n, minimum and maximum will be presented. If n=3, then only n, minimum, median and maximum will be presented. The other descriptive statistics will be reported as missing ("-").

5.1.1.2.3 Anti-drug antibody data

Detailed rules for immunogenicity data reporting and summaries are provided in Section 5.5.1.

5.1.1.2.4 Dates and times

Partial dates/times may be imputed for the following reasons:

- Classification of AEs as treatment-emergent
- Classification of medications as prior or concomitant

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

The following rules will be applied for partial start dates/times:

- If only the start month and year are specified, and these are not the same as the month and year of dosing then use the 1st of the month, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If time is missing this will be imputed as 00:00 h;
- If only the start month and year are specified, and the month and year of dosing are the same as the month and year of the start date, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use the 1st of the start month, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use the 1st of the month). If the imputed date is the date of dosing then time will be imputed as the start time of the sc injection (i.e., event will be regarded as treatment-emergent);
- If only the year is specified, and the year of dosing is not the same as the year of the start date then use January 01 of the year of the start date. If time is missing this will be imputed as 00:00 h;
- If only the year is specified, and the year of dosing is the same as the year of the start date, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the start date, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of dosing then time will be imputed as the start time of the sc injection (i.e., event will be regarded as treatment-emergent);
- If the start date is completely unknown, then use the date of dosing. If this results in an imputed start date that is after the specified end date, then use January 01 of the year of the end date, or the date of Screening if this is later (if the latter imputation results in an end date that is earlier than the start date, then use January 01). If the imputed date is the date of dosing then time will be imputed as the start time of the sc injection (i.e., event will be regarded as treatment-emergent).

Any medication with a start date on the dosing date and time unknown, will be assumed to be concomitant.

The following rules will be applied for partial stop dates:

- If only the month and year are specified, then use the last day of the month;

- If only the year is specified, then use December 31 of the known year;
- If the stop date is completely unknown, do not impute the stop date.

Missing or partially missing date and/or times will be imputed as described in Table 5–2 for the calculation of duration of each AE. Adverse event duration is computed and reported in day and time format: xx d hh:mm.

Table 5–2: Calculation rules for duration (days) of AEs (applicable also to ADEs)

Data Availability	Onset Date/Time	Outcome Date/Time	Calculation Rules
Complete data	D1/T1	D2/T2	Duration = [(D2 – D1) *24 + (T2 – T1)]/24 d
End time missing	D1/T1	D2/--	End time is substituted by time 23:59h (=23.98 in decimal format). Duration = < [(D2 – D1) *24 + (23.98 – T1)]/24 d
Start time missing	D1/--	D2/T2	Onset time is substituted by 00:00h. Duration = < [(D2 – D1) *24 + T2]/24 d
Start and end time missing	D1/--	D2/--	Duration = < (D2 – D1) + 1
Start day and time missing	--/--	D2/T2	Duration = < [(D2 – D0) *24 + (T2 – T0)] / 24 d For a participant in the SS, D0 and T0 are the date and time of dosing and for screen failures, D0 = the Screening Visit date and T0 = 0.
End day and time missing	D1/T1	--/--	For ongoing AE duration = > Discharge day – D1 d For resolved AE duration = < Discharge day – D1 d Where Discharge Day refers to the date of the SFU Visit or date of discontinuation. For any AEs with known start date/time after the date of discontinuation, the date of last contact will be used as the discharge day.
Start and end date missing	--/--	--/--	For ongoing AE duration = > Discharge day – D0 d For resolved AE duration = < Discharge day – D0 d Where Discharge Day refers to the date of the SFU Visit or date of discontinuation. For a participant in the SS, D0 is the date of dosing and for screen failures, D0 = the Screening Visit date.

ADE=Adverse Device Effect; AE = Adverse Event; SS=Safety Set

5.1.1.2.5 Impact of COVID-19

The FDA and EMA (see Section 7) have provided guidance to help assure the safety of study participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to study integrity during the COVID-19 pandemic. One of the recommendations is a risk assessment of the impact of COVID-19 on study integrity and interpretability of potential study results. In particular, the major statistical principles need to be considered regarding the impact of COVID-19 on studies and how to handle missing or delayed assessments resulting from the pandemic. The impact of the COVID-19 pandemic, at the visit level, will be assessed by data collected on a specific COVID-19 impact CRF. Any dropouts due to COVID-19 will be handled

in the same way as dropouts for other reasons. Should one of the ongoing reviews of COVID-19 related PDs (see Section 5.1.1.4) suggest that the impact of COVID-19 is more significant than expected, the SAP may be updated to include details of strategies to handle missing data and/or sensitivity analyses.

5.1.1.3 Handling of repeated and unscheduled measurements

All repeated and unscheduled measurements will be presented in the listings. Repeated and unscheduled measurements will not be used for statistical analysis or summary tables, unless the repeated measurement was performed due to technical reasons, or the repeated measurement occurred prior to IMP administration and is defined as the 'Baseline'. The following general rules will apply to all repeated and unscheduled measurements:

- For repeated measurements obtained prior to the IMP administration, the latest reported value (which may be scheduled or unscheduled) will be used in the calculation of descriptive statistics
- For repeated measurements obtained at any time point after dosing, the first reported value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics.

5.1.1.4 Protocol deviations

Important protocol deviations (IPDs) are identified as part of the data cleaning process in the Data Cleaning Plan (DCP). The objective of the data cleaning meeting will be to review and update (if necessary) the important protocol deviations in the DCP and discuss exclusion of study participants from analysis populations.

Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meetings (DEMs). Through this data cleaning and evaluation process, all decisions regarding important protocol deviations and exclusions from analysis populations will be made. Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be listed separately.

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the trial master file (TMF).

After resolution of all issues, and documentation of all decisions, the database will be locked.

5.1.1.4.1 COVID-19 related protocol deviation

UCB guidance on deviations and amendments related to SARS-CoV2 pandemic states that the identified COVID-19 related PDs need to be reviewed on an ongoing basis in case they collectively or individually may give reason to consider a protocol amendment (for example study design changes or changes to primary analysis methods etc). To facilitate this ongoing review, IPDs will be categorized as related to COVID-19 within the Clinical Trial Management System (CTMS). The COVID-19 related IPDs will be listed separately for consideration at the DEM.

5.1.1.5 Treatment assignment and treatment groups

Treatment assignment for the SS and PKS will be according to the actual treatment received.

Listings and summaries will be presented by treatment group and overall where applicable. The following order will be used in the TFLs:

- Bimekizumab-AI-2mL: Single dose sc injection, bimekizumab 1x320mg, device presentation 2mL AI
- Bimekizumab-AI-2x1mL: Single dose sc injection, bimekizumab 2x160mg, device presentation 1mL AI
- All study participants

For analysis conducted using the all study participants set, an additional group for participants not randomized may be displayed, as applicable.

5.1.1.6 Coding dictionaries

All AEs and medical history will be coded for analysis according to the Medical Dictionary for Regulatory Activities (MedDRA® 19.0) coding dictionary. Prior and concomitant medications will be coded for analysis using the World Health Organization Drug dictionary (WHO-DD Mar 2021). Medical procedures will not be coded.

5.1.1.7 Multicenter studies

This is a multicenter study with participation of at a maximum of 2 sites. In general, the data from both sites will be pooled for the purpose of the analysis. However, the effect of center on results will be evaluated in sensitivity analysis as mentioned in Section 5.4.2.3.

5.2 Participant Dispositions

Participant screening and primary reason for screen failure will be summarized using the All Study Participants Set. The summary will include the following:

- Number of participants screened
- Number and proportion of participants with screen failures (Not counting successfully rescreened participants)
- Number and proportion of screen failures by primary reason for screen failure (based on the later screening visit, in case of rescreen).

Additionally, the reasons for screen failures will be summarized by during and post the COVID-19 pandemic based on the screen failure date relative to the pandemic cut-off date.

Disposition of analysis sets will be summarized using the All Study Participants Set. The summary will include the total number of participants in the All Study Participants Set, as well as the number and percentage of participants in each analysis set by treatment group. The percentages will be calculated based on the RS.

Study completion/discontinuation and primary reason for discontinuation will be summarized by treatment group and overall using the RS. The summary will include the following:

- Number and percentage of participants that started the study
- Number and percentage of participants completing the study
- Number and percentage of participants discontinuing the study
- Number and percentage of participants discontinuing the study by primary reason for discontinuation.

Study participants that started the study are defined as participants that were randomized. Study participants completing the study are those participants completing the SFU Visit, i.e., the participant will be regarded as a completer if the SFU (Day 140) Visit was completed.

Study discontinuation due to AEs will be summarized using the RS. The summary will present the number and percentage of participants who discontinued the study due to an AE by treatment group and overall.

By-participant listings of study participant disposition will be provided by treatment group using the All Study Participants Set, and will include the following:

- Study termination/completion status
- Date of informed consent
- Date of randomization
- Date and time of study medication administration
- Date of last contact
- Date of premature study termination for successfully screened participants dropping out of the study
- Date of screen failure for screen failure participants (based on the later screening visit in case of rescreen)
- Primary reason for premature study termination, as applicable
- Primary reason for screen failure, as applicable (based on the later screening visit in case of rescreen).

By-participant listings of study discontinuation will be presented by treatment group using the RS. The listing will include the primary reason for discontinuation and the number of days since IMP administration.

By-participant listings of visit dates will be presented by treatment group using the SS.

By-participant listings of study participants who did not meet study eligibility criteria will be presented by treatment group using the All Study Participants Set. The listing will include inclusion criteria that were not met and the exclusion criteria that were met. A glossary listing of inclusion and exclusion criteria will also be provided.

By-participant listings of study participant inclusion in each analysis set will be presented by treatment group using the All Study Participants Set.

5.3 Efficacy Analyses

Efficacy is not evaluated in this study.

5.4 Pharmacokinetics and Pharmacodynamics Analyses

5.4.1 Pharmacokinetics

Unless otherwise specified, all analysis described in this section will be performed on the PKS.

5.4.1.1 Descriptive analysis of Pharmacokinetics data

Concentration Listings

Individual plasma concentrations of bimekizumab will be listed by treatment group for the SS and will include the actual and nominal PK sampling times, the corresponding time deviations and concentrations. The window allowance document will define the acceptable deviations at each timepoint; samples obtained outside this tolerance will be considered as protocol deviations. All protocol deviations will be discussed at the DEM (Section 5.1.1.4). If a concentration measurement is to be excluded from the analysis of PK parameters, it will be flagged in the listings and the reason for exclusion will be listed/footnoted.

When reporting individual data in listings the following rules will apply:

- Missing data should be reported as no value (NV)
- Concentrations below the lower limit of quantification (LLOQ) will be presented as below the limit of quantification (BLQ) in the listings and the LLOQ value presented as a footnote.
- Concentrations should be listed to the same number of significant figures supplied by the bioanalytical laboratory. Concentrations will be reported in µg/mL.

Concentration Summary Tables

Plasma concentrations of bimekizumab will be summarized by treatment group and nominal sampling time for the PKS. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, n(BLQ), arithmetic mean, SD, geometric mean, 95% CI for the geometric mean, geometric CV%, median, minimum, and maximum values.

The geoCV will be calculated using the following formula where SD is the standard deviation of the log-transformed values:

$$Geometric\ CV\ (\%) = \sqrt{(\exp(SD^2) - 1)} \times 100$$

When summarizing the data in tables the following rules will apply:

- To calculate descriptive statistics, all BLQs will be set to half the LLOQ, and the number of BLQs and non-BLQs at each scheduled time point will be reported. Also missing values should be excluded.
- When the total number of BLQ and missing values exceeds one third of the total then only minimum and maximum should be reported for this time point. Other descriptive statistics should be reported as missing ("-"). The minimum should be reported as BLQ.
- When the mean value includes one or more replaced BLQ values then a footnote should be included to say "contains one or more BLQ value replaced by half the LLOQ value".
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-").
- Blood samples for BKZ plasma concentrations collected -/+7 days from the scheduled study assessment will be excluded from the descriptive statistics.

Concentration Figures

Individual study participant plasma concentration-time profiles of bimekizumab will be displayed graphically on linear and semi-logarithmic scale for the SS. In addition, combined individual (spaghetti) plots will be displayed by treatment group with all study participants in a given treatment group overlaid on the same plot (linear and semi-logarithmic scale) for the SS.

For individual linear/linear and log/linear graphs, actual sampling times should be used and all BLQ values will be substituted as follows:

- BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero. When using log/linear scale, these timepoints will be considered missing.
- BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
- Single BLQs which fall between two measurable concentrations will be set to missing.
- Consecutive BLQs which fall between measurable concentrations will be set to missing.

When summarizing the data in figures the following rules will apply:

- The data plotted in the figure should match the data presented in the summary table (with the exception of missing values prior to C_{max} which should be set to 0 in the figure to capture lag-time).
- Geometric mean should be plotted (as opposed to arithmetic mean) due to the log-normal distribution of concentrations. Variability should be plotted as detransformed SD computed on ln-transformed data.
- Nominal sampling times should be used.
- Both linear and semi-logarithmic scales should normally be presented.
- All BLQ values will be substituted with ½ the LLOQ and displayed in the figures.

Geometric mean profiles for each treatment group with lower and upper limits of the 95% CI for the linear scale and the semilogarithmic scale will be displayed for the PKS. The plots on the linear and semilogarithmic scales will be displayed on the same page.

All figures will include a reference line for the LLOQ on the semi-logarithmic panel.

Figures will be generated in black and white using unique line style and marker for each plot in the graph. For all PK concentration-time plots, linear scale will be used for x-axis (e.g., do not use an ordinal scale).

5.4.1.2 Pharmacokinetics Parameters

PK parameters will be calculated by Non-Compartmental Analysis (NCA) methods from the concentration-time data using Phoenix® WinNonlin® Version <8.2> or higher following these guidelines:

- Actual time from dose will be used in the calculation of all derived pharmacokinetic parameters.

- There will be no imputation of missing data.
- Handling of BLQ samples for derivation of plasma PK parameters after single dose administration
    - BLQs at the beginning of a participant profile (i.e., before the first incidence of a measurable concentration) will be assigned to zero.
    - BLQs at the end of a participant profile (i.e., after the last incidence of a measurable concentration) will be set to missing.
    - Single BLQs which fall between two measurable concentrations will be set to missing.
    - Consecutive BLQs which fall between measurable concentrations will be set to missing.
- If participants withdrew early from the study the PK scientist's best knowledge will determine which PK parameters from these study participants shall be included in the statistical analysis. The impact of any excluded values will be assessed in the sensitivity analysis.

Pharmacokinetic parameters will be estimated according to the guidelines presented in Table 5–3.

Table 5–3: Pharmacokinetic Parameter and Estimation

Parameter	Guideline for Derivation
AUC_{0-t}	The AUC from zero time (pre-dose) to the time of last quantifiable concentration will be calculated by a combination of linear and logarithmic trapezoidal methods. Unless specifically requested and justified, the linear up/log down trapezoidal method will be employed. The AUC_{0-t} is the sum of areas up to the time of the last quantifiable sample: $AUC_{0-t} = \int_0^t C_{last} * dt$
AUC	The area from zero time extrapolated to infinite time will be calculated as follows: $AUC = AUC_{0-t} + \frac{C_{last}}{\lambda_z}$ where C_{last} is the last observed quantifiable concentration.
$\%AUC_{extr}$	The percentage of AUC obtained by extrapolation will be calculated as follows: $\%AUC_{extr} = \frac{AUC - AUC_{0-t}}{AUC} * 100$ Unless otherwise determined by PK Scientist's best knowledge and judgment, if the $\%AUC_{extr}$ is greater than 20% the value, $\%AUC_{extr,}$ and all dependent parameters (ie, AUC, MRT, Vz and CL) will be flagged in summary tables and will still be included in the calculation of summary statistics. The reason for flagging will be listed/footnoted in parameter summary tables.
C_{max}	Maximum concentration, obtained directly from the observed concentration versus time curve. In the case of bioequivalence studies, the FDA guidance[1] should be followed: if the predose concentration is ≤ 5 percent of the C_{max} value in that study participant, the study participant's data without any adjustments can be included in all pharmacokinetic measurements and calculations. It is recommended that if the predose value is > 5 percent of $C_{max,}$ the study participant be dropped from all bioequivalence study evaluations.

Parameter	Guideline for Derivation
CL/F	Apparent systemic clearance of parent drug will be calculated from: $$CL/F = \frac{Dose}{AUC}$$
λz	First order terminal elimination constant or apparent first order terminal elimination rate constant, for compound representing release/absorption as limiting steps 1. The apparent terminal phase rate-constant (λz) will be estimated by linear regression of concentration versus time data presented in a log-linear scale. 2. Data are primarily monotonically decreasing in magnitude and are representative of the actual decline in the log concentration-time curve. 3. Only those data points that are judged to describe the terminal log-linear decline will be used in the regression. 4. A minimum number of three data points in the terminal phase will be used in calculating λz with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope). Unless otherwise determined by PK Scientist's best knowledge and judgment or if instructed by the Sponsor, if the adjusted correlation coefficient (R2 adjusted) is <0.8, then λz and all the λz dependent parameters (i.e. t½, AUC, CL, MRT, and Vz) will be flagged in summary tables of PK parameters and will still be included in the calculation of the summary statistics. The reason for flagging will be listed/footnoted in parameter summary tables. 5. Unless otherwise determined by PK Scientist's best knowledge and judgment, the interval used to determine λz should be equal or greater than 2-fold the estimated t½, and if less than 2-fold, λz will be flagged in summary tables and statistical analysis of PK parameters and will still be included in the calculation of the summary statistics. All the derived parameters (i.e. t½, AUC, CL, MRT, and Vz) may also be flagged in summary tables of PK parameters. The reason for flagging will be listed/footnoted in parameter summary tables. 7. Best practice is to let Phoenix determine the terminal λ_z automatically. Each determination must then be checked manually. Data points may be dropped from the linear regression if the PK Scientist considers the reported values to be anomalous. Any data points so designated should remain in the PK concentration listings with a footnote and be identified in the study report with a rationale for exclusion.
t_{max}	Time of C_{max}, obtained directly from the observed concentration versus time curve [if two identical values are recorded for C_{max}, the first one will be considered t_{max}]
t½	The terminal elimination half-life will be calculated as follows: $$t_{1/2} = \frac{Ln2}{\lambda_z} = \frac{0.693}{\lambda_Z}$$
V_z/F	Apparent volume of distribution $$V_z = \frac{CL/F}{\lambda_z}$$

[1] FDA Guidance for Industry: Bioavailability and Bioequivalence – Studies for Orally Administered Drug Products – General Considerations (2003)

PK Parameter Summaries

PK parameters will be listed in summary tables by participant for the PKS.

When reporting individual data in summary tables the following rules will apply:

- Individual PK parameters should be reported to 3 significant figures.
- If a parameter cannot be calculated it should be reported as NE (not estimable ie, if input data is missing which prevents calculation).

- Based on the rules in Table 5–3, individual PK parameters in the summary tables that are flagged as unreliable will be footnoted with the reason and will be included in the calculation of the summary statistics.

Biostatistics group will consider the derived PK parameters as source data and will use this data without rounding for calculation of PK parameters summary statistics tables.

PK parameters will be summarized by treatment group for the PKS.

When summarizing the data in tables the following rules will apply:

- Tabular summaries for PK parameters will report N (number of study participants per treatment group) and n (number of study participants with non-missing values).
- For most PK parameters (ie, for continuous variables) the following descriptive statistics should be calculated: arithmetic mean, median, SD, minimum, maximum, geometric mean, geoCV and 95% CI for the geometric mean. For t_{max} (ie, for discontinuous variables) only median, minimum and maximum should be reported.
- Descriptive statistics should be reported to 4 significant figures for mean, median and SD and to 3 significant figures for all others.
- If at least two thirds of the study participants have a PK parameter reported then descriptive statistics will be calculated, otherwise only minimum and maximum will be reported for this PK parameter and all other descriptive statistics will be reported as NE (ie, not estimable).
- A minimum of 3 values are required to calculate summary statistics. If only 2 values are available, then these should be presented as the minimum and maximum with other descriptive statistics reported as missing ("-").

PK Parameter Figures

Box plots of primary PK parameters (AUC, AUC_{0-t} and C_{max}) will be generated comparing two treatment groups.

5.4.2 Statistical analysis of bioequivalence

5.4.2.1 Primary analysis

Following log_e-transformation, the primary PK parameters (AUC, $AUC_{(0-t)}$ and C_{max}) will each be evaluated according to an analysis of variance (ANOVA) model with a fixed effect term for pair and treatment.

For comparison of bimekizumab-AI-2mL (test) versus bimekizumab-AI-2x1mL (reference) treatment, the difference between the least squares means (LSMs) will be estimated and back transformed in order to obtain the GMR and associated 90% CI for the ratio. Bioequivalence will be concluded if the 90% CIs for the ratio of the comparison is fully included in the acceptance range from 0.8 (80%) to 1.25 (125%) for AUC, $AUC_{(0-t)}$, and C_{max}.

All study participants in the PKS will be included in the analysis as far as the data permit; a study participant may be included in the analysis for one or more PK parameters (i.e., if it was not possible to calculate AUC for a given participant, the participant may be included in the analysis of BE for $AUC_{(0-t)}$ and C_{max}).

The results of the BE analysis will be tabulated, including the geometric LSMs and 95% CI for treatment group, the estimated GMR and 90% CI, and CV% for the bimekizumab-AI-2mL (test) versus bimekizumab-AI-2x1mL (reference) treatment.

5.4.2.2 Secondary analysis

A similar ANOVA, as described in Section 5.4.2.1, will be performed on $\log_e$-transformed $t_{½}$ to compare elimination characteristics between treatment groups.

The point estimate and the 90% CI for the median treatment differences for t_{max} will be computed according to the Hodges-Lehmann's method.

5.4.2.3 Sensitivity analysis

The following sensitivity analyses will be performed following the same model as described for the primary analysis (Section 5.4.2.1):

1. Including main effect of site
2. Including both main effect of site and site-by-treatment interaction
3. Based on all nonpositive ADAb study participants (defined as any positive ADAb observed post-Baseline)
4. Including body weight at Day -1 as covariate
5. Corrected for measured protein content:

For compliance with Canadian Health ministry guidance, AUC and C_{max} ratio estimates and 90% CIs will be also presented as corrected for measured protein content (potency). A correction factor (CF) will be obtained as the ln-transformed ratio of the percent protein content (Reference/Test). Then, this factor will be added to the difference in LSMs to obtain, by exponentiation, the corrected AUC and C_{max} geometric mean ratios and the corresponding 90% CIs.

For a given Reference/Test, the correction factor will be calculated using the below formula:

$$CF = \ln\left(\frac{\%\ Measured\ Content\ Reference}{\%\ Measured\ Content\ Test}\right) \qquad [3]$$

The corrected ratio estimate for the PK parameter (AUC or C_{max}) is calculated using the below formula:

$$Ratio = 100 \times \exp(LSM\ difference + CF) \qquad [4]$$

Where,

$$LSM\ difference = LSM(Test) - LSM(Reference) \qquad [5]$$

The corrected 90% CI for the ratio is obtained using the below formula:

$$90\%\ CI = 100 \times \exp[(LSM\ difference + CF) \pm t_{0.05,df} \times se(LSM\ difference)] \qquad [6]$$

6. Including all excluded and available PK parameters

5.5 Immunogenicity Analyses

5.5.1 Anti-drug antibodies

Antidrug antibodies will be measured using a 3-tiered assay approach: screening assay, confirmatory assay and titration assay.

A screening cut point will be determined by the bioanalytical laboratory that will be used to determine the status of ADAb as "Positive Screen" (PS) or "Negative Screen" (NS). For samples presenting ADAb levels as PS, further confirmatory assay will be performed, and the result of which will be reported as either "Positive Immunodepletion" (PI) or "Negative Immunodepletion" (NI). Samples that are confirmed as positive (reported as PI) will be titrated, and the titer (reciprocal dilution factor including minimum required dilution [MRD]: 100) will be reported.

ADAb status at any time point:

- An ADAb status of positive (ADAb+) will be concluded for any sample with an ADAb level that is PS and PI;
- An ADAb status of negative (ADAb-) will be concluded for any sample with an ADAb level that is either NS or PS and NI;
- Missing or a non-evaluable sample will be defined as missing;

Study participant Classification:

- A study participant will be classified as having ADAb positivity at Baseline if the Day 1, Predose result is ADAb+;
- A study participant will be classified as overall positive if at least one post-Baseline measurement is ADAb+;
- A study participant will be classified as overall negative if at all post-Baseline visits the ADAb status is negative (this includes study participants who have ADAb+ results at Baseline) or only one sample is missing and all other ADAb samples are negative;
- Missing if the study participant has missed more than one ADAb sample and all other available ADAb samples are negative;
- A participant will be classified as having treatment-emergent ADAb positivity when meeting one of the following criteria:
  - The Baseline result is ADAb-, and at least one post-Baseline time point is ADAb+;
  - The Baseline result is ADAb+, and at least one post-Baseline measurement shows a 1.81-fold increase in titer from the Baseline value (the Minimum Significant Ratio [MSR] in healthy study participants).

Analysis:

Immunogenicity will be assessed through summary tables and figures and listing of individual results by study participant. All analyses will be run on the SS, unless specified otherwise. For all tabulations, percentages will be calculated based on the number of study participants with non-missing data.

- All individual participant-level ADAb results will be listed by treatment group. This will include the screening assay, confirmatory assay, and titer (if applicable). ADAb samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged.
- Number and percentage of participants with a positive and negative ADAb status will be summarized at the time of each visit and overall, separated by treatment group and for all bimekizumab treated participants.
- In addition, the first occurrence of treatment-emergent ADAb positivity (based on the definitions above) will be summarized (number and percentage of study participants) at each post-Baseline visit, based on the SS. This tabulation will present the number and percentage of study participants at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent positivity; study participants will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, study participants will be counted in the denominator (assuming a measurement is available). For all tabulations, percentages will be based on the number of observations at each visit. This summary will exclude any samples with bimekizumab concentrations confirmed to be above the drug tolerance.

A listing will be presented showing the bimekizumab concentrations and ADAb measurements in the same output in adjacent columns, based on the SS. The listing will include the bimekizumab concentration, ADAb status (positive or negative) and screening assay results (PS or NS) and confirmatory assay results if applicable (PI or NI), together with the titer if applicable. Titer values will be reported as <100 or as 100 (Minimum Required Dilution, MRD) and above in the listing. In addition, the time since the administration of study medication will be reported (in days).

5.6 Safety Analyses

Unless otherwise stated, all safety analyses will be presented for the SS.

5.6.1 Extent of Exposure

All IMP administration details (including date/time of administration), injection site (left thigh or right thigh), duration of injection (seconds) and comments reported during the administration with the medical device will be listed using the SS. In addition, a listing of batch and devices numbers used will be created using the SS.

5.6.2 Adverse Events

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded (Section 5.1.1.6) and categorized by relationship to bimekizumab.

The following definitions will be used in the analysis of AEs:

- A TEAE is defined as any event not present prior to the administration of IMP or any unresolved event already present before administration of IMP that worsens in intensity following exposure to study treatment
- An ADE is defined as an adverse event related to the use of an investigational medical device. This definition includes any adverse events resulting from insufficient or inadequate

instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

- An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. Potential Hy's Law, defined as ≥3xULN alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), confirmed by repeat measurement, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (i.e., without waiting for any additional etiologic investigations to have been concluded).

By definition, all ADEs are also classified as TEAEs.

The number and percentage of participants who experience TEAEs will be summarized by treatment group, SOC, and PT, based on the SS (unless otherwise stated).

If it is not possible (due to partial dates) to determine whether an AE is treatment emergent or not, it will be assumed to be a TEAE (Section 5.1.1.2.4).

An overview of the occurrence and incidence of TEAEs will be provided by treatment group and overall. The overview will present individual occurrences as well as number and percentage of (unique) study participants experiencing each of the following:

- TEAEs
- Serious TEAEs
- Discontinuation due to TEAEs
- Drug related TEAEs
- Severe TEAEs
- All Deaths (AEs leading to death)
- Deaths (TEAEs leading to death)
- ADEs

Summaries of the occurrence and incidence of TEAEs and SAEs will be provided by treatment group and overall. The summary will present individual occurrences as well as number and percentage of (unique) participants, by MedDRA SOC and PT. These summaries will be provided for the following:

- Incidence of TEAEs
- Incidence of serious TEAEs
- Incidence of TEAEs by maximum causal relationship with IMP
- Incidence of TEAEs by maximum intensity
- Incidence of serious TEAEs by maximum causal relationship with IMP
- Incidence of fatal TEAEs by causal relationship with IMP

- Incidence of non-serious TEAEs above threshold of 5% of participants

In summaries including intensity, the following intensity categories will be summarized: 'Mild', 'Moderate', 'Severe'. Study participants who experience the same event multiple times will be included in the most severe category for tabulations by maximum intensity. Events with missing intensity will be considered as 'Severe' events for summary purposes but recorded as missing in the listings.

In summaries including causal relationship to IMP, the following relationships will be summarized: 'Not related', 'Related'. Study participants who experience the same event multiple times will be included in the most related category for tabulations by maximum relationship. Events with missing causal relationship to IMP will be considered as 'Related' for the tabulations but presented as missing in the listings.

For the summary of non-serious TEAEs above threshold of 5% of participants, only TEAEs which are reported in 5% of participants within a treatment group will be included.

Adverse event summaries will be ordered by alphabetical SOC and decreasing frequency of PT within SOC in terms of bimekizumab-AI-2mL for tables including event counts. For tables including only number and percentage of participants, summaries will be ordered by alphabetical SOC and decreasing incidence of PT within SOC in terms of bimekizumab-AI-2mL.

A listing will be presented by treatment group and participant for all AEs. This will include the onset date/time and outcome date/time of the event (including relative days), the AE duration, pattern of event, intensity, relationship, action taken and outcome. In addition, the listing will flag TEAEs, hospitalization, SAEs, ADEs and AE of special interest. Confirmed and suspected cases of SARS-CoV-2 infection will be recorded as AEs (or SAE, as required).

5.6.3 Additional Safety Assessments

5.6.3.1 Clinical laboratory evaluations

Laboratory variables will be grouped according to the laboratory function panel (Table 5–4) and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory.

Table 5–4: Clinical laboratory measurements

Category	Panel	Variables
Serology	Serology	HbsAg, HBc-Ab (both IgG and IgM), HCV-Ab, HIV1-Ab, HIV1-Ag, HIV-2 Ab, SARS-CoV-2 RT-PCR
Hematology	Red blood cell	Hemoglobin, hematocrit, RBC
	Platelet	Platelet count
	White blood cell	WBC count

Table 5–4: Clinical laboratory measurements

Category	Panel	Variables
	White blood cell differential	Absolute counts: neutrophils, basophils, eosinophils, lymphocytes, monocytes Percentages: neutrophils/leukocytes, basophils/leukocytes, eosinophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes.
Coagulation/Hemostasis	Coagulation	Prothrombin time, aPTT
Clinical Chemistry	Electrolytes	Sodium, chloride, potassium, total calcium
	Enzymes	Creatine kinase
	Hormones	FSH
	Metabolic	Glucose
	Kidney function	BUN, creatinine
	Proteins	Total protein, albumin
	Liver function	AST, ALT, GGT, ALP, LDH, total bilirubin
	Lipids	Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides
Urinalysis	Dipstick	pH, protein, glucose, ketone, urobilinogen, bilirubin, blood, specific gravity, nitrite, and leukocytes
Other tests	Urine alcohol test/drug screen	Ethanol (measured using a urine alcohol test). Urine drug screen: amphetamines/methamphetamines, barbiturates, benzodiazepines, tetrahydrocannabinol, cocaine, tricyclic antidepressants, phencyclidine, and morphine/opiates
	Pregnancy	Prior to dosing, a serum pregnancy test (hCG) will be performed; post dosing the test may be performed in urine. The FSH test will be performed in postmenopausal women at the Screening Visit.

Table 5–4: Clinical laboratory measurements

Category	Panel	Variables

ALP=alkaline phosphatase; ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle stimulating hormone; GGT=gamma glutamyl transferase; HBc-Ab=hepatitis B core antibody; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HCV-Ab=hepatitis C virus antibody; HDL=high density lipoprotein; HIV=human immunodeficiency virus; HIV1/2-Ab=HIV1/2 antibody; HIV1-Ag=HIV1 antigen; LDH=lactate dehydrogenase; IgG=immunoglobulin G; IgM=immunoglobulin M; LDL=low density lipoprotein; RBC=red blood cell; RT-PCR=real-time reverse transcriptase polymerase chain reaction; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; WBC=white blood cell

For hematology, coagulation/hemostasis, clinical chemistry and urinalysis laboratory variables the following summaries will be presented by treatment group:

- Observed results and change from Baseline for numeric variables at each post-Baseline time point. These summaries will report the number of participants with non-missing values, mean, SD, median, minimum and maximum.
- Shift tables from Baseline to each post-Baseline time point. These summaries will present a cross-tabulation of Baseline values against post-Baseline values categorized as below normal range, within normal range and above normal range. Each cell will include the corresponding number and percentage of participants. These summaries will be presented for Hematology and Clinical Chemistry variables in Table 5–4.

The above-mentioned laboratory variables and change from Baseline for numeric variables will be listed for the SS by treatment group and time point. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 5.1.1.2.2. Values outside the normal ranges will be flagged and the listings will present reference ranges. Additionally, laboratory results outside reference ranges will be listed by treatment group and time point for the SS.

Data for the following will only be listed using the SS by treatment group and time point:

- Serology
- Urine alcohol test/drug screen
- Pregnancy tests (serum and urine)
- Follicle stimulating hormone (FSH) (only for postmenopausal women).

5.6.3.1.1 Potential drug-induced liver injury

A separate listing will present participants who meet one or more of the following potential drug induced liver injury (PDILI) criteria at any visit:

- Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) ≥3x Upper limit of normal (ULN) and Total bilirubin <2x ULN who do not exhibit temporally associated symptoms of hepatitis or hypersensitivity
- ALT or AST ≥3x ULN and Total bilirubin ≥2x ULN
- ALT or AST ≥3x ULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity

Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The listing will display only visits for which at least one of the above criteria was fulfilled for a given study participant and will display all results obtained at that visit for the specified parameters.

A summary of study participants who met the criteria for PDILI will be presented together with any additional relevant data collected, if applicable.

5.6.3.2 Vital Signs

The following vital signs measurements will be obtained:

- Pulse rate
- Systolic and diastolic blood pressure
- Tympanic body temperature
- Weight

Descriptive statistics will be reported for the above vital sign measurements. Measured values and changes from Baseline will be summarized by vital sign variable and time point for each treatment group. These summaries will be presented for the SS.

By-participant listings of all vital sign measurements and change from Baseline will be presented by treatment group and time point for the SS. The listing will also flag abnormal absolute values as per Table 5–5.

Table 5–5: Reference ranges for vital signs

Variable	Unit	Low	High
Systolic blood pressure	mmHg	Value <90	Value >140
Diastolic blood pressure	mmHg	Value <50	Value >90
Pulse rate	beats/min	Value <45	Value >90
Temperature	°C	Value <35	Value >37.5
Weight	kg	Change from Baseline <=-10%	Change from Baseline >=10%

5.6.3.3 Electrocardiograms

Single 12-lead ECG recordings will be taken prior blood sampling and with the study participant resting in the supine position for at least 3 minutes. The following variables will be reported:

- Heart rate
- PR interval
- RR interval
- QRS duration
- QT interval

- QT corrected for heart rate using Fridericia's formula ($QTcF = QT/RR^{1/3}$)

The results of all ECG variables will be reported in the by-participant listings for the SS. The listing will also include the change from Baseline and percentage change from Baseline and will be presented by treatment group and visit/timepoint.

Measured values, changes from Baseline, and percentage changes from Baseline will be summarized for the SS for each variable by treatment group and visit/timepoint.

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

Raw QTcF data:

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

Change from Baseline QTcF:

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

Electrocardiogram findings will be listed separately.

5.6.3.4 Physical examinations

Study participants with abnormalities in the physical examination will be listed including details of the abnormality.

5.7 Other Analyses

A listing of comments will be provided, if applicable. This will be based on the RS.

5.8 Subgroup Analyses

Not applicable.

5.9 Interim Analyses

No formal interim analysis is planned for this study.

5.10 Data Monitoring Committee (DMC) or Other Review Board

Not applicable.

6 SUPPORTING DOCUMENTATION

6.1 Appendix 1: Non-key analysis specifications

6.1.1 Baseline characteristics and demographics

6.1.1.1 Demographics

Baseline demographic variables will be summarized by treatment group and overall using the RS and SS.

The following continuous variables will be summarized using descriptive statistics:

- Age (years), as recorded in the electronic Case Report Form (eCRF) (will not be derived)
- Height (cm)
- Weight at screening (kg) (at Screening, Day -1 and Day 140)
- Body Mass Index (BMI) (kg/m^2)

The BMI value collected in the eCRF at Screening will not be used for this summary. The BMI will be recalculated based on weight at Day -1 using the following formula and reported to 1 decimal place:

$$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{(Height\ (m))^2} \qquad [7]$$

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

- For the EudraCT reporting, the age categories will include:
  - 18 - < 65 years
  - 65 - < 85 years
  - ≥ 85 years
- For the clinicaltrials.gov reporting, the age categories will include:
  - ≤18 years
  - 19 to <65 years
  - ≥65 years
- Gender
- Race
- Ethnicity

By-participant listings of demographic data will be provided by treatment group using the All Study Participants Set. This will include age (years), gender, race and ethnicity, height (cm), weight at Screening (kg), weight at Day -1 (kg), weight at Day 140 (kg), BMI (kg/m^2) based on weight at Screening, and BMI (kg/m^2) based on weight at Day -1.

By-participant listings of childbearing potential information will be provided by treatment group using the All Study Participants Set.

6.1.1.2 Other Baseline characteristics

Lifestyle will be summarized by treatment group and overall using the SS. The following categorical variables will be summarized using frequency counts and percentages:

- Alcohol use (Never, Current, Former)
- Caffeinated beverages use (Never, Current, Former)
- Tobacco use (Never, Current, Former)
- Illicit drug use (Never, Current, Former).

By-participant listings of lifestyle data will be provided by treatment group for the All Study Participants Set. In addition to the items presented above, the listing will include stop date of tobacco use (or ongoing, as applicable) and illicit drug use.

6.1.2 Important protocol deviations

IPDs will be identified and classified by the deviation types listed in the IPD specification document.

IPDs will be summarized by treatment group and overall using the RS. The summary will include the following:

- Number and percentage of participants with no IPDs
- Number and percentage of participants with at least one IPD
- Number and percentage of participants by type of IPD

By-participant listings of IPDs as identified in the DEMs will be provided by treatment group using the RS. This will include deviation type, deviation description, and whether the deviation led to exclusion from the PKS. Similar listings and tables will be produced for IPDs related to COVID-19.

6.1.3 Impact of COVID-19 on study visits

A listing of visits impacted by COVID-19 will be presented for all study participants based on the All Study Participants Set. This will include visit, visit date, relative day, impact category, relationship to COVID-19 and the narrative of the event. The number and percentage of study participants with visits impacted by COVID-19 will be summarized for treatment group for relationship to COVID-19 and impact category by country. The denominator for the percentages will be the number of study participants in the All Study Participants Set.

6.1.4 Medical history and concomitant diseases

Previous and ongoing medical history conditions will be summarized by treatment group and overall using the SS. The summary will include the following:

- Number and percentage of participants with any previous and ongoing medical history conditions.

- Number and percentage of participants with previous and ongoing medical history conditions by MedDRA system organ class (SOC) and preferred term (PT).

By-participant listings of previous and ongoing medical history conditions will be provided by treatment group for the SS. This will include MedDRA SOC and PT, reported condition, start date and stop date (or status ongoing, as applicable).

By-participant listings of procedure history and concomitant medical procedures will be provided, by treatment group for the All Study Participants Set. This will include reported procedure term and procedure date.

6.1.5 Prior and concomitant medications

6.1.5.1 Definitions of prior and concomitant medications

If a participant takes a medication before the date of study medication administration, this medication will be categorized as 'prior medication'. With this definition, any medication recorded that has been taken for at least 1 day before the date of study medication administration will be considered as prior. This includes medications that started prior to study medication administration and continued after.

Medication not stopped before the date of study medication administration will be classified as 'concomitant medication'. Medication will also be labeled as 'concomitant medication' when the start date is between the date (including the date) of study medication administration and the date of the participant's last study visit.

From the definitions above, any medication that started prior to dosing and continued after dosing will be classified as both prior and concomitant.

Any medications with missing dates and/or times will be handled as described in Section 5.1.1.2.4 in order to classify them as prior or concomitant.

6.1.5.2 Presentation of prior and concomitant medications data

Prior and concomitant medications will be summarized by treatment group and overall using the SS. The summary will include the following:

- Number and percentage of participants with any prior medications.
- Number and percentage of participants with prior medications by ATC class, presenting WHO-DD Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC Level 3), and preferred term.
- Number and percentage of participants with any concomitant medications.
- Number and percentage of participants with concomitant medications by ATC class, presenting WHO-DD Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC Level 3), and preferred term.

By-participant listings of prior and concomitant medications will be provided by treatment group for the SS. This will include Anatomical Main Group, Pharmacological Subgroup, preferred term, reported term, dose per intake and unit, frequency, formulation, route, indication, category (prior/concomitant/prior and concomitant), start date and end date (or ongoing, as applicable).

6.1.6 Compliance

As this is a single dose study and dosing is performed in-house by the investigator or member of staff, no specific assessment or compliance is warranted. Any dosing deviation will be addressed in the DEM and described in the CSR.

6.2 Appendix 2: Changes to Protocol-Planned Analyses

Not applicable.

7 REFERENCES

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