# STATISTICAL ANALYSIS PLAN

## Study: UP0068

## Product: Bimekizumab

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

| SAP/Amendment Number | Date |
|---|---|
| Final SAP | 17 Nov 2020 |

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| | |
|---|---|
| $\%AUC_{ex}$ | percentage of the AUC extrapolated from $C_{last}$ |
| ACP | above the cut point |
| 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 |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the plasma concentration-time curve from time zero to infinity. |
| $\%AUC_{ex}$ | percentage of the AUC extrapolated from $C_{last}$ |
| $AUC_{0-t}$ | area under the plasma concentration-time curve from time zero to last quantifiable concentration. |
| BCP | below the cut-point |
| 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 will be calculated as dose/AUC |
| $C_{max}$ | maximum observed plasma drug concentration |
| COVID-19 | coronavirus disease 2019 |
| CP | confirmed positive |
| CRO | contract research organization |
| CSR | clinical study report |
| CV% | between subject variability |
| DCP | data cleaning plan |
| DEM | data evaluation meeting |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| EMA | European Medicines Agency |
| ES | enrolled set |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FAS | full analysis set |

| | |
|---|---|
| FDA | Food and Drug Administration |
| FSH | follicle stimulating hormone |
| geoCV | geometric coefficient of variation |
| geoMean | geometric mean |
| GGT | gamma glutamyl transferase |
| HbA1c | glycosylated hemoglobin |
| 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 |
| 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 |
| max | maximum |
| MedDRA | Medical Dictionary for Regulatory Activities |
| min | minimum |
| n | number of participants with available measurements |
| NCP | not confirmed positive |
| PDILI | potential drug-induced liver injury |
| PK | pharmacokinetic |
| PKCS | Pharmacokinetic Concentration Set |
| PK-PPS | pharmacokinetic per protocol set |
| PT | preferred term |
| QTcF | QT corrected for heart rate using Fridericia's formula |
| RBC | red blood cell |
| RS | randomized set |
| RT-PCR | real-time reverse transcriptase polymerase chain reaction |
| SADE | serious adverse device effect |
| 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 syringe |
| 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 will be calculated as CL/λz |
| WBC | white blood cell |
| WHO-DD | World Health Organization Drug Dictionary |
| $\lambda_z$ | apparent terminal elimination rate constant |

# 1 INTRODUCTION

Bimekizumab 320mg is currently administered as 2x1mL subcutaneous (sc) injections of 160mg (the dose being assessed in the Phase 3 psoriasis studies). To provide additional options to healthcare professionals and patients, it is considered of benefit (by UCB) to develop 320mg bimekizumab device presentations (i.e., secondary functional packaging) where the dose can be delivered as a single 2mL sc injection. Study UP0068 aims to compare the pharmacokinetics (PK) of bimekizumab 320mg when administered sc using a 2mL safety syringe (SS; bimekizumab-SS-2mL, test 1) versus 2x1mL safety syringe (bimekizumab-SS-2x1mL, reference 1) or when administered sc using a 2mL auto-injector (AI; bimekizumab-AI-2mL, test 2) versus 2x1mL auto-injector (bimekizumab-AI-2x1mL, reference 2) to support the development of the 2mL SS and AI presentations.

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required statistical analyses of study UP0068. 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 the original study protocol amendment 1, dated 24 Jul 2020.

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 Harmonization (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.

# 2 PROTOCOL SUMMARY

## 2.1 Study objectives

### 2.1.1 Primary objective

The primary objective of the study is:

- To compare the PK of bimekizumab 320mg when administered sc using the bimekizumab-SS-2mL presentation (test 1) versus the bimekizumab-SS-2x1mL presentation (reference 1) or the bimekizumab-AI-2mL presentation (test 2) versus the bimekizumab-AI-2x1mL presentation (reference 2) in healthy study participants

### 2.1.2 Secondary objectives

The secondary objectives of the study are:

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

### 2.1.3 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-SS-2x1mL, bimekizumab-SS-2mL, 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-SS-2x1mL, bimekizumab-SS-2mL, 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-SS-2x1mL, bimekizumab-SS-2mL, bimekizumab-AI-2x1mL or bimekizumab-AI-2mL presentation in healthy study participants

## 2.2 Study variables

### 2.2.1 Pharmacokinetic variables

The PK parameters provided in this section will be derived from the plasma concentration data.

#### 2.2.1.1 Primary pharmacokinetic variables

The primary PK parameters are:

- AUC: Area under the plasma concentration-time curve from time zero to infinity, calculated as calculated as $AUC=AUC_t+C_{last}/\lambda_z$, where $C_{last}$ is the last observed quantifiable plasma drug concentration and $\lambda_z$ is the apparent terminal elimination rate constant
- $AUC_{(0-t)}$: Area under the plasma concentration-time curve from time zero to the last quantifiable concentration, as determined using the linear trapezoidal rule
- $C_{max}$: Maximum observed plasma drug concentration

#### 2.2.1.2 Secondary pharmacokinetic variables

The secondary PK parameters are:

- $t_{½}$: Apparent terminal half-life, reported in units of days, as determined via simple linear regression (slope=$-\lambda_z$) of natural log (ln) concentration vs time for data points in the terminal phase of the concentration-time curve. $t_{½}$ is calculated as $ln_2/\lambda_z$
- $t_{max}$: Time to occurrence of $C_{max}$

#### 2.2.1.3 Other/Exploratory pharmacokinetic variables

The other/exploratory PK parameters are:

- $\%AUC_{ex}$: Percentage of the AUC extrapolated from $C_{last}$
- CL/F: Apparent total body clearance after sc administration, calculated as Dose/AUC
- $V_z/F$: Apparent volume of distribution, calculated as $CL/\lambda_z$

### 2.2.2 Safety variables

#### 2.2.2.1 Secondary safety variables

The secondary safety and tolerability endpoints are:

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

#### 2.2.2.2 Other/Exploratory safety variables

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

### 2.2.3 Immunogenicity variable

#### 2.2.3.1 Other/Exploratory immunogenicity variable

The other/exploratory immunogenicity endpoint is:

- Incidence of bimekizumab antidrug antibodies (ADAbs)

## 2.3 Study design and conduct

This is a Phase 1, open-label, single-center, randomized, parallel-group, single-dose, 4-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. The SS and AI device presentations will be assessed. The 4 arms will be:

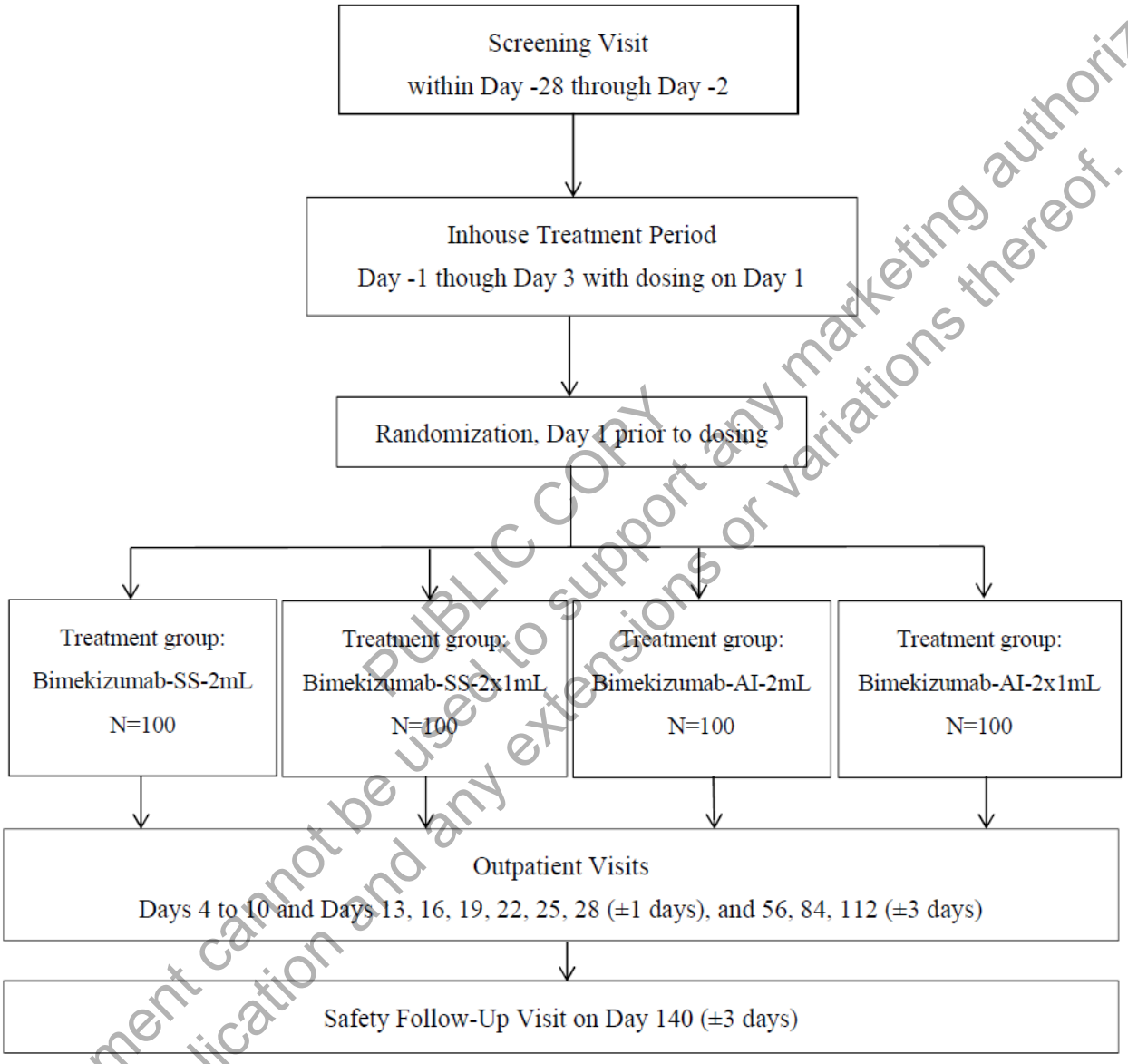
1. bimekizumab-SS-2mL (test 1)
2. bimekizumab-SS-2x1mL (reference 1)
3. bimekizumab-AI-2mL (test 2)
4. bimekizumab-AI-2x1mL (reference 2)

Two independent comparisons will be made: test 1 versus reference 1 and test 2 versus reference 2.

Four hundred healthy male and female study participants will participate in the study (approximately 100 study participants in each of 4 arms). Each study participant will receive a single-dose administration of bimekizumab 320mg. 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 2–1.

**Figure 2–1: Study Schematic**




AI=auto-injector; SS=safety syringe

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

## 2.4 Determination of sample size

This is a formal BE study to compare the PK of bimekizumab-SS-2mL (test 1) versus bimekizumab-SS-2x1mL (reference 1), and bimekizumab-AI-2mL (test 2) versus bimekizumab-

AI-2x1mL (reference 2). Two independent comparisons will be made (i.e., test 1 versus reference 1 and test 2 versus reference 2).

The between subject variability (CV%) observed in previous small studies following a single dose administration of bimekizumab in healthy study participants (i.e., UP0031, RA0124, UP0033, and UP0074) was 21% to 25% for AUC and 23% to 33% for Cmax.

Assuming a geometric mean ratio of 0.9 between each pair of formulations and a between subject variability (CV%) of 33%, 93 study participants per group are required to assess BE (using an acceptance range of 0.8 to 1.25) with 80% power at the 5% significance level. If the true mean ratio between each pair of formulations is 0.95, then with the same assumptions on variability and significance level there is >95% power to determine BE for that pair of formulations.

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

Assuming a dropout rate and non-evaluable study participants of approximately 10%, 100 study participants per group for a total of 400 study participants are to be enrolled in the study. If this 10% rate is likely to be exceeded, due to unforeseen circumstances during the COVID-19 pandemic, then participants may be replaced.

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 General presentation of summaries and analyses

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 variables will be based on the observed values. No imputation will be used.

Whenever the same data are reported both locally and via the central laboratory, analysis will be based on centrally analyzed data.

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.

## 3.2 General study level definitions

### 3.2.1 Analysis time points

Relative day for an event will be derived with the date of the sc injection of study drug as reference.

Relative days for an event or measurement occurring before the date of the sc injection of study drug 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 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.

### 3.2.2 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). Subjects 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.

## 3.3 Definition of Baseline values

Baseline will be the last assessment prior to the sc injection of study drug, 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 3–1. If an unscheduled measurement occurs after the planned baseline measurement time point but before injection, then the unscheduled measurement will be used.

**Table 3–1: Expected Baseline Visits**

| Measurement | Definition of Baseline |
|---|---|
| Vital signs | Day 1, Pre-dose 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, Pre-dose 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 Pre-dose value |

ADAb=anti-drug antibody; ECG=electrocardiogram

## 3.4 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.

### 3.4.1 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.

## 3.5 Analysis sets

### 3.5.1 Enrolled Set

The Enrolled Set (ES) will consist of all study participants who signed the informed consent form (ICF).

### 3.5.2 Randomized Set

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

### 3.5.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized study participants who received full or partial Investigational Medicinal Product (IMP) according to the treatment the study participants actually received. The FAS will be used for summaries of demographics, medical history, prior and concomitant medications, IMP exposure, and general safety outcomes such as adverse events (AEs), laboratory parameters, vital signs, and ECGs.

### 3.5.4 Pharmacokinetic Concentration Set

The PK Concentration Set (PKCS) will be a subset of the FAS, consisting of those study participants that received at least 1 dose of IMP and have at least 1 reported plasma concentration. All participants in the PKCS will be included in the listings. Participants with no protocol deviations to impact observed concentrations will be included in summary tables and figures of concentration-time profiles.

### 3.5.5 Pharmacokinetic Per-Protocol Set

The PK Per-Protocol Set (PK-PPS) will be a subset of the FAS, consisting of those study participants who had no important protocol deviations affecting the PK variables and for whom a sufficient number of samples are available to determine at least 1 PK parameter. This analysis set will be used for all summaries and analyses of the PK parameters.

## 3.6 Treatment assignment and treatment groups

Treatment assignment for the FAS and PK-PPS 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-SS-2mL: Single dose sc injection, bimekizumab 1x320mg, device presentation 2mL SS
- Bimekizumab-SS-2x1mL: Single dose sc injection, bimekizumab 2x160mg, device presentation 1mL SS
- 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 ES, an additional group for participants not randomized may be displayed, as applicable.

### 3.7 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, using the latest MedDRA version available. Prior and concomitant medications will be coded for analysis using the latest version of the World Health Organization Drug dictionary (WHO-DD Sep 2015). Medical procedures will not be coded.

### 3.8 Changes to protocol-defined analyses

None.

## 4 STATISTICAL/ANALYTICAL ISSUES

### 4.1 Adjustments for covariates

There are no planned analyses including adjustments for covariates.

### 4.2 Handling of dropouts or missing data

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

#### 4.2.1 Pharmacokinetic concentration data

Measurements that are BLQ will be imputed with half of the LLOQ for the purpose of calculating the geoMean and its 95% CI, the geoCV, the arithmetic mean, and SD for summaries and figures. If any summary value (geoMean, arithmetic mean, lower CI level or minimum) is lower than LLOQ, then 'BLQ' will be displayed.

For the individual figures, any concentrations that are BLQ will be regarded as missing, with the exception of pre-dose measurements BLQ on Day 1, which will be imputed with zero for linear scale plots.

Additional rules for PK data summaries are provided in Section 9.1.1.

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 due to COVID-19 can be made in an unbiased manner.

### 4.2.2 Safety laboratory data

Measurements below the limit of quantification (BLQ) will be imputed with half of the lower limit of quantification (LLOQ) for the purpose of calculating change 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 left blank.

### 4.2.3 Anti-drug antibody data

Levels of ADAb that are BLQ will be regarded as missing for all individual ADAb figures.

### 4.2.4 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 4-1 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 4-1: 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).<br>Duration = < [(D2 – D1) *24 + (23.98 – T1)]/24 d |
| Start time missing | D1/-- | D2/T2 | Onset time is substituted by 00:00h.<br>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<br>For a participant in the FAS, D0 and T0 are the date and time of dosing and for screen failures, D0 = the Screening Visit date and T0 = 0. |

**Table 4-1: Calculation rules for duration (days) of AEs (applicable also to ADEs)**

| Data Availability | Onset Date/Time | Outcome Date/Time | Calculation Rules |
|---|---|---|---|
| End day and time missing | D1/T1 | --/-- | For ongoing AE duration = > Discharge day – D1 d<br>For resolved AE duration = < Discharge day – D1 d<br>Where Discharge Day refers to the date of the SFU visit or date of discontinuation.<br>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<br>For resolved AE duration = < Discharge day – D0 d<br>Where Discharge Day refers to the date of the Safety<br>Follow-Up visit or date of discontinuation.<br>For a participant in the FAS, D0 is the date of dosing and for screen failures, D0 = the screening visit date. |

ADE=Adverse Device Effect; AE = Adverse Event; FAS=Full Analysis Set

### 4.2.5 Impact Of COVID 19

The FDA and EMA (see REFERENCES) 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. At the time of writing, the impact of the pandemic is still evolving and regulators continue to clarify their position. 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 that need to be consider when considering 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. Drop outs due to COVID-19 will be handled in the same way as drop out for other reasons. Should one of the ongoing reviews of COVID-19 related PDs (see Section 3.4) suggest that the impact of COVID-19 is more significant than expected e.g. in the case of a second wave, the SAP may be updated to include details of strategies to handle missing data and/or sensitivity analyses.

## 4.3 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 unreliable values/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 reliable 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 reliable value of any repeated measurements will be used in the calculation of changes from Baseline and for the descriptive statistics.

## 4.4 Interim analyses and data monitoring

No formal interim analysis is planned for this study.

Two DEMs will be performed for this study prior to the final analysis. The purpose of these DEM reviews will be to review all protocol deviations, define the analysis sets as defined in Section 3.5 and check the quality of the data. The reviews will also help decide how to manage problems in the participants' data (e.g. missing values and withdrawals).

Accepted deviations from planned time points will be described in the appropriate documents and included in the Study Master File. After the pre-analysis review, resolution of all issues, and documentation of all decisions (including inclusion into each of the analysis sets) at the final DEM, the database will be locked.

# 5 STUDY POPULATION CHARACTERISTICS

## 5.1 Subject disposition

Participant screening and primary reason for screen failure will be summarized using the ES. The summary will include the following:

- Number of participants screened
- Number and proportion of participants rescreened
- 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).

Disposition of analysis sets will be summarized using the ES. The summary will include the total number of participants in the ES, 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.

Participants that started the study are defined as participants that were randomized. 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 AE of the by treatment group and overall.

By-participant listings of participant disposition will be provided by treatment group using the ES, 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 study medication administration.

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

By-participant listings of participant who did not meet study eligibility criteria will be presented by treatment group, using the ES. 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 participant inclusion in each analysis set will be presented by treatment group, using the ES.

## 5.2 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 protocol deviation

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 PK-PPS. Similar listings and tables will be produced for IPDs related to COVID-19.

### 5.3 Impact COVID-19 on study visits

A listing of visits impacted by COVID-19 will be presented for all participants based on the ES. 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 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 participants in the ES.

## 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

### 6.1 Demographics

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

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 (m)
- Weight at screening (kg) (at Screening and at Admission [Day -1])
- Body Mass Index (BMI) (kg/m$^2$)

The BMI value collected in the eCRF will not be used for this summary. The BMI will be recalculated using the following formula and reported to 1 decimal place:

$$BMI\ (kg/m^2) = \frac{Weight\ (kg)}{(Height\ (m))^2} \qquad [3]$$

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
- Sex

- Race
- Ethnicity

By-participant listings of demographic data will be provided by treatment group using the ES. This will include year of birth, age (years), sex, race and ethnicity, height (m), weight at screening (kg), weight at admission (kg), and BMI ($kg/m^2$).

By-participant listings of childbearing potential information will be provided by treatment group using the ES.

## 6.2 Other Baseline characteristics

Lifestyle will be summarized by treatment group and overall using the FAS. 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).

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

## 6.3 Medical history and concomitant diseases

Previous and ongoing medical history conditions will be summarized by treatment group and overall using the FAS. 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 FAS. 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 ES. This will include reported procedure term and procedure date.

## 6.4 Prior and concomitant medications

### 6.4.1 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 4.2.4 in order to classify them as prior or concomitant.

### 6.4.2 Presentation of prior and concomitant medications data

Prior and concomitant medications will be summarized by treatment group and overall using the FAS. 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 FAS. 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).

# 7 MEASUREMENTS OF TREATMENT 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.

# 8 EFFICACY ANALYSES

Efficacy is not evaluated in this study.

# 9 PHARMACOKINETICS AND PHARMACODYNAMICS

## 9.1 Pharmacokinetics

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

### 9.1.1 Descriptive analysis of Pharmacokinetics data

Individual plasma concentrations of bimekizumab will be listed by treatment group for the FAS and will include the actual and nominal sampling times and the corresponding time deviations. 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 and any exclusion from analysis will be documented accordingly (Section 3.4).

Plasma concentrations of bimekizumab will be summarized by treatment group and nominal sampling time. This will include number of participants, arithmetic mean, median, SD, minimum, maximum, geometric mean and geometric CV and 95% CI for the geometric mean (assuming log-normally distributed data).

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

Geometric mean profiles with lower and upper limits of the 95% CI for the linear scale and without confidence limits for the semilogarithmic scale will be displayed. The mean plots will be displayed on the same graph.

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

The following PK parameters (see definitions in Section 2.2.1) will be derived from the plasma concentrations of bimekizumab:

- Primary PK parameters
  - AUC, $AUC_{(0\text{-}t)}$, $C_{max}$
- Secondary PK parameters
  - $t_{½}$, $t_{max}$
- Other/Exploratory PK parameters
  - $\%AUC_{ex}$
  - CL/F
  - $V_z$/F

For calculation of the PK variables, the actual sampling times will be used.

All PK variables will be listed and summarized by treatment group for the PK-PPS including number of participants, arithmetic mean, median, SD, minimum, maximum, geometric mean, geoCV and 95% CI for the geometric mean.

The following rules will apply for the PK data summaries:

- Values below the LLOQ will be reported as BLQ for individual data and will be substituted with LLOQ/2 for the descriptive statistics
- Descriptive statistics of PK concentrations will be calculated only if at least ⅔ of the individual data at a specific sampling timepoint are measured and are quantifiable (i.e., above LLOQ) and if $n \geq 4$. If $n < 3$, then only n, minimum and maximum will be presented and if n=3, then only n, median, minimum and maximum will be presented and the other descriptive statistics will be left blank

- Descriptive statistics of PK parameters will be calculated only if at least ⅔ of the individual data are calculable and if n≥4. If n<3, then only n, minimum and maximum will be presented and if n=3, then only n, median, minimum and maximum will be presented and the other descriptive statistics will be left blank. For $t_{max}$, only n, median, minimum and maximum will be presented
- If no participant has data, only n=0 will be presented
- The 95% lower and upper CI should be left blank if the SD (or equivalently the geoCV) is equal to 0
- The geoCV will be calculated using the following formula where SD is the standard deviation of the log-transformed values:

$$Geometric\ CV\ (\%) = \sqrt{(\exp(SD^2) - 1)}\ \text{x}\ 100 \qquad [3]$$

## 9.2 Statistical analysis of bioequivalence

### 9.2.1 Primary analysis

The primary PK parameters (AUC, $AUC_{(0\text{-}t)}$ and $C_{max}$) will be evaluated according to a univariate model of analysis of variance (ANOVA). The model will include treatment group as a fixed effect. The dependent variables will be logarithmically transformed by natural logarithms (ln) prior to analysis.

Two independent comparisons will be made:

- Test 1: Bimekizumab-SS-2mL versus Reference 1: Bimekizumab-SS-2x1mL
- Test 2: Bimekizumab-AI-2mL versus Reference 2: Bimekizumab-AI-2x1mL

For each comparison, the difference between the least squares means (LSM) will be estimated and back transformed in order to obtain the geometric mean ratio for the corresponding Test/Reference together with the 90% CI for the ratio.

For each of the respective comparisons, BE will be concluded if the 90% CIs for the ratio of the respective comparison are fully included in the acceptance range from 0.8 to 1.25 for AUC, $AUC_{(0\text{-}t)}$ and $C_{max}$.

All participants in the PK-PPS will be included in the analysis as far as the data permit; a participant may be included in the analysis for one or more PK variables (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 $AUC_{(0\text{-}t)}$ and $C_{max}$).

The results of the BE analysis will be tabulated, for each comparison, including the geometric least squares means and 90% CI for treatment group, the estimated geometric mean ratio and 90% CI for the corresponding Test/Reference as well as the CV%.

### 9.2.2 Secondary analysis

A similar ANOVA, as described in Section 9.2.1, will be performed on log-transformed t½ to compare elimination characteristics between treatment groups (i.e., Test 1 versus Reference 1 and Test 2 versus Reference 2).

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.

### 9.2.3 Sensitivity analysis

The following sensitivity analyses will be performed following the same model as described for the primary analysis (Section 9.2.1):

1. Based on all nonpositive ADAb participants (Defined as any positive ADAb observed post baseline)
2. Including body weight at Day -1 as covariate
3. 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 its 90 % CIs.

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

$$CF = 100 \times \exp\left(\frac{\%\ Measured\ Content\ Reference}{\%\ Measured\ Content\ Test}\right) \quad [4]$$

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

$$Ratio = 100 \times \exp(LSM\ difference + CF) \quad [5]$$

Where,

$$LSM\ difference = LSM(Test) - LSM(Reference) \quad [6]$$

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

$$90\%\ CI = 100 \times \exp[(LSM\ difference + CF) \pm t_{0.05,n} \times se(LSM\ difference)] \quad [7]$$

# 10 IMMUNOGECITY ANALYSIS

## 10.1 Anti-drug antibodies

ADAb 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 above the cut point (ACP) or below the cut point (BCP). Samples presenting ADAb levels ACP are considered "potentially ADAb positive" and will be further evaluated in the confirmatory assay, the result of which will be reported as either "confirmed positive" (CP) or "not confirmed positive" (NCP). Confirmed positive samples (reported as CP) will be titrated, and the titer (reciprocal dilution factor including minimum required dilution) reported.

ADAb status at any time point:

- An ADAb status of positive (ADAb+) will be concluded for any participant with an ADAb level that is ACP and CP;
- An ADAb status of negative (ADAb-) will be concluded for any participant with an ADAb level that is either BCP or ACP and NCP;

Participant Classification:

- A participant will be classified as having ADAb positivity at Baseline if the Day 1, pre-dose result is ADAb+;
- A participant will be classified as overall positive if at least one post-Baseline measurement is ADAb+ (see definition above) (this includes participants who have negative and positive results at baseline);
- A participant will be classified as overall negative if at all post-Baseline visits the ADAb status is negative (this includes participants who have positive and negative results at Baseline);
- 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 pre-defined fold increase in titer or units/mL (as applicable) from the Baseline value (the fold increase from Baseline required to meet these criteria will be defined with the development of the assay and will be included in the TFLs).

Analysis:

Immunogenicity will be assessed through summary tables and figures and listing of individual results by participant. All analyses will be run on the FAS, unless specified otherwise. For all tabulations, percentages will be calculated based on the number of 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).
- 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-induced ADAb positivity (based on the definitions above) will be summarized (number and percentage of participants) at each post-Baseline visit, based on the PK-PPS. This tabulation will present the number and percentage of participants at each post-Baseline visit who fulfill at least one of the above defined criteria for treatment-emergent positivity; participants will be counted in the numerator based on the earliest visit at which one of these criteria is fulfilled. At other visits, 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 separate listing will be presented showing the bimekizumab concentrations and ADAb measurements in the same output in adjacent columns, based on the PK-PPS. The listing will include the bimekizumab concentration, ADAb status (positive or negative) and screening assay results (ACP or BCP) and confirmatory assay results if applicable (NCP or CP), together with the titer if applicable. In addition, the time since the administration of study medication will be reported (in days). ADAb samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged.

Finally, individual participant plots will be presented displaying the ADAb titer and bimekizumab concentrations overlaid on the same figure for the FAS. The ADAb data will be plotted using a semi-logarithmic scale. ADAb samples that are negative but have drug concentration above the drug tolerance characteristics of the assay will be flagged on the plot.

The rules for handling values that are BLQ in the bimekizumab concentration data are described Section 4.2.1. For the ADAb data, any negative results for which there are no titers or units/mL (as applicable) available at a specific visit will be substituted with 0.001 for the purpose of the figure.

# 11 SAFETY ANALYSES

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

## 11.1 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 FAS. In addition, a listing of batch and devices numbers used will be created using the FAS.

## 11.2 Adverse events

Adverse events will be recorded from the time of informed consent until study completion. All AEs will be coded (Section 3.7) 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 any AE related to the use of an investigational medicinal device i.e., where the causality to the device constituent is assessed as ‘related’ by the Investigator
- A serious ADE (SADE) is an ADE that results in any of the consequences defined for a SAE, i.e., where the causality to the device constituent is assessed as ‘related’ by the Investigator and the AE is considered as SAE
- 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 and SADEs 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 FAS (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 4.2.4).

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) 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
- SADEs.

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’. 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'. 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 the overall column 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 the overall column.

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).

## 11.3 Clinical laboratory evaluations

Laboratory variables will be grouped according to the laboratory function panel (Table 11–1) and categorized as normal, high or low, if applicable, based on the reference range supplied by the analytical laboratory.

**Table 11–1: Clinical laboratory measurements**

| Category | Panel | Variable |
|---|---|---|
| Serology | Serology | HbsAg, HBc-Ab (both IgG and IgM), HCV-Ab, HIV1-Ab, HIV1-Ag, HIV-2 Ab |
| Hematology | Red blood cell | Hemoglobin[a], hematocrit, RBC[a] |
| | Platelet | Platelet count[a] |
| | White blood cell | WBC count[a] |
| | White blood cell differential | Absolute counts: ANC[a], basophils, eosinophils, ALC, monocytes<br>Percentages: neutrophils/leukocytes[a], eosinophils/leukocytes[a], lymphocytes/leukocytes[a], monocytes/leukocytes[a]. |
| Coagulation/hemostasis | Coagulation | Prothrombin time, aPTT |
| Clinical chemistry | Electrolytes | Sodium, chloride, potassium, total calcium |
| | Enzymes | Creatine kinase |
| | Hormones | FSH |

**Table 11–1: Clinical laboratory measurements**

| Category | Panel | Variable |
|---|---|---|
| | Metabolic | Glucose |
| | Kidney function | BUN, creatinine |
| | Proteins | Total protein, albumin[a] |
| | Liver function | AST[a], ALT[a], GGT, ALP, LDH, total bilirubin |
| | Lipids | Total cholesterol[a], LDL cholesterol[a], 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).<br>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.<br>The FSH test performed in postmenopausal women at the Screening Visit. |

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; LDL=low density lipoprotein; RBC=red blood cell; WBC=white blood cell

[a] Shift table will be presented for this variable

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 only be presented for selected variables in Table 11–1.

The above-mentioned laboratory variables and change from Baseline for numeric variables will be listed for the FAS by treatment group and time point. Any laboratory measurements that are BLQ or ALQ will be handled as described in Section 4.2.2. 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 FAS.

Data for the following will only be listed using the ES 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).

### 11.3.1 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 no exhibit temporally associated symptoms of hepatitis or hypersensitivity
- ALT or AST increase ≥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 participant and will display all results obtained at that visit for the specified parameters.

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

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

### 11.4.1 Vital signs

The following vital signs measurements will be obtained:

- Pulse rate
- Systolic and diastolic blood pressure
- Oral body temperature

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 FAS.

By-participant listings of all vital sign measurements and change from Baseline will be presented by treatment group and time point for the FAS.

### 11.4.2 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
- 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 FAS. 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 and percentage changes from Baseline will be summarized for the FAS, for each variable by treatment group and visit/timepoint.

The following cut-points in QTcF (raw data and change from Baseline) will be summarized for the FAS, categorically by treatment group (number and percentage of participants) and visit/timepoint. The denominator for the percentages will be the number of 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.

### 11.4.3 Physical examinations

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

# 12 OTHER ANALYSES

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

# 13 REFERENCES

1. Phillips, A. and Haudiquet, V. (2003), ICH E9 guideline 'Statistical principles for clinical trials': a case study. Statist. Med., 22: 1-11. doi:10.1002/sim.1328
2. Food and Drug Administration. Guidance for Industry. Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs —General Considerations. US Dept of Health and Human Services, Center for Drug Evaluation and Research. Biopharmaceutics. March 2017.
3. EMEA/CHMP/BMWP/42832/2005 Rev. 1 Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non -clinical and clinical issues , 18 Dec 2014.
4. CPMP/EWP/QWP/1401/98 Rev. 1/Corr Guideline on the investigation of bioequivalence (EMEA), 20 January 2010.
5. Health Canada Guidance, Conduct and Analysis of Comparative Bioavailability Studies, 8 Jun 2018.
6. Health Canada Guidance, Comparative Bioavailability Standards: Formulations use for Systemic Effects, 8 Jun 2018.
7. EMA. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic. Version 3. 28 Apr 2020. Available at: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf

# 14 APPENDICES

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# 15 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP) (IF APPLICABLE)

<Enter text>

## 15.1 AMENDMENT 1

**Rationale for the amendment**

<Enter text>

**Modifications and changes**

**Global changes**

<Enter text>

**Specific changes**

<Enter text>

Has been changed to:

<Enter text>

## 15.2 AMENDMENT 2

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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.

# Approval Signatures

**Name:** UP0068-SAP

**Version:** 1.0

**Document Number:** CLIN-000162152

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| Document Approvals | |
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| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 18-Nov-2020 19:28:15 GMT+0000 |
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