# STATISTICAL ANALYSIS PLAN

## Study: DV0004

## Product: Bimekizumab

## NORTH AMERICA AND EU SUBSTUDY TO PA0012

A MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE SAFE AND EFFECTIVE USE OF THE PREFILLED SAFETY SYRINGE OR AUTO-INJECTOR FOR THE SUBCUTANEOUS SELF-INJECTION OF BIMEKIZUMAB SOLUTION BY SUBJECTS WITH ACTIVE PSORIATIC ARTHRITIS

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| ADAb | anti-bimekizumab antibody |
| ADE | adverse device effect |
| AE | adverse event |
| ATC | anatomical therapeutic chemical |
| bimekizumab-AI-1mL | 1mL bimekizumab auto-injector |
| bimekizumab-SS-1mL | 1mL bimekizumab safety syringe |
| BMI | body mass index |
| CI | confidence interval |
| CRF | case report form |
| CV | coefficient of variation |
| eCRF | electronic case report form |
| ES | Enrolled Set |
| ET | early termination |
| FAS | Full Analysis Set(s) |
| FAS-a | Full Analysis Set for the bimekizumab-AI-1mL |
| FAS-s | Full Analysis Set for the bimekizumab-SS-1mL |
| HLT | high level term |
| IFU | instructions for use |
| IMP | investigational medicinal product |
| LLOQ | lower level of quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PFS | prefilled syringe |
| PK | pharmacokinetic(s) |

| | |
|---|---|
| PK-PPS | Pharmacokinetic Per Protocol Set |
| PK-PPS-a | Pharmacokinetic Per Protocol Set for the bimekizumab-AI-1mL |
| PK-PPS-s | Pharmacokinetic Per Protocol Set for the bimekizumab-SS-1mL |
| PsA | psoriatic arthritis |
| PT | preferred term |
| Q4W | every 4 weeks |
| SADE | serious adverse device effect |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| sc | subcutaneous |
| SD | standard deviation |
| SFU | safety follow-up |
| SIAQ | Self-injection Assessment Questionnaire |
| SOC | system organ class |
| SOP | standard operating procedure |
| SS | Safety Set(s) |
| SS-a | Safety Set for the bimekizumab-AI-1mL |
| SS-s | Safety Set for the bimekizumab-SS-1mL |
| TEADE | treatment-emergent adverse device effect |
| TEAE | treatment-emergent adverse event |
| USADE | unanticipated serious adverse device effect |
| VAS | visual analog scale |
| WHO | World Health Organization |
| WHO-DD | World Health Organization Drug Dictionary |

# 1 INTRODUCTION

This statistical analysis plan (SAP) defines the scope of the statistical analyses and provides a detailed description of the statistical methodology for subject data obtained in this substudy of PA0012. The SAP is based on the following study documents:

- Protocol amendment DV0004, 14 May 2020,
- Electronic Case Report Form PA0012_DV0004 (v6.0), 03 June 2020.

All references to the study protocol hereafter refer to this version of the protocol.

To avoid premature unblinding of the PA0010 and PA0011 Feeder Study treatment allocation, a Blinding Maintenance Plan has been created for the PA0012/DV0004 studies. Please refer to this document for specifics regarding the handling of pharmacokinetic and pharmacodynamic data. The blinding plan is only applicable until both feeder studies have unblinded.

# 2 PROTOCOL SUMMARY

## 2.1 Study objectives

### 2.1.1 Primary objective

The primary objective of the study is to evaluate for each self-injecting device the ability of subjects with psoriatic arthritis (PsA) to safely and effectively self-inject bimekizumab 4 weeks after training in the self-injection technique using the 1mL bimekizumab safety syringe (bimekizumab-SS-1mL) or the 1mL bimekizumab auto-injector (bimekizumab-AI-1mL).

### 2.1.2 Secondary objective

The secondary objective of the study is to evaluate the ability of subjects with PsA to safely and effectively self-inject bimekizumab immediately after training in the self-injection technique using the bimekizumab-SS-1mL or the bimekizumab-AI-1mL.

### 2.1.3 Other objectives

Other objectives of the study are to evaluate the following:

- Subject experience of self-injection as assessed by the pain visual analogue scale (VAS) for injection site pain and the Self-injection Assessment Questionnaire (SIAQ)
- Trough pharmacokinetic (PK) (trough bimekizumab) levels associated with self-injection using the test self-injecting device, injection by study personnel using the 1mL prefilled syringe (PFS), injection site (abdomen or thigh), and body mass index (BMI) category (by tertile)
- Immunogenicity of bimekizumab associated with self-injection using the self-injecting device presentations and injection by study personnel using the 1mL PFS
- The structural and mechanical integrity of the bimekizumab-SS-1mL and the bimekizumab-AI-1mL after completion of self-injection
- The functional integrity of the bimekizumab-SS-1mL and the bimekizumab-AI-1mL after completion of self-injection

- The overall safety and tolerability of self-injections using the self-injecting device presentations.

## 2.2 Study variables

### 2.2.1 Outcome variables

#### 2.2.1.1 Primary outcome variable

The primary outcome variable is the ability to self-administer safe and effective injections using the bimekizumab-SS-1mL or the bimekizumab-AI-1mL at Week 4.

Safe and effective self-injection will be evaluated by the study personnel and is defined as:

- Complete dose delivery: Subject self-injects the complete dose of bimekizumab as confirmed by a visual inspection of the bimekizumab-SS-1mL or the bimekizumab-AI-1mL, which shows that the investigational medicinal product (IMP) is delivered completely (i.e., container is empty), and
- No adverse device events (ADEs) that would preclude continued use of the device for self-injection (i.e., no serious adverse device events [SADEs] and/or ADEs leading to withdrawal from the DV0004 substudy).

#### 2.2.1.2 Secondary outcome variable

The secondary outcome variable is the ability to self-administer safe and effective injections using the bimekizumab-SS-1mL or the bimekizumab-AI-1mL at DV0004 Baseline (for first self-injection visit, immediately after training in the self-injection technique).

Safe and effective self-injection will be evaluated by study personnel and is defined using the same criteria as the primary outcome variable (see Section 2.2.1.1).

#### 2.2.1.3 Other variables

##### 2.2.1.3.1 Outcome variables

The other outcome variables are:

- Responses to pre-injection SIAQ (versions 2.0 and 2.1) at DV0004 Baseline

  Whenever SIAQ is assessed, version 2.0 of the SIAQ will be used to assess bimekizumab-SS-1mL and version 2.1 of the SIAQ will be used to assess bimekizumab-AI-1mL.
- Injection site pain (using a VAS; 100mm) by visit after self-injection using the assigned self-injecting device presentations at DV0004 Baseline and Week 4.
- Responses to post-injection SIAQ (versions 2.0 and 2.1) by visit following self-injection using the assigned self-injecting device presentations at DV0004 Baseline and Week 4.
- The structural and mechanical integrity of the bimekizumab-SS-1mL and the bimekizumab-AI-1mL after completion of the self-injection using the assigned self-injecting device presentations. This is based on a visual examination of the device that shows clear evidence of damage and/or compromised structural or mechanical integrity.

- The functional integrity of the bimekizumab-SS-1mL and the bimekizumab-AI-1mL after completion of self-injection using the assigned self-injecting device presentations. This is based on a visual examination of the device that shows clear evidence of damage and/or compromised functional integrity.

#### 2.2.1.3.2 Pharmacokinetic variable

The PK variable is trough PK (bimekizumab) levels associated with self-injection using the test self-injecting device presentations, injection by study personnel using the 1mL PFS, injection site (abdomen or thigh), and BMI category (by tertile). Trough levels will be assessed at DV0004 Baseline, DV0004 Week 4, and PA0012 Week 8.

#### 2.2.1.3.3 Immunological variable

The immunological variable is the anti-bimekizumab antibody, which will be collected as described in the PA0012 study protocol.

#### 2.2.1.3.4 Safety variable

The other safety variable is the occurrence of ADEs. An ADE is an adverse event (AE) related to the use of an investigational device. An ADE must meet 1 or more of the following criteria:

- Adverse event resulting from insufficiencies or inadequacies in the instructions for use (IFU), the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
- Adverse event that is a result of a use error or intentional misuse of the investigational device.

Additional safety and tolerability variables will be collected as described in the PA0012 study protocol.

## 2.3 Study design and conduct

### 2.3.1 Study description

DV0004 is a Phase 3, multicenter, open-label, randomized, noncomparator, North America and Europe substudy to PA0012. PA0012 will evaluate the long-term safety, tolerability, and efficacy of 160mg bimekizumab every 4 weeks (Q4W) in adult subjects with PsA; study personnel will administer bimekizumab to subjects in a 1mL PFS. The DV0004 substudy will evaluate 2 self-injection investigational devices: the 1mL bimekizumab-SS-1mL and the 1mL bimekizumab-AI-1mL.

In the DV0004 substudy, the safe and effective use of the bimekizumab-SS-1mL or the bimekizumab-AI-1mL for the sc self-injection of bimekizumab solution by adult subjects with PsA will be evaluated.

Subjects from selected sites in the PA0012 feeder studies, PA0010 and PA0011, will be eligible for the DV0004 substudy. The DV0004 substudy will maintain all study assessments of the main PA0012 study from DV0004 Baseline to Week 4 (inclusive). However, only subjects in the DV0004 substudy will self-administer bimekizumab using the bimekizumab-SS-1mL or the bimekizumab-AI-1mL at DV0004 Baseline and Week 4. At DV0004 Baseline, each subject will be provided with training in self-injection and will receive the IFU and any other applicable

training materials. Subjects in the DV0004 substudy will perform self-injections at the DV0004 Baseline (corresponding to the Entry Visit of PA0012) with a subsequent self-injection at the DV0004 Week 4 Visit (corresponding to Week 4 of PA0012).

### 2.3.2 Treatment Period

During the 4-week Treatment Period of DV0004, subjects will receive bimekizumab 160mg Q4W. This dose regimen will remain stable for the entire 4-week Treatment Period of DV0004 (consistent with PA0012).

Eligible subjects will be randomly assigned in a 1:1 ratio to perform self-injection using either the bimekizumab-SS-1mL or the bimekizumab-AI-1mL. Subjects will perform self-injection with the assigned device presentation at DV0004 Baseline (corresponding to the Entry Visit of PA0012) and at Week 4 (corresponding to Week 4 of PA0012). After Week 5 of the DV0004 substudy, subjects will continue in PA0012 (the next visit after DV0004 completion will be the Week 8 Visit in PA0012).

### 2.3.3 Safety Follow-Up

A device Safety Follow-up (SFU) telephone call will occur 1 week after the last self-administration (at Week 5). Subjects who are withdrawn from DV0004 but continue their PA0012 study participation will be required to perform an SFU telephone call 1 week after their final DV0004 dosing visit.

### 2.3.4 Withdrawal

Subjects who are withdrawn from bimekizumab treatment (PA0012 study) during the course of DV0004 will also be required to follow the PA0012 withdrawal procedures that means subjects will undergo the Early Termination (ET) Visit assessments and will enter the SFU Period.

### 2.3.5 Study duration per subject

The maximum DV0004 substudy duration will be 4 weeks for each subject. Subjects will then continue to receive treatment in PA0012 for the duration of the PA0012 study. The end of the DV0004 substudy is defined as the date on which the last subject completes his/her DV0004 Week 4 Visit or withdraws from the study.

### 2.3.6 Planned number of subjects

It is planned to enroll approximately 200 subjects; each device presentation arm will consist of approximately 100 subjects. It is anticipated that this study will involve up to 150 sites in North America and Europe.

## 2.4 Determination of Sample Size

This study will not be powered with respect to any endpoint, and sample size is based on practical considerations. In order to maintain blinding in the PA0012 feeder studies (PA0010 and PA0011), DV0004 will recruit all subjects who complete the PA0010 and PA0011 studies (including those treated with a comparator or placebo in the feeder study) up to a total of about 200 subjects. A total of 100 subjects (50 subjects per device presentation arm) are planned for PK trough level analyses, but these analyses will only be performed on subjects who were treated

with bimekizumab 160mg Q4W (i.e., not with placebo or comparator) to ensure that 100 subjects with stable (160mg Q4W bimekizumab) PK trough levels are available for PK trough analysis.

Subjects who enroll in the DV0004 substudy will be randomly assigned to the bimekizumab-SS-1mL or the bimekizumab-AI-1mL device presentation arms (each device presentation arm will consist of approximately 100 subjects). Within each device presentation arm, subjects will be divided into tertiles by BMI; there will be approximately 33 subjects per tertile, which is expected to yield approximately 16 to 17 subjects per tertile who are evaluable for steady state trough PK level analyses (approximately 100 subjects in total).

# 3 DATA ANALYSIS CONSIDERATIONS

## 3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.3 or higher. 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 subjects with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum.

For categorical variables, the number and proportion of subjects, will be presented. In addition, for the primary, secondary and other variables the 90% confidence interval (CI) based on the Exact Binomial, will also be presented. Unless otherwise noted, the denominator for percentages should be based on the number of subjects included in the respective analysis set. Subjects 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 subjects in the analysis set and include a "Missing" category (corresponding to subjects with missing data for the variable being summarized) as the last row in the list of categories being summarized.
- For summaries of outcome and safety variables, unless otherwise specified: percentages will be summarized based only on those subjects with observed data for the variable being summarized. As the denominator may be different from the number of subjects in the analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be "n/NSub (%)", unless otherwise specified.

Percentages will be presented to 1 decimal place. If the percentage is 100 or 0, no decimal will be presented. Typically, the % sign should be presented in the column header, but not with each individual value.

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

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

- "n" will be an integer

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

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

A complete set of data listings containing all documented data as well as calculated data will be generated.

## 3.2 General study level definitions

### 3.2.1 Baseline values

The DV0004 Baseline value is defined as the last non-missing measurement prior to the first self-injection at Visit 1 (Baseline). If a scheduled Baseline assessment is taken on the same day as the first administration of study medication, then the assessment will be assumed to have been performed prior to study medication.

### 3.2.2 Relative Day

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

- If the start (stop) date occurred on or after the first dose in DV0004, but prior to the drug stop date, relative day is calculated as start (stop) date minus first dose date + 1
- If the start (stop) date occurred after the last dose of bimekizumab, the relative day to the most recent dose is calculated as start (stop) date minus most recent dose date. The relative day in this situation should be preceded by a '+'
- If the start (stop) date occurred before the first dose in DV0004, the relative day is calculated as start (stop) date minus first dose date. The relative day in this situation should be preceded by a '-'.

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

## 3.3 Protocol deviations

Important protocol deviations are deviations from the protocol which could potentially have a meaningful impact on the primary objective of the study. The criteria for identifying important protocol deviations and the classification of important protocol deviations will be defined within the project Data Cleaning Plan. To the extent feasible, the rules for identifying protocol deviations will be defined without review of the data and without consideration of the frequency of occurrence of such deviations. Whenever possible, criteria for identifying important protocol deviations will be implemented algorithmically to ensure consistency in the classification of important protocol deviations across all subjects.

Following the declaration of the global COVID-19 pandemic by the World Health Organization in March 2020, protocol deviations will be identified as "related to COVID-19" where applicable.

## 3.4 Analysis sets

### 3.4.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent for DV0004.

### 3.4.2 Safety Set

Two different Safety Sets (SS) will be generated (1 for each device presentation): the bimekizumab-SS-1mL Safety Set (SS-s) and the bimekizumab-AI-1mL Safety Set (SS-a). Each SS will consist of all subjects in the study who receive at least 1 dose of bimekizumab by the indicated self-injecting device presentations. Safety variables will be analyzed using the SS-s and SS-a.

### 3.4.3 Full Analysis Set

Two different Full Analysis Sets (FAS) will be generated (1 for each device presentation): the bimekizumab-SS-1mL Full Analysis Set (FAS-s) and the bimekizumab-AI-1mL Full Analysis Set (FAS-a). Each FAS will consist of all subjects in the SS-s or SS-a who self-inject at least 1 dose of bimekizumab using the given device and who have an assessment of self-injection. All self-injection related endpoints will be analyzed using the FAS-s and FAS-a.

### 3.4.4 Pharmacokinetic Per Protocol Set

Two different Pharmacokinetic Per Protocol Sets (PK-PPS) will be generated (1 for each device presentation): the bimekizumab-SS-1mL PK-PPS (PK-PPS-s) and the bimekizumab-AI-1mL PK-PPS (PK-PPS-a). Each PK-PPS will consist of all subjects who receive the same bimekizumab administration (frequency and dose) in the PA0012 feeder studies as in the DV0004 substudy and who have at least 1 evaluable PK assessment in the DV0004 substudy without important protocol deviations that would affect the concentration. Pharmacokinetic variables will be analyzed using the PK-PPS-s and PK-PPS-a.

All PK assessments after baseline assessments from the feeder study will be considered for the one evaluable PK assessment.

## 3.5 Treatment assignment, treatment and device groups

This is an open-label study and as such all subjects will be summarized according to the treatment that was assigned. The treatment group will be allocated in PA0012 and the device group will be allocated in DV0004.

**PA0012 treatment groups**

This refers to the study treatment assigned to the subject at the beginning of PA0012 and does not account for the treatment received in the relevant Feeder Study.

All subjects will receive bimekizumab 160mg Q4W sc.

**DV0004 device groups**

This refers to the study device assigned to the subject at the beginning of DV0004. The DV0004 device groups are as follows:

- Bimekizumab-SS-1mL
- Bimekizumab-AI-1mL.

The outcome variables will be summarized by assigned DV0004 device group. The different DV0004 device groups are reflected in the use of the corresponding analysis set SS-s, SS-a, FAS-s, FAS-a, PK-PPS-s and PK-PPS-a.

## 3.6 Center pooling strategy

No pooling of centers is planned for this study.

## 3.7 Coding dictionaries

All ADEs will be coded and classified by system organ class (SOC), high level term (HLT), and preferred term (PT) according version 19.0 of the Medical Dictionary for Regulatory Activities (MedDRA®).

All medications other than the study drug will be classified by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC Level 3), and preferred term (PT), using version SEP/2015 of the World Health Organization Drug Dictionary (WHO-DD), according to UCB standard operating procedures (SOP).

Previous and ongoing medical history will be classified by version 19.0 of MedDRA® SOC and PT.

## 3.8 Changes to protocol-defined analyses

1. Study duration per subject in the protocol is specified as 5 weeks. In this document it is defined as 4 weeks. This accounts for 4 weeks of treatment. The additional week of Safety Follow-Up is still included in the allocation of adverse device events, which includes events occurring up to last dose + 7 days.
2. The analysis sets to be used for the PK data have been amended from the PK Analysis set to the PK Per Protocol Analysis set (PK-PPS) throughout which will allow the exclusion of subjects with important protocol deviations related to PK from the primary analysis.
3. Subjects who had important protocol deviations affecting the primary outcome variable, as confirmed during ongoing data cleaning meetings prior to database lock, will not be excluded from the FAS-s or FAS-a.
4. The pharmacokinetic assessment of anti-bimekizumab antibody status will be measured before self-injection at DV0004 Baseline, and after self-injection at DV0004 Baseline and DV0004 Week 4 (the assessment is taken at Week 4 and Week 8 visits). This is different from the protocol, which incorrectly stated the following:

- Blood samples will be taken before self-injection at the Baseline Visit (PK trough and anti-bimekizumab antibody analysis), Visit 2 Week 4 (PK trough analysis only) and Week 8 of PA0012 (PK trough and anti-bimekizumab antibody analysis).

This text has been updated to the following as presented in Section 9.1:

- […] blood samples will be taken before self-injection using the assigned self-injecting device presentation at the DV0004 Baseline Visit and DV0004 Week 4 (Visit 2), and before injection by site personnel at PA0012 Week 8 (Visit 3 of PA0012).

### 3.8.1 Changes related to COVID-19

The impact of the COVID-19 pandemic on study procedures and/or conduct and on the primary safety endpoints (TEADEs, serious TEADEs, and study withdrawal due to TEADEs) will be investigated and additional outputs provided as appropriate. These analyses were not planned as part of the protocol as the pandemic scale was unprecedented.

The additional analyses are described in the following sections of the SAP:

- Subject disposition, including details of impacted visits and effects on collection and reporting of efficacy data (Section 5.1.1)
- Protocol deviations potentially related to COVID-19 (Section 5.2)
- Impact of COVID-19 on study (Section 5.3 )
- Demographics, baseline characteristics (Sections 6.1 and 6.2 )
- Adverse events (Section 10.2.2)
- Primary outcome variable (Section 11.1 )

# 4 STATISTICAL/ANALYTICAL ISSUES

## 4.1 Adjustments for covariates

Not applicable.

## 4.2 Handling of dropouts or missing data

For analyses of ADEs and concomitant medication usage, a complete date must be established in order to correctly identify the ADE or medication as occurring during treatment or not. For purposes of imputing missing components of partially-reported start and stop dates for ADEs and for medication use, the algorithms listed below will be followed. Start and stop dates of ADEs or concomitant medication will be displayed as reported in the subject data listings (i.e., no imputed values will be displayed in data listings).

Partial ADE and concomitant medication start dates will be imputed as follows:

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start date, then use the date of first dose

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

Imputation of Partial Stop Dates

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

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

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

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

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

There will be no special procedures for handling missing data for any other data points.

## 4.3 Interim analyses and data monitoring

No interim analysis is planned for this study. No Data Monitoring Committee will be established for this study.

## 4.4 Multicenter studies

Individual center results will not be directly presented. Centers are only located in North America and Europe.

## 4.5 Multiple comparisons/multiplicity

Not applicable.

## 4.6 Use of an efficacy subset of subjects

Not applicable.

## 4.7 Active-control studies intended to show equivalence

Not applicable.

## 4.8 Examination of subgroups

Not applicable.

## 4.9 Additional study-specific information

The subjects of DV0004 are ongoing subjects of PA0012. Data cut off for the final analysis in DV0004 will be after the follow-up of the last subject. Data cut off rules will be applied for ongoing ADEs and ongoing concomitant medication, such that any ADE or concomitant medication which has no stop date, or a stop date after the data cut off for DV0004 will be assigned as "Ongoing".

A number of parameters in the PA0012 and DV0004 studies have the potential to break the blinding of the feeder study treatment allocations. In order to safeguard against unscheduled unblinding of the PA0010 and PA0011 studies before their respective database locks, a blinding maintenance plan will be developed and implemented for DV0004 and PA0012. This will ensure both PA00012 & DV0004 remain blinded to feeder study treatment allocation, until after both feeder studies have been unblinded. This plan will document in detail how the DV0004 Data Evaluation Meetings and final delivery will be handled prior to Feeder Study unblinding.

### 4.9.1 COVID-19 category definition

The coronavirus disease of 2019 (COVID-19) pandemic was declared by the WHO on 11 March 2020. The worldwide pandemic restricted travel and had potential impact on ongoing clinical trials. The following definitions will be used to present pre-specified summaries:

- *Pre-pandemic:* Events or assessments occurring before 11-Mar-2020
- *During pandemic*: Events or assessments occurring on or after 11-Mar-2020

A post-pandemic definition is not applicable to this short study.

# 5 STUDY POPULATION CHARACTERISTICS

## 5.1 Subject disposition

The disposition of subjects including the number of subjects in ES and all device-specific analysis sets (SS-s, FAS-s, PK-PPS-s or SS-a, FAS-a, PK-PPS-a) will be summarized. This summary will be based on ES and will present subjects overall and by site and country/region (North America/Europe).

The number and percentage of subjects who entered the substudy, completed, discontinued with the reasons for discontinuation of the substudy will be presented. This summary will be based on the ES and will present all bimekizumab treated subjects broken out by DV0004 device group.

The following listings for subject disposition will be produced based on the ES and presented by DV0004 device group:

- A listing of subjects who did not meet the eligibility criteria
- A listing of subject disposition
- A listing of discontinuation
- A listing of visit dates
- A listing of subjects excluded from analysis sets
- A listing of subject analysis sets

### 5.1.1 Impact of COVID-19 on subject disposition

Subject disposition will also be summarized by COVID-19 enrollment period (pre- and during-pandemic), as defined in Section 4.9.1. The number of completed, missed and partial visits will be presented by COVID-19 enrollment period.

## 5.2 Protocol deviations

A summary of number and percentage of subjects with an important protocol deviation (including a summary of subjects excluded from any analysis set due to important protocol deviations) by DV0004 device group will be provided for the SS-s and SS-a. A summary of COVID-19 related important device protocol deviations will be presented by visit for the SS-s and SS-a. COVID-19 related important protocol deviations will be identified by the prefix of "COVID" in the deviation verbatim text.

By-subject listings of important protocol deviations and COVID-related important device protocol deviations will be provided separately.

## 5.3 Impact of COVID-19

The impact of the COVID-19 pandemic on study procedures and conduct, such as missed/remote visits, interruption of study treatment, will be documented using the information collected on a dedicated eCRF page. The number and percentage of subjects impacted by COVID-19 will be presented overall and by country.

A by-subject listing of the impact of COVID-19 on study visits will be provided.

# 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

All summaries detailed in this section will be performed on the SS-a and SS-s. Demographics and other baseline characteristics will be extracted from the Feeder Study Baseline data.

## 6.1 Demographics

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

- Age at the time of Feeder Study entry (years)
- Height at Feeder Study Baseline (cm)
- Weight (kg) at DV0004 Baseline: This will be derived from the weight from the last visit of the feeder study or DV0004 Entry Visit, since these visits will occur on the same day and weight is only collected once
- DV0004 Baseline BMI (kg/m$^2$)

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

$$BMI = \frac{Weight\ (kg)\ at\ DV0004\ Baseline}{[Height\ (m)\ at\ Feeder\ Study\ Baseline]^2}$$

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

- Age group (≤18, 19-<65, ≥65 years)
- Body Weight at DV0004 Baseline (≤100kg, >100kg)
- BMI (<25 kg/m$^2$, 25 to <30 kg/m$^2$, ≥30 kg/m$^2$)
- BMI tertiles (≤t1 kg/m$^2$, >t1 kg/m$^2$ to ≤t2 kg/m$^2$, >t2 kg/m$^2$) based on the respective PK populations (PK-PPS-s, PK-PPS-a)
- Gender
- Race
- Ethnicity
- Country

By-subject listings of demographics will be provided.

Demographics will also be summarized by COVID-19 enrollment period (pre- and during-pandemic), as defined in Section 4.9.1.

## 6.2 Other Baseline characteristics

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

- Duration of disease (years)

Duration of disease (years) will be calculated as:

$$Disease\ duration = \frac{(Date\ of\ randomization\ in\ DV0004\ -\ Date\ of\ onset\ of\ PsA^{1})}{365.25}$$

[1] If the date of onset of PsA is partial, it should be imputed to the most recent feasible date (i.e., last day of the month if only day is missing, or last day of the year if day and month are missing).

Baseline characteristics will also be summarized by COVID-19 enrollment period (pre- and during-pandemic), as defined in Section 4.9.1.

## 6.3 Medical history and concomitant diseases

Previous and ongoing medical history from the feeder study will be based on SS-s and SS-a and summarized by system organ class (SOC) and preferred term (PT) using MedDRA®. Medical procedures are not coded.

Previous and ongoing medical history will be presented in a by-subject listing for SS-s and SS-a, respectively.

All medical conditions not yet occurred and reported in the feeder studies will be presented in a table and a by-subject listing for SS-s and SS-a, respectively.

## 6.4 Prior and concomitant medications

Concomitant medication details are collected at each visit of DV0004. Concomitant medications are medications taken with at least one day in common with the DV0004 study medication dosing period (DV0004 Baseline to DV0004 Week 4).

Imputation of missing start and stop dates are described in Section 4.2.

All concomitant medication will be listed for SS-s and SS-a, respectively.

Concomitant medication which started before DV0004 Week 4 and were ongoing at the data cut off will be included with the status remaining as ongoing. Concomitant medication which were ongoing at DV0004 Week 4 but with an end date before the data cut off will be included with their end date as recorded.

# 7 MEASUREMENTS OF TREATMENT COMPLIANCE

During the Treatment Period of this study, IMP administration (either self-administration or study personnel-administration) will be performed in the clinic and observed by the Investigator or his/her designee; monitoring subject compliance is therefore not applicable.

# 8 EFFICACY ANALYSES

No efficacy summaries are planned for the DV0004 substudy.

# 9 PHARMACOKINETICS AND PHARMACODYNAMICS

## 9.1 Pharmacokinetics

The statistical analyses of the PK data will be descriptive in nature and will be summarized using the relevant device presentation-specific population (PK-PPS-s or PK-PPS-a). Data will be analyzed overall for each device presentation by injection type (self-administered or study personnel-administered), by injection site (abdomen or thigh), by anti-bimekizumab antibody visit status, and by BMI category. Three BMI categories will be defined based on tertiles derived from subjects' DV0004 Baseline BMI values. See Section 9.2 for details on classification of anti-bimekizumab antibody status.

To allow for an analysis of bimekizumab PK trough levels, blood samples will be taken before self-injection using the assigned self-injecting device presentation at the DV0004 Baseline Visit

and DV0004 Week 4 (Visit 2), and before injection by site personnel at PA0012 Week 8 (Visit 3 of PA0012).

PK samples at DV0004 baseline will be summarized under administration by site personnel (since the previous dose was given by site personnel). PK samples associated with self-administration (at Week 4 and Week 8), but where the previous injection was done by site personnel or care-giver, will be listed but not be used for summary statistics.

Only pre-dose (trough) concentrations will be included while summarizing tables and figures. If the dosing for a visit is +/- 7 days out of window, then the plasma concentration from that visit will be excluded from the PK summary. PK samples are expected to be collected prior to dosing. PK samples collected >14 days after the preceding dose and no later than 1 hour after the current dose will be included in the summary. PK samples collected later than 1 hour after dosing will be excluded from summary statistics. PK results at visits following a previous non-dosing visit will be excluded from summary statistics.

PK summaries will be based on observed values. No imputation will be used. However, if plasma concentration measurements are below the level of quantification, then for calculation of the derived statistics the result will be set to ½ of the lower level of quantification (LLOQ). Descriptive statistics including the geometric mean, geometric coefficient of variation, and geometric mean 95% confidence interval (CI) if applicable will be calculated if at least ⅔ of the values of interest are above the LLOQ. If this is not the case, only median, minimum, and maximum will be presented. Time from previous bimekizumab dose to DV0004 visit will be summarized by device presentation.

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.

Boxplots and summaries of plasma concentration will be presented by visit, by device presentation, and by cumulative ADAb status considering DV0004 alone and considering DV0004 and the feeder studies (see Section 9.2). Cumulative ADAb status is defined in Section 9.2. Boxplots and summaries of plasma concentration will be presented by visit, by device presentation and by injection site, and by BMI tertile.

All PK results will be listed. Baseline PK samples are the PK samples prior to first dose of Bimekizumab at DV0004 entry visit.

In addition, the PK results from all subjects not in PK-PPS-s or PK-PPS-a will be listed based on the SS-a and SS-s. All concentrations will be listed as received, prior to any substitution of BLQ and LLOQ values. The listing will include flags for concentration that were excluded from the summary statistics, with the reason for exclusion.

## 9.2 Immunogenicity

The immunological variable is anti-bimekizumab antibodies (ADAb) evaluated at DV0004 Baseline and Week 4, and PA0012 Week 8 visits. To allow for an analysis of ADAb, blood samples will be taken before self-injection at the DV0004 Baseline Visit and DV0004 Week 4 (Visit 2), and before injection by site personnel at PA0012 Week 8 (Visit 3 of PA0012). ADAb

status at or prior to the PK sampling (at DV0004 Baseline, DV0004 Week 4, and PA0012 Week 8) will be used in the summaries.

The ADAb will be assessed using a 3-tiered assay approach: Screening, confirmatory, and titration assays. Screening, confirmatory and titer cut points of the respective assays will be determined by the bioanalytical laboratory. The relevant statistical reports will be provided as part of the bioanalytical reports.

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

Positive immunodepletion samples will be titrated, and the ADAb titer (reciprocal dilution factor including minimum required dilution [MRD]) reported.

ADAb status for each visit will be derived as follows:

- Sample values that are either NS or PS and NI, and where the BKZ concentration is less than the validated ADAb assay drug tolerance limit (200 µg/mL), will be defined as **ADAb negative.**
- Sample values that are either NS or PS and NI and where the BKZ concentration exceeds the validated ADAb assay drug tolerance limit (200 µg/mL) will be defined as **inconclusive.**
- Sample values that are PS and PI will be defined as **ADAb positive** (regardless whether a titer is available or not)
- Missing if it does not go into one of the above categories.

If a sample is collected within 21 days (inclusive) before or after the visit date at which the drug was administered, the ADAb results for that sample will be associated with the scheduled visit and summarized accordingly. Samples collected outside this window will be excluded from the by-visit ADAb summaries and figures and will be listed only. This window will not apply to the summary of cumulative ADAb status, all available data will be used to derive the cumulative ADAb status.

The number and percentage of ADAb-positive and ADAb-negative subjects before self-injection (DV0004 Baseline) and after self-injection (at DV0004 Week 4 and PA0012 Week 8) will be summarized by visit. The ADAb visit status will be based on the confirmatory assay at the respective visit. This visit status and the overall status (considering data in DV0004 only and data in DV0004 and the feeder studies) will be used for the summary tables and will be based on the Safety Set.

Cumulative ADAb status is used for the box plots and summaries described in Section 9.1. Cumulative and overall ADAb status is derived as follows:

a. Considering data in DV0004 only:

- If a subject is ADAb positive at any time during DV0004 up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status for that and all subsequent

visits. This will be based on the confirmatory assay at each visit in DV0004 (Baseline, Week 4, Week 8).

- If a subject has only negative ADAb samples or only one missing/inconclusive sample with all negative ADAb samples up to that timepoint, the subject will be classified as negative.
- Otherwise, the study participant will be classified in the missing ADAb category.

b. Considering data in the feeder studies (PA0010, PA00011) and DV0004:

- If a subject is ADAb positive at any time in PA0010/PA0011 and DV0004 up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status for that and all subsequent visits. This will be based on the cumulative status at DV0004 Entry Visit (last visit in Feeder Study) and the confirmatory assay results in DV0004 (Week 4 and Week 8).
- If a subject has only negative ADAb samples or only one missing/inconclusive sample with all negative ADAb samples up to that timepoint, the subject will be classified as negative.
- Otherwise, the study participant will be classified in the missing ADAb category.

# 10 SAFETY ANALYSES

All safety analysis will be performed for SS-s and SS-a.

## 10.1 Extent of exposure

Extent of exposure is not relevant for the DV0004 substudy. Occurrence of adverse device effects in this substudy will not be affected by the duration of medication exposure.

## 10.2 Adverse events

All AEs (including serious adverse events [SAEs]) will be reported in a common database for PA0012 and DV0004, but only adverse device effects (ADEs), serious adverse device effects (SADEs), and device deficiencies will be summarized in the DV0004 substudy. Specifically, only those AEs related to the use of the investigational medical devices bimekizumab-SS-1mL or bimekizumab-AI-1mL (based on the Investigator's judgement) will be assessed. All AEs (including SAEs) which are not assessed to be related to the investigational devices will be summarized separately in the report for the main PA0012 study. An exception are AEs that are indicated as injection site reactions during self-injection. These will be listed in DV0004 as well as in PA0012.

### 10.2.1 Adverse device effects

Adverse events are recorded at the AE CRF page at the time when they occur. If an AE is related to the device by assessment of the investigator it is counted as an ADE.

All ADE data will be listed, and no statistical testing will be performed. Only treatment-emergent ADEs will be included in the summary tables. Treatment-emergent ADEs (TEADEs) will be defined as events related to the study device that have a start date on or following the first self. administration of study treatment in DV0004 through the final self-administration of study treatment + 7 days. The device SFU will occur 1 week after the last self-administration.

All ADEs will be coded and classified by system organ class, high level term, and preferred term. Adverse device effects will be summarized by the frequency and percentage of subjects having 1 or more of the events in question. Additional planned summaries include overall ADEs and SADEs. Summaries to be presented include:

- Incidence of TEADEs – Overview
- Incidence of TEADEs by SOC, HLT, and PT
- Incidence of serious TEADEs by SOC, HLT, and PT
- Incidence of TEADEs leading to death
- Incidence of TEADEs leading to discontinuation
- Incidence of non-TEADEs (only listed and not summarized in a table)

For definition of serious, unanticipated and unanticipated serious ADEs (USADEs) see protocol of DV0004.

Adverse device effects which started before DV0004 Week 4 and were ongoing at the data cut off will be included with the status remaining as ongoing. Adverse device effects which were ongoing at DV0004 Week 4 but with an end date before the data cut off will be included with their end date as recorded.

### 10.2.2 Impact of COVID-19 on adverse events

In order to assess the impact of the COVID-19 global pandemic on the primary safety endpoint of incidence of TEADEs and serious TEADEs, additional summaries will be presented. Summaries of TEADEs and Serious TEADEs will be presented by COVID-19 enrollment period and timing of the ADE relative to the WHO declared COVID-19 pandemic (enrolled prior to pandemic – ADE prior to pandemic, enrolled prior to pandemic – ADE during pandemic, enrolled during pandemic– ADE during pandemic), as defined in Section 4.9.1. ADEs leading to discontinuation will be presented by COVID-19 enrollment period and timing of ADE relative to the pandemic period as well.

For reporting purposes, AEs will be assigned to ‘Prior to COVID-19 pandemic’ or ‘During the COVID-19 pandemic’ based on the following:

- If the date of AE or ADE onset (based on imputed start date) is prior to 11 March 2020 the AE/ADE will be assigned as ‘Prior to COVID-19 pandemic’
- If the date of AE or ADE onset (based on imputed start date) is on or after 11 March 2020 the AE/ADE will be assigned as ‘During the COVID-19 pandemic’

A ‘Post the COVID-19 pandemic’ phase will not be assigned for AE reporting as the pandemic is expected to be ongoing at the time of last subject last visit.

### 10.2.3 Injection site reaction

Injection site reactions are recorded on the AE CRF page at the time when they occur. All AEs will be coded and classified by system organ class, high level term, and preferred term. An AE with High Level Terms of “Administration site reactions NEC” and “Injection site reactions” will be evaluated as injection site reaction.

All injection site reactions for self-injection with a start date on or following the first self-administration of study treatment through the final self-administration of study treatment + 7 days will be listed.

### 10.3 Clinical laboratory evaluations

All clinical laboratory evaluations including hematology, chemistry and urinalysis will be collected in PA0012.

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

Electronic case report form (eCRF) data of vital signs, electrocardiograms, physical examination and pregnancy test results will be collected in PA0012.

## 11 OTHER ANALYSES

This section contains a detailed description of the analysis of the primary, secondary and other outcome variables. All statistical analyses will be descriptive in nature. No inferential statistical analyses are planned. The analysis is done on FAS-s and FAS-a, respectively.

### 11.1 Primary outcome variable

The primary outcome variable is the percentage of all subjects able to self-administer safe and effective injections using the given device at DV0004 Week 4. Safe and effective self-injection will be evaluated by the study personnel as defined below:

- Complete dose delivery: Subject self-injects the complete dose of bimekizumab as confirmed by a visual inspection of the bimekizumab-SS-1mL or the bimekizumab-AI-1mL which shows that the IMP is delivered completely (i.e., the container is empty), and
- No ADEs that would preclude continued use of the device presentations for self-injection (i.e., no SADEs and/or ADEs leading to withdrawal from the DV0004 substudy).

All data to assess the primary outcome is collected on the subject self-injection of bimekizumab CRF page for DV0004 Week 4. For the number of subjects with safe and effective self-injections simply the cases which indicated “yes” for the question “Did the subject self-inject the complete dose of Bimekizumab” and “no” for the question “Were there any AEs related to use of the investigational device for self-injection” at DV0004 Week 4 are counted.

The number and percentage of subjects with safe and effective self-injections will be tabulated separately for each device presentation using the relevant FAS population (FAS-s or FAS-a). The 90% CIs based on the Exact Binomial method will be reported as well. The number and percentage of subjects with safe and effective self-injections is tabulated for each device presentation by COVID-19 enrollment period, as described in Section 4.9.1.

Assessments where the self-injection was not performed by the subject will not be included in any summary statistics.

### 11.2 Secondary outcome variable

The secondary outcome variable is the percentage of subjects able to self-administer safe and effective injections using the given device at DV0004 Baseline (the first self-injection visit,

immediately after training in the self-injection technique). Safe and effective self-injection will be evaluated by the study personnel.

The secondary outcome variable will be analyzed in the same manner as the primary outcome variable. All data to assess the secondary outcome is collected on "Subject self-injection of Bimekizumab" CRF page for DV0004 Baseline.

Assessments where the self-injection was not performed by the subject will not be included in any summary statistics.

## 11.3 Other outcome variables

The other outcome variables will be summarized using descriptive statistics and they will be tabulated separately for each device using the relevant FAS population.

Assessments where the self-injection was not performed by the subject will not be included in any summary statistics.

### 11.3.1 Pre-injection SIAQ (versions 2.0 and 2.1)

The pre-injection SIAQ (versions 2.0 and 2.1) will be performed at DV0004 Baseline prior to subject self-administration of treatment. Version 2.0 of the SIAQ will be used to assess bimekizumab-SS-1mL and version 2.1 of the SIAQ will be used to assess bimekizumab-AI-1mL. There are no differences in Version 2.0 to Version 2.1 in pre-injection SIAQ.

The pre-injection SIAQ consists of 7 items each with a scale of 1 to 5. There are three individual subscales (feelings about injections [FL, 3 items], self-confidence [CO, 3 items] and satisfaction with current mode of administration [SA, 1 item]). Each subscale score will be calculated using the average of the individual transformed item scores. The item score will be transformed using the following rule:

$$Transformed\ Item\ Score = \big((raw\ item\ score) - 1\big) \times 2.5$$

In the case of missing values, no subscale score will be calculated if more than 50% of the items within the subscale are missing. The subscale scores will be calculated out of the non-missing individual transformed item scores.

Higher individual scores of the pre-injection indicate more confidence, higher satisfaction and less concerns with self-injections.

Summary statistics for all individual items and each subscale score will be produced for DV0004 Baseline.

#### 11.3.1.1 Additional Analyses for Pre-injection SIAQ summaries

There will be an additional analysis to present the summary described in Section 11.3.1 for the subgroup of subjects who completed both the pre-injection SIAQ and the post-injection SIAQ correctly. This is defined as the pre-injection SIAQ being administered before injection, and the post-injection SIAQ being administered after injection. The subgroup will include subjects who completed both the pre-injection SIAQ and post-injection SIAQ correctly in relation to injection administration, and also completed the correct version of the questionnaire assigned based on the device group. A pre-injection SIAQ is considered to be impacted if it is administered after self-

injection. Summary statistics for all individual items and each subscale score will be produced for DV0004 Baseline.

### 11.3.2 Post-injection SIAQ (versions 2.0 and 2.1)

The post-injection SIAQ (versions 2.0 and 2.1) will be performed after subject self-administration of treatment. This will be performed at DV0004 Baseline and Week 4. Version 2.0 of the SIAQ will be used to assess bimekizumab-SS-1mL and version 2.1 of the SIAQ will be used to assess bimekizumab-AI-1mL. Version 2.0 and 2.1 of the SIAQ are identical, except for Question 11 due to different handling of the devices.

The post-injection SIAQ consists of 21 items on 6 individual subscales (FL [3 items], self-image [IM, 1 item], CO [3 items], injection-site reactions [RE, 2 items], ease of use [EU, 5 items] and satisfaction with self-injection [SA, 7 items]). The items of the individual subscale EU have a score range of 1 to 6, the other individual subscales have a score range of 1 to 5. Each subscale score will be calculated using the average of the individual transformed item scores. The item scores for the EU subscale will be transformed using the following rule:

$$Transformed\ Item\ Score = \big((raw\ item\ score) - 1\big) \times 2$$

The item scores for the other remaining subscales will be transformed using the following rule:

$$Transformed\ Item\ Score = \big((raw\ item\ score) - 1\big) \times 2.5$$

In the case of missing values, no subscale score will be calculated if more than 50% of the items within the subscale are missing. The subscale scores will be calculated out of the non-missing individual transformed item scores. If a subject completed the incorrect version of the questionnaire (for example, a subject randomized to bimekizumab-SS-1mL and completed version 2.1 of the post-injection SIAQ), then Q11 will be excluded from the derivation of Ease of Use subscale.

Higher individual subscale scores of the post-injection indicate more confidence, higher satisfaction and less concerns with self-injections.

Summary statistics for all individual items and each subscale score will be produced for DV0004 Baseline and Week 4.

#### 11.3.2.1 Additional Analysis for Post-injection SIAQ summaries

There will be an additional analysis performed for post-injection SIAQ. It will repeat the analysis described in Section 11.3.2 only including the subgroup of subjects who completed both the pre-injection SIAQ and the post-injection SIAQ correctly. A post-injection questionnaire is considered to be impacted if it is administered before self-injection, or if the incorrect post-injection SIAQ version has been administered for the randomized device group. Version 2.0 of the SIAQ will be used to assess bimekizumab-SS-1mL and version 2.1 of the SIAQ will be used to assess bimekizumab-AI-1mL. Subjects who either have an impacted pre- or post-injection SIAQ at any visit will be excluded from the summary. Note that subjects complete both pre- and post-injection questionnaires at Baseline, and only post-injection SIAQ at Week 4. Summary statistics for all individual items and each subscale score will be produced for DV0004 Baseline and Week 4.

### 11.3.3 Injection site pain

The visual analog scale (VAS) of injection site pain indicates the level of pain during the injection. It reaches from 0-100 mm with higher values for more severe pain and 0 for no pain.

Summary statistics of actual values at DV0004 Baseline and Week 4 and change from DV0004 Baseline values will be used to summarize injection site pain by visit after self-injection.

#### 11.3.3.1 Additional Analysis for Injection site pain

There will be an additional analysis of the summary described in Section 11.3.3 limited to subjects who correctly completed the visual analog scale of injection site pain after the injection at both visits. Summary statistics of actual values at DV0004 Baseline and Week 4 and change from DV0004 Baseline values will be used to summarize injection site pain by visit after self-injection.

### 11.3.4 Structural and mechanical integrity of the devices

The structural and mechanical integrity of the device after completion of self-injection will be assessed by the investigator after each injection in the "Subject self-injection of bimekizumab" CRF page. The assessment will be done using the questions for structural integrity. The structural integrity is based on a visual examination of the device that shows clear evidence of damage, compromised structural or mechanical integrity not superficial and/or cosmetic imperfections.

Frequency tables will be produced to show the number and percentage of devices with used bimekizumab-SS-1mL and bimekizumab-AI-1mL syringes identified as having structural integrity issues after completion of self-injection.

The 90% CIs based on the Exact Binomial method will be reported as well.

### 11.3.5 Functional integrity of the devices

The functional integrity of the device after completion of self-injection will be assessed by the investigator after each injection in the "Subject self-injection of bimekizumab" CRF page. The assessment will be done using the questions for function compromise. The functional integrity will be based on a visual examination of the device that shows clear evidence of damage and/or device does not function normally.

Frequency tables will be produced to show the number and percentage of devices with used bimekizumab-SS-1mL and bimekizumab-AI-1mL syringes identified as functionally compromised.

The 90% CIs based on the Exact Binomial method will be reported as well.

# 12 REFERENCES

# 13 APPENDICES

## 13.1 SAP Amendment 1

**Rational for the amendment**

Details regarding the handling of the early termination visit mapping, and the handling of missing dates have been updated following developments on other BKZ studies.

**Modifications and changes**

**Global changes**

The following changes were made throughout the SAP:

- The DV0004 study number was added before the study visit where it was necessary to distinguish it from the PA0012 study visits.
- The list of abbreviations was updated accordingly.
- Minor spelling, editorial, and formatting changes were made throughout the document.
- "Study participant" has been updated to "subject" throughout the document.
- Note that large sections of unchanged text have been substituted in this section with "[…]".

**Specific changes**

In addition to the global changes, the following specific changes have been made:

**Change #1**

**Section 2.3.5 Study duration per subject**

The maximum DV0004 substudy duration will be 5 weeks for each study subject. Study subjects will then continue to receive treatment in PA0012 for the duration of the PA0012 study. The end of the DV0004 substudy is defined as the date on which the last study subject completes his/her Week 5 Visit or withdraws from the study.

**Has been changed to:**

The maximum DV0004 substudy duration will be **4** weeks for each subject. Subjects will then continue to receive treatment in PA0012 for the duration of the PA0012 study. The end of the DV0004 substudy is defined as the date on which the last subject completes his/her **DV0004** Week **4** Visit or withdraws from the study.

**Change #2**

**Section 4.2 Handling of dropouts or missing data**

Partial ADE and concomitant medication start dates will be imputed as follows:

Imputation of Partial Start Dates

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date, then use the 1st of the month

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

Imputation of Partial Stop Dates

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

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

**Has been changed to:**

Partial ADE and concomitant medication start dates will be imputed as follows:

Imputation of Partial Start Dates

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

Imputation of Partial Stop Dates

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

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

- **If the year of start date is the same as the year of first dose and the stop date is after the date of first dose then set the start date to the date of first dose**

- **Otherwise set to the 1st January of the year of the start date**

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

**Change #3**

**Section 6.1 Demographics**

[…]

- DV0004 Baseline Weight (kg): will be derived from the weight from the last visit of the feeder study
- DV0004 Baseline BMI (kg/m$^2$)

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

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

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

- Age group (≤18, 19-<65, ≥65 years)
- DV0004 Body Weight (≤100kg, >100kg)

**Has been changed to:**

[…]

- Weight (kg) at **DV0004 Baseline: This will be derived from the weight from the last visit of the feeder study or DV0004 Entry Visit, since these visits will occur on the same day and weight is only collected once**
- **DV0004** Baseline BMI (kg/m$^2$)

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

$$BMI = \frac{Weight\ (kg)\ \boldsymbol{at\ DV0004\ Baseline}}{[Height\ (m)\ \boldsymbol{at\ Feeder\ Study\ Baseline}]^2}$$

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

- Age group (≤18, 19-<65, ≥65 years)
- Body Weight **at DV0004 Baseline** (≤100kg, >100kg)

**Change #4**

**Section 6.2 Other Baseline characteristics**

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

- Duration of disease (years)

Duration of disease (years) will be calculated as:

$$Disease\ duration = \frac{(Date\ of\ randomization\ in\ FS - Date\ of\ onset\ of\ PsA^{1})}{365.25}$$

[1] If the date of onset of PsA is partial, it should be imputed to the most recent feasible date (i.e., last day of the month if only day is missing, or last day of the year if day and month are missing).

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

- Duration of disease (<median, ≥median) based on the respective SS populations (SS-s and SS-a).

**Has been changed to:**

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

- Duration of disease (years)

Duration of disease (years) will be calculated as:

$$Disease\ duration = \frac{(Date\ of\ randomization\ \boldsymbol{in\ DV0004}\ - Date\ of\ onset\ of\ PsA^{1})}{365.25}$$

[1] If the date of onset of PsA is partial, it should be imputed to the most recent feasible date (i.e., last day of the month if only day is missing, or last day of the year if day and month are missing).

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

- Duration of disease (<median, ≥median) based on the respective SS populations (SS-s and SS-a).

**Change #5**

**Section 9.1 Pharmacokinetics**

The statistical analyses of the PK data will be descriptive in nature and will be summarized using the relevant device presentation-specific population (PK-PPS-s or PK-PPS-a). Data will be analyzed overall for each device presentation by injection type (self-administered or study personnel-administered), by injection site (abdomen or thigh), by anti-bimekizumab antibody status, and by BMI category. Three BMI categories will be defined based on tertiles derived from participants' Baseline BMI values. […]

Bimekizumab PK trough levels associated with injection by study personnel using the 1mL PFS (in PA0010 or PA0011) will be analyzed from the pre-injection PK sample collected at Baseline. Bimekizumab PK trough levels associated with participant self-injection using the assigned self-injecting device presentation will be analyzed from the pre-injection PK samples collected at Week 4 and Week 8 (of PA0012).

[…]

PK samples for self-administration where the injection was done by site personnel will be listed but not be used for summary statistics. PK samples for personnel administration where the

injection was done by the participant or caregiver, if applicable, will be listed but not be used for summary statistics.

[…]

Boxplots of plasma concentration will be presented by visit and by device presentation.

All PK results will be listed.

In addition, the PK results from all participants not in PK-PPS-s or PK-PPS-a will be listed based on the SS-a and SS-s.

**Has been changed to:**

The statistical analyses of the PK data will be descriptive in nature and will be summarized using the relevant device presentation-specific population (PK-PPS-s or PK-PPS-a). Data will be analyzed overall for each device presentation by injection type (self-administered or study personnel-administered), by injection site (abdomen or thigh), by anti-bimekizumab antibody visit status, and by BMI category. Three BMI categories will be defined based on tertiles derived from subjects' **DV0004** Baseline BMI values. **See Section 9.2 for details on classification of anti-bimekizumab antibody status. […]**

~~Bimekizumab PK trough levels associated with injection by study personnel using the 1mL PFS (in PA0010 or PA0011) will be analyzed from the pre-injection PK sample collected at Baseline. Bimekizumab PK trough levels associated with subject self-injection using the assigned self-injecting device presentation will be analyzed from the pre-injection PK samples collected at **DV0004** Week 4 and **PA0012** Week 8 (of PA0012).~~

[…]

PK samples for self-administration where the injection was done by site personnel **or care-giver** will be listed but not be used for summary statistics. PK samples for personnel administration where the injection was done by the subject or caregiver, if applicable, will be listed but not be used for summary statistics.

**Only pre-dose (trough) concentrations will be included while summarizing tables and figures. If the dosing for a visit is +/- 7 days out of window, then the plasma concentration from that visit and all subsequent visits will be excluded from the PK summary. PK samples collected after dosing will be excluded from summary statistics.**

[…] **Time from previous bimekizumab dose to DV0004 visit will be summarized by device presentation.**

Boxplots of plasma concentration will be presented by visit and by device presentation, **overall and by cumulative ADAb status. Cumulative ADAb status is defined in Section 9.2.**

All PK results will be listed. **Baseline PK samples are the PK samples prior to first dose of Bimekizumab at DV0004 entry visit.**

In addition, the PK results from all subjects not in PK-PPS-s or PK-PPS-a will be listed based on the SS-a and SS-s.

**Change #6**

**Section 9.2 Pharmacodynamics**

Not applicable.

**Has been changed to**

**Section 9.2 Pharmacodynamics and Immunogenicity**

The immunological variable is ADAb evaluated at DV0004 Baseline and DV0004 Week 4 visits.

ADAb will be assessed using a tiered approach: screening, confirmatory, and titer assays will be used.

**Samples will first be evaluated in the screening assay using a false positivity rate of 5% (reported as 'above the cut-point' ACP or 'below the cut-point' [BCP]), followed by analysis of screened positive samples (reported as ACP) in the confirmatory assay (which is a drug depletion assay) to confirm the true positivity of the samples (reported as either 'confirmed positive' [CP] or 'not confirmed positive' [NCP]). Samples that are CP will be evaluated in a titration assay to quantify the ADA level and will be reported as titer (reciprocal dilution factor including minimum required dilution [MRD]). Screening, confirmatory and titer cut points of the respective assays will be determined by the bioanalytical laboratory which will report the bioanalytical result from the respective assays.**

**If a sample is collected within 7 days (inclusive) before or after the visit date at which the drug was administered, the ADAb results for that sample will be associated with the scheduled visit and summarized accordingly. Samples collected outside this window and all subsequent samples for that subject will be excluded from the ADAb summaries and figures and will be listed only.**

**ADAb status will be derived as follows:**

- **Samples that are either BCP or ACP and NCP will be defined as ADAb negative.**
- **Sample values that are ACP and CP will be defined as ADAb positive (regardless of whether or not a titer is available)**

**The number and percentage of ADAb-positive and ADAb-negative subjects before self-injection (DV0004 Baseline) and after self-injection (at DV0004 Baseline and DV0004 Week 4) will be summarized by visit. The ADAb visit status will be based on the confirmatory assay at the respective visit. This visit status will be used for the summary tables.**

**Cumulative ADAb status is used for the box plots described in Section 9.1. Cumulative ADAb status is derived as follows:**

- **If a subject is ADAb positive at any time up to and including the respective visit, they are assigned ADAb cumulative positive status for that and all subsequent visits.**
- **Otherwise, the subject remains negative at that respective visit and assigned ADAb cumulative negative.**

**Change #7**

**Section 10.2 Adverse events**

All AEs (including serious adverse events [SAEs]) will be reported in a common database for PA0012 and DV0004, but only adverse device effects (ADEs), serious adverse device effects (SADEs), and device deficiencies will be summarized in the DV0004 substudy. Specifically, only those AEs related to the use of the investigational medical devices bimekizumab-SS-1mL or bimekizumab-AI-1mL (based on the Investigator's judgement) will be assessed. All AEs (including SAEs) which are not assessed to be related to the investigational devices will be summarized separately in the report for the main PA0012 study.

[…]

Additional planned summaries include overall ADEs and SADEs. Summaries to be presented include:

- Incidence of TEADEs – Overview
- Incidence of TEADEs by SOC, HLT, and PT
- Incidence of serious TEADEs by SOC, HLT, and PT
- Incidence of TEADEs leading to death
- Incidence of TEADEs leading to discontinuation
- Incidence of non-TEADEs

For definition of serious, unanticipated and unanticipated serious ADEs (USADEs) see protocol of DV0004.

Adverse device effects which started before Week 4 and were ongoing at the data cut off will be included with the status remaining as ongoing. Adverse device effects which were ongoing at Week 4 but with an end date before the data cut off will be included with their end date as recorded.

**Has been changed to:**

**10.2 Adverse events**

All AEs (including serious adverse events [SAEs]) will be reported in a common database for PA0012 and DV0004, but only adverse device effects (ADEs), serious adverse device effects (SADEs), and device deficiencies will be summarized in the DV0004 substudy. Specifically, only those AEs related to the use of the investigational medical devices bimekizumab-SS-1mL or bimekizumab-AI-1mL (based on the Investigator's judgement) will be assessed. All AEs (including SAEs) which are not assessed to be related to the investigational devices will be summarized separately in the report for the main PA0012 study. **An exception are AEs that are indicated as injection site reactions during self-injection. These will be listed in DV0004 as well as in PA0012.**

**10.2.1 Adverse device effects**

Adverse events are recorded at the AE CRF page at the time when they occur. If an adverse event is related to the device by assessment of the investigator it is counted as an adverse device event.

[…]

Additional planned summaries include overall ADEs and SADEs. Summaries to be presented include:

- Incidence of TEADEs – Overview
- Incidence of TEADEs by SOC, HLT, and PT
- Incidence of serious TEADEs by SOC, HLT, and PT
- Incidence of TEADEs leading to death
- Incidence of TEADEs leading to discontinuation
- **Incidence of non-TEADEs (only listed and not summarized in a table)**

For definition of serious, unanticipated and unanticipated serious ADEs (USADEs) see protocol of DV0004.

Adverse device effects which started before Week 4 and were ongoing at the data cut off will be included with the status remaining as ongoing. Adverse device effects which were ongoing at Week 4 but with an end date before the data cut off will be included with their end date as recorded.

### 10.2.2 Injection site reaction

**Injection site reactions are recorded at the AE CRF page at the time when they occur. All AEs will be coded and classified by system organ class, high level term, and preferred term. An AE with High Level Terms of "Administration site reactions NEC" and "Injection site reactions" will be evaluated as injection site reaction.**

**All injection site reactions for self-injection with a start date on or following the first self-administration of study treatment through the final self-administration of study treatment + 7 days will be listed.**

## 13.2 SAP Amendment 2

**Rational for the amendment**

Details regarding the handling of COVID-19 pandemic data have been added to the SAP. The summaries for the PK data have been updated following discussions in the Data Evaluation Meeting (#2). A sensitivity analysis for the SIAQ data has been added following DEM2.

**Modifications and changes**

**Global changes**

The following changes were made throughout the SAP:

- The addition of clarification of which outputs are to be presented to assess the impact of COVID-19 pandemic.
- Sections have been renumbered to account for new COVID-related sections. These will not be individually noted.

**Specific changes**

**Change #1**

Text added at the end of Section.

**Section 3.3 Protocol deviations**

**[..] Following the declaration of the global COVID-19 pandemic by the World Health Organization in March 2020, protocol deviations will be identified as "related to COVID-19" where applicable.**

**Change #2**

Subsection added for Section 3.8 Changes to protocol-defined analyses.

**Section 3.8.1 Changes related to COVID-19**

The impact of the COVID-19 pandemic on study procedures and/or conduct and on the primary safety endpoints (TEADEs, serious TEADEs, and study withdrawal due to TEADEs) will be investigated and additional outputs provided as appropriate. These analyses were not planned as part of the protocol as the pandemic scale was unprecedented.

The additional analyses are described in the following sections of the SAP:

- Subject disposition, including details of impacted visits and effects on collection and reporting of efficacy data (Section 5.1.1)
- Protocol deviations potentially related to COVID-19 (Section 5.2)
- Impact of COVID-19 on study (Section 5.3 )
- Demographics, baseline characteristics (Sections 6.1 and 6.2 )
- Adverse events (Section 10.2.2)
- Primary outcome variable (Section 11.1 )

**Change #3**

Subsection added to Section 4.9 Additional study-specific information.

**Section 4.9.1 COVID-19 category definition**

The coronavirus disease of 2019 (COVID-19) pandemic was declared by the WHO on 11 March 2020. The worldwide pandemic restricted travel and had potential impact on ongoing clinical trials. The following definitions will be used to present pre-specified summaries:

- *Pre-pandemic:* Events or assessments occurring before 11-Mar-2020
- *During pandemic*: Events or assessments occurring on or after 11-Mar-2020

A post-pandemic definition is not applicable to this short study.

**Change #4**

Subsection added to Section 5.1 Subject disposition.

**Section 5.1.1 Impact of COVID-19 on subject disposition**

Subject disposition will also be summarized by COVID-19 enrollment period (pre- and during-pandemic), as defined in Section 4.9.1. The number of completed, missed and partial visits will be presented by COVID-19 enrollment period.

**Change #5**

**Section 5.2 Protocol deviations**

A summary of number and percentage of subjects with an important protocol deviation (including a summary of subjects excluded from any analysis set due to important protocol deviations) by DV0004 device group will be provided for the SS-s and SS-a.

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

**Has been changed to**

A summary of number and percentage of subjects with an important protocol deviation (including a summary of subjects excluded from any analysis set due to important protocol deviations) by DV0004 device group will be provided for the SS-s and SS-a. **A summary of COVID-19 related important device protocol deviations will be presented by visit for the SS-s and SS-a. COVID-19 related important protocol deviations will be identified by the prefix of "COVID" in the deviation verbatim text.**

By-subject listings of important protocol deviations **and COVID-related important device protocol deviations** will be provided separately.

**Change #6**

Section added:

**Section 5.3 Impact of COVID-19**

The impact of the COVID-19 pandemic on study procedures and conduct, such as missed/remote visits, interruption of study treatment, will be documented using the information collected on a

dedicated eCRF page. The number and percentage of subjects impacted by COVID-19 will be presented overall and by country.

A by-subject listing of the impact of COVID-19 on study visits will be provided.

**Change #7**

Text added to section.

**9.1 Pharmacokinetics**

**PK samples at DV0004 baseline will be summarized under administration by site personnel (since the previous dose was given by site personnel).** PK samples associated with self-administration (at Week 4 and Week 8), but where the previous injection was done by site personnel or care-giver, will be listed but not be used for summary statistics.

Only pre-dose (trough) concentrations will be included while summarizing tables and figures. If the dosing for a visit is +/- 7 days out of window, then the plasma concentration from that visit will be excluded from the PK summary. **PK samples are expected to be collected prior to dosing. PK samples collected >14 days after the preceding dose and no later than 1 hour after the current dose will be included in the summary.** PK samples collected **later than 1 hour** after dosing will be excluded from summary statistics. **PK results at visits following a previous non-dosing visit will be excluded from summary statistics.**

[…]

Boxplots of plasma concentration will be presented by visit, by device presentation, and by cumulative ADAb status. Cumulative ADAb status is defined in Section 9.2. **Boxplots of plasma concentration will be presented by visit, by device presentation and by injection site, and by BMI tertile.**

All PK results will be listed. Baseline PK samples are the PK samples prior to first dose of Bimekizumab at DV0004 entry visit.

In addition, the PK results from all subjects not in PK-PPS-s or PK-PPS-a will be listed based on the SS-a and SS-s. **All concentrations will be listed as received, prior to any substitution of BLQ and LLOQ values. The listing will include flags for concentration that were excluded from the summary statistics, with the reason for exclusion.**

**Change #8**

Section 9.2 “Pharmacodynamics and Immunogenicity” renamed to “Immunogenicity”.

[..]

If a sample is collected within 7 days (inclusive) before or after the visit date at which the drug was administered, the ADAb results for that sample will be associated with the scheduled visit and summarized accordingly. Samples collected outside this window and all subsequent samples for that subject will be excluded from the ADAb summaries and figures and will be listed only.

[..]

Cumulative ADAb status is used for the box plots described in Section 9.1. Cumulative ADAb status is derived as follows:

- If a subject is ADAb positive at any time up to and including the respective visit, they are assigned ADAb cumulative positive status for that and all subsequent visits.
- Otherwise, the subject remains negative at that respective visit and assigned ADAb cumulative negative.

**Has changed to**

[..]

If a sample is collected within **21** days (inclusive) before or after the visit date at which the drug was administered, the ADAb results for that sample will be associated with the scheduled visit and summarized accordingly. Samples collected outside this window ~~and all subsequent samples for that subject~~ will be excluded from the by-visit ADAb summaries and figures and will be listed only. **This window will not apply to the summary of cumulative ADAb status, all available data will be used to derive the cumulative ADAb status.**

[..]

Cumulative ADAb status is used for the box plots described in Section 9.1. Cumulative ADAb status is derived as follows:

**a. Considering data in DV0004 only:**

- If a subject is ADAb positive at any time **during DV0004** up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status for that and all subsequent visits. **This will be based on the confirmatory assay at each visit in DV0004 (Baseline, Week 4, Week 8).**
- Otherwise, the subject remains negative at that respective **DV0004** visit and assigned ADAb cumulative negative.

**b. Considering data in the feeder studies (PA0010, PA00011) and DV0004:**

- **If a subject is ADAb positive at any time in PA0010/PA0011 and DV0004 up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status for that and all subsequent visits. This will be based on the cumulative status at DV0004 Entry Visit (last visit in Feeder Study) and the confirmatory assay results in DV0004 (Week 4 and Week 8).**
- **Otherwise, the subject remains negative at that respective DV0004 visit and assigned ADAb cumulative negative.**

**Change #9**

Subsection 10.2.2 Impact of COVID-19 on adverse events added.

**Section 10.2.2 Impact of COVID-19 on adverse events**

In order to assess the impact of the COVID-19 global pandemic on the primary safety endpoint of incidence of TEADEs and serious TEADEs, additional summaries will be presented. Summaries of TEADEs and Serious TEADEs will be presented by COVID-19 enrollment period

and timing of the ADE relative to the WHO declared COVID-19 pandemic (enrolled prior to pandemic – ADE prior to pandemic, enrolled prior to pandemic – ADE during pandemic, enrolled during pandemic– ADE during pandemic), as defined in Section 4.9.1. ADEs leading to discontinuation will be presented by COVID-19 enrollment period and timing of ADE relative to the pandemic period as well.

For reporting purposes, AEs will be assigned to 'Prior to COVID-19 pandemic' or 'During the COVID-19 pandemic' based on the following:

- If the date of AE or ADE onset (based on imputed start date) is prior to 11 March 2020 the AE/ADE will be assigned as 'Prior to COVID-19 pandemic'
- If the date of AE or ADE onset (based on imputed start date) is on or after 11 March 2020 the AE/ADE will be assigned as 'During the COVID-19 pandemic'

A 'Post the COVID-19 pandemic' phase will not be assigned for AE reporting as the pandemic is expected to be ongoing at the time of last subject last visit.

**[..]**

## 13.3 SAP Amendment 3

**Rational for the amendment**

An additional set of analyses for the SIAQ and VAS data has been added following data cleaning. The details for this analysis have been added to the SAP text in Section 11.3.1, Section 11.3.2 and Section 11.3.3.

**Modifications and changes**

**Specific changes**

**Change #1**

Clarification added to the derivation of the subscale scores when missing data occurs.

**Section 9.1 Pharmacokinetics**

[…]

PK summaries will be based on observed values. No imputation will be used. However, if plasma concentration measurements are below the level of quantification, then for calculation of the derived statistics the result will be set to ½ of the lower level of quantification (LLOQ). Descriptive statistics including the geometric mean, geometric coefficient of variation, and geometric mean 95% confidence interval (CI) if applicable will be calculated if at least ⅔ of the values of interest are above the LLOQ. If this is not the case, only median, minimum, and maximum will be presented. Time from previous bimekizumab dose to DV0004 visit will be summarized by device presentation.

**Has changed to**

**[…]**

PK summaries will be based on observed values. No imputation will be used. However, if plasma concentration measurements are below the level of quantification, then for calculation of the derived statistics the result will be set to ½ of the lower level of quantification (LLOQ). Descriptive statistics including the geometric mean, geometric coefficient of variation, and geometric mean 95% confidence interval (CI) if applicable will be calculated if at least ⅔ of the values of interest are above the LLOQ. If this is not the case, only median, minimum, and maximum will be presented. Time from previous bimekizumab dose to DV0004 visit will be summarized by device presentation.

**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**

**Change #2**

Clarification added to the derivation of the subscale scores when missing data occurs.

**Section 11.3.1 Pre-injection SIAQ (versions 2.0 and 2.1)**

[…]

In the case of missing values, no subscale score will be calculated if more than 50% of the items within the subscale are missing.

**Has changed to**

**[…]**

In the case of missing values, no subscale score will be calculated if more than 50% of the items within the subscale are missing. **The subscale scores will be calculated out of the non-missing individual transformed item scores.**

**Change #3**

Subsection 11.3.1.1 has been added.

**Section 11.3.1.1 Additional Analysis for Pre-injection SIAQ**

There will be an additional analysis to present the summary described in Section 11.3.1 for the subgroup of subjects who completed both the pre-injection SIAQ and the post-injection SIAQ per protocol. The subgroup will include subjects who completed the pre-injection SIAQ and post-injection SIAQ correctly in relation to injection administration, and also completed the correct version of the questionnaire assigned based on the device group. A pre-injection SIAQ is considered to be impacted if it is administered after self-injection. Summary statistics for all individual items and each subscale score will be produced for DV0004 Baseline.

**Change #4**

Clarification added to the derivation of Ease of Use subscale and the derivation of the subscale scores when missing data occurs.

**Section 11.3.2 Post-injection SIAQ (versions 2.0 and 2.1)**

[…]

In the case of missing values, no subscale score will be calculated if more than 50% of the items within the subscale are missing.

**[…]**

**Has changed to**

**[…]**

In the case of missing values, no subscale score will be calculated if more than 50% of the items within the subscale are missing. **The subscale scores will be calculated out of the non-missing individual transformed item scores. If a subject completed the incorrect version of the questionnaire (for example, a subject randomized to bimekizumab-SS-1mL and completed version 2.1 of the post-injection SIAQ), then Q11 will be excluded from the derivation of Ease of Use subscale.**

**[…]**

**Change #5**

Subsection 11.3.2.1 has been added.

**Section 11.3.2.1 Additional Analysis for Post-injection SIAQ**

There will be an additional analysis performed for post-injection SIAQ. It will repeat the analysis described in Section 11.3.2 only including the subgroup of subjects who completed both the pre-injection SIAQ and the post-injection SIAQ correctly as described in the protocol. A post-injection questionnaire is considered to be impacted if it is administered before self-injection, or longer than 30 minutes after self-injection, or if the incorrect post-injection SIAQ version has been administered for the randomized device group. Version 2.0 of the SIAQ will be used to assess bimekizumab-SS-1mL and version 2.1 of the SIAQ will be used to assess bimekizumab-AI-1mL. Subjects who have an impacted pre- or post-injection SIAQ at any visit will be excluded from the summary. Note that subjects complete both pre- and post-injection questionnaires at Baseline, and only post-injection SIAQ at Week 4. Summary statistics for all individual items and each subscale score will be produced for DV0004 Baseline and Week 4.

**Change #6**

Subsection 11.3.3.1 has been added.

**Section 11.3.3.1 Additional Analysis for Injection site pain**

There will be an additional analysis of the summary described in Section 11.3.3 limited to subjects who correctly completed the visual analog scale of injection site pain after the injection at both visits. Summary statistics of actual values at DV0004 Baseline and Week 4 and change from DV0004 Baseline values will be used to summarize injection site pain by visit after self-injection.

## 13.4 SAP Amendment 4

**Rational for the amendment**

Aligning the immunogenicity text to use the terminology for ADAb samples consistent with the BKZ program. No change to analyses, administrative change.

**Specific Changes**

**Change #1**

**Section 9.1 Pharmacokinetics**

[…]

Boxplots of plasma concentration will be presented by visit, by device presentation, and by cumulative ADAb status. Cumulative ADAb status is defined in Section 9.2. Boxplots of plasma concentration will be presented by visit, by device presentation and by injection site, and by BMI tertile.

[…]

**Has been updated to**

[…]

Boxplots **and summaries** of plasma concentration will be presented by visit, by device presentation, and by cumulative ADAb status **considering DV0004 alone and considering DV0004 and the feeder studies (see Section 9.2**). Cumulative ADAb status is defined in Section 9.2. Boxplots **and summaries** of plasma concentration will be presented by visit, by device presentation and by injection site, and by BMI tertile.

**[…]**

**Change #2**

**Section 9.2 Immunogenicity**

The immunological variable is anti-bimekizumab antibodies (ADAb) evaluated at DV0004 Baseline and Week 4, and PA0012 Week 8 visits. To allow for an analysis of ADAb, blood samples will be taken before self-injection at the DV0004 Baseline Visit and DV0004 Week 4 (Visit 2), and before injection by site personnel at PA0012 Week 8 (Visit 3 of PA0012). ADAb status at or prior to the PK sampling (at DV0004 Baseline, DV0004 Week 4, and PA0012 Week 8) will be used in the summaries.

ADAb will be assessed using a tiered approach: screening, confirmatory, and titer assays will be used.

Samples will first be evaluated in the screening assay using a false positivity rate of 5% (reported as 'above the cut-point' ACP or 'below the cut-point' [BCP]), followed by analysis of screened positive samples (reported as ACP) in the confirmatory assay (which is a drug depletion assay) to confirm the true positivity of the samples (reported as either 'confirmed positive' [CP] or 'not confirmed positive' [NCP]). Samples that are CP will be evaluated in a titration assay to quantify the ADAb level and will be reported as titer (reciprocal dilution factor including minimum required dilution [MRD]). Screening, confirmatory and titer cut points of the respective assays

will be determined by the bioanalytical laboratory which will report the bioanalytical result from the respective assays.

If a sample is collected within 21 days (inclusive) before or after the visit date at which the drug was administered, the ADAb results for that sample will be associated with the scheduled visit and summarized accordingly. Samples collected outside this window will be excluded from the by-visit ADAb summaries and figures and will be listed only. This window will not apply to the summary of cumulative ADAb status, all available data will be used to derive the cumulative ADAb status.

ADAb status will be derived as follows:

- Samples that are either BCP or ACP and NCP will be defined as **ADAb negative.**
- Sample values that are ACP and CP will be defined as **ADAb positive** (regardless of whether or not a titer is available)

[…]

The number and percentage of ADAb-positive and ADAb-negative subjects before self-injection (DV0004 Baseline) and after self-injection (at DV0004 Week 4 and PA0012 Week 8) will be summarized by visit. The ADAb visit status will be based on the confirmatory assay at the respective visit. This visit status will be used for the summary tables.

[…]

The number and percentage of ADAb-positive and ADAb-negative subjects before self-injection (DV0004 Baseline) and after self-injection (at DV0004 Week 4 and PA0012 Week 8) will be summarized by visit. The ADAb visit status will be based on the confirmatory assay at the respective visit. This visit status and the overall status (considering data in DV0004 only and data in DV0004 and the feeder studies) will be used for the summary tables and will be based on the Safety Set.

Cumulative ADAb status is used for the box plots and summaries described in Section 9.1. Cumulative ADAb status is derived as follows:

a. Considering data in DV0004 only:

- If a subject is ADAb positive at any time during DV0004 up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status for that and all subsequent visits. This will be based on the confirmatory assay at each visit in DV0004 (Baseline, Week 4, Week 8).
- Otherwise, the subject remains negative at that respective DV0004 visit and assigned ADAb cumulative negative.

b. Considering data in the feeder studies (PA0010, PA00011) and DV0004:

- If a subject is ADAb positive at any time in PA0010/PA0011 and DV0004 up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status for that and all subsequent visits. This will be based on the cumulative status at DV0004

Entry Visit (last visit in Feeder Study) and the confirmatory assay results in DV0004 (Week 4 and Week 8).

- Otherwise, the subject remains negative at that respective DV0004 visit and assigned ADAb cumulative negative.

**Has been updated to**

The immunological variable is anti-bimekizumab antibodies (ADAb) evaluated at DV0004 Baseline and Week 4, and PA0012 Week 8 visits. To allow for an analysis of ADAb, blood samples will be taken before self-injection at the DV0004 Baseline Visit and DV0004 Week 4 (Visit 2), and before injection by site personnel at PA0012 Week 8 (Visit 3 of PA0012). ADAb status at or prior to the PK sampling (at DV0004 Baseline, DV0004 Week 4, and PA0012 Week 8) will be used in the summaries.

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

~~Samples will first be evaluated in the screening assay using a false positivity rate of 5% (reported as 'above the cut-point' ACP or 'below the cut-point' [BCP]), followed by analysis of screened positive samples (reported as ACP) in the confirmatory assay (which is a drug depletion assay) to confirm the true positivity of the samples (reported as either 'confirmed positive' [CP] or 'not confirmed positive' [NCP]). Samples that are CP will be evaluated in a titration assay to quantify the ADAb level and will be reported as titer (reciprocal dilution factor including minimum required dilution [MRD]). Screening, confirmatory and titer cut points of the respective assays will be determined by the bioanalytical laboratory which will report the bioanalytical result from the respective assays.~~

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

**ADAb status for each visit will be derived as follows:**

- **Samples that are either NS or PS and NI will be defined as ADAb negative.**
- **Sample values that are either NS or PS and NI and where the BKZ concentration exceeds the validated ADAb assay drug tolerance limit (200 µg/mL) will be defined as inconclusive.**
- **Sample values that are PS and PI will be defined as ADAb positive (regardless whether a titer is available or not)**
- **Missing if it does not go into one of the above categories.**

If a sample is collected within 21 days (inclusive) before or after the visit date at which the drug was administered, the ADAb results for that sample will be associated with the scheduled visit and summarized accordingly. Samples collected outside this window will be excluded from the by-visit ADAb summaries and figures and will be listed only. This window will not apply to the summary of cumulative ADAb status, all available data will be used to derive the cumulative ADAb status.

~~ADAb status will be derived as follows:~~

- ~~Samples that are either BCP or ACP and NCP will be defined as **ADAb negative.**~~
- ~~Sample values that are ACP and CP will be defined as **ADAb positive** (regardless of whether or not a titer is available)~~

[…]

The number and percentage of ADAb-positive and ADAb-negative subjects before self-injection (DV0004 Baseline) and after self-injection (at DV0004 Week 4 and PA0012 Week 8) will be summarized by visit. The ADAb visit status will be based on the confirmatory assay at the respective visit. This visit status **and the overall status (considering data in DV0004 only and data in DV0004 and the feeder studies)** will be used for the summary tables **and will be based on the Safety Set**.

[…]

The number and percentage of ADAb-positive and ADAb-negative subjects before self-injection (DV0004 Baseline) and after self-injection (at DV0004 Week 4 and PA0012 Week 8) will be summarized by visit. The ADAb visit status will be based on the confirmatory assay at the respective visit. This visit status and the overall status (considering data in DV0004 only and data in DV0004 and the feeder studies) will be used for the summary tables and will be based on the Safety Set.

Cumulative ADAb status is used for the box plots and summaries described in Section 9.1. Cumulative **and overall** ADAb status is derived as follows:

a. Considering data in DV0004 only:

- If a subject is ADAb positive at any time during DV0004 up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status for that and all subsequent visits. This will be based on the confirmatory assay at each visit in DV0004 (Baseline, Week 4, Week 8).
- ~~Otherwise, the subject remains~~ **If a subject has only** negative ~~at that respective DV0004 visit and assigned~~ ADAb ~~cumulative~~ **samples or only one missing/inconclusive sample with all negative ADAb samples up to that timepoint, the subject will be classified as** negative.
- **Otherwise, the study participant will be classified in the missing ADAb category.**

b. Considering data in the feeder studies (PA0010, PA00011) and DV0004:

- If a subject is ADAb positive at any time in PA0010/PA0011 and DV0004 up to and including the respective DV0004 visit, they are assigned ADAb cumulative positive status

for that and all subsequent visits. This will be based on the cumulative status at DV0004 Entry Visit (last visit in Feeder Study) and the confirmatory assay results in DV0004 (Week 4 and Week 8).

- ~~Otherwise, the subject remains~~ **If a subject has only** negative ~~at that respective DV0004 visit and assigned~~ ADAb ~~cumulative~~ **samples or only one missing/inconclusive sample with all negative ADAb samples up to that timepoint, the subject will be classified as** negative.
- **Otherwise, the study participant will be classified in the missing ADAb category.**

# 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

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