STATISTICAL ANALYSIS PLAN AMENDMENT 5

Study: AS0008

Product: Bimekizumab

A multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose ranging study to evaluate the efficacy and safety of bimekizumab in subjects with active ankylosing spondylitis

SAP/Amendment Number	Date
Final SAP	4 Apr 2017
Amendment 1	16 Aug 2017
Amendment 2	06 Nov 2017
Amendment 3	02 Mar 2018
Amendment 4	30 Jul 2018
Amendment 5	07 Sep 2018

Confidentiality Statement

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LIST OF ABBREVIATIONS

A	Assessment
AbAb	Anti-bimekizumab antibody
ACP	Above the cut point
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AS	Ankylosing spondylitis
ASAS20,40,5/6	Assessment in SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score-C-reactive protein
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score major improvement
ASQoL	Ankylosing Spondylitis Quality of Life
ASspiMRI-a	Ankylosing Spondylitis spine Magnetic Resonance Imagine-activity
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCP	Below the cut point
BKZ	Bimekizumab
BLQ	Below the level of quantification
BMI	Body mass index
BUN	Blood urea nitrogen
cDBRS	corrected Dose-Blind Responder Set
CDISC	Clinical Data Interchange Standards Consortium
cESS	corrected Escape Subject Set

CP	Confirmed positive
CPK	Creatine phosphokinase
CRP	C-reactive protein
CV	Coefficient of variance
DBRS	Dose-Blind Responder Set
DBS	Dose-Blind Set
DEM	Data evaluation meeting
DMARD	Disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
EAER	Exposure adjusted event rate
EAIR	Exposure adjusted incidence rate
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eC-SSRS	Electronic Columbia-Suicide Severity Rating Scale
ES	Enrolled Set
ESS	Escape Subject Set
GGT	Gamma glutamyltransferase
H	High
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale—Anxiety
HADS-D	Hospital Anxiety and Depression Scale—Depression
HBcAb-IgM	Hepatitis B core antibody-IgM
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLGT	High-level group terms
HLT	High Level Terms
hs-CRP	High sensitivity C-reactive protein
IIT	Intent-to-treat
IL	Interleukin
IMP	Investigational medicinal product
INR	International normalized ratio

FAS	Full Analysis Set
L	Low
LDH	Lactate dehydrogenase
IgM	Immunoglobulin M
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
LOCF	Last non-missing observation
MAR	Missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Index
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCMC	Markov-Chain Monte Carlo
MCS	Mental component summary
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MOS	Medical Outcomes Study
MRI	Magnetic resonance imaging
N/A	Not applicable
N	Number of subjects
n	Number of observations
NCP	Not confirmed positive
NRI	Non-responder imputation
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OMERACT	Outcome Measures in Rheumatology Clinical Trials
OR	Odds ratio
PCS	Physical component summary
PD	Pharmacodynamics
PDILI	Potential drug-induced liver injury
PD-PPS	Pharmacodynamics Per-Protocol Set
PGADA	Patient's Global Assessment of Disease Activity

PhGADA	Physician's Global Assessment of Disease Activity
PK	Pharmacokinetic
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PT	Preferred term
Q4W	Every 4 weeks (monthly)
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RCTC	Rheumatology Common Toxicity Criteria
RNA	Ribonucleic acid
RS	Randomized Set
S	Score
SAE	Serious adverse event
SAP	Statistical analysis plan
sc	Subcutaneous(ly)
SD	Standard deviation
SE	Standard error
SF-36	Short-Form 36-item Health Survey
SFU	Safety Follow-up
SI	Sacroiliac
SOC	System organ class
SMQ	Standard MedDRA query
SPARCC	Spondyloarthritis Research Consortium of Canada
SS	Safety Set
STIR	Short-tau-inversion recovery
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TFLs	tables, figures, and listings
TNF	Tumor necrosis factor
TNFα	Tumor necrosis factor alpha

LCL	Lower confidence limit
UCL	Upper confidence limit
ULN	Upper limit of normal
VU	Vertebral units
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required interim and final statistical analysis for study AS0008. It also defines the summary tables, figures, and listings (TFLs) to be generated in the clinical study report according to the final protocol (29 Jul 2016), Protocol Amendment 1 (15 Mar 2017), and Protocol Amendment 2 (09 Mar 2018).

The content of this SAP is compatible with the International Conference on Harmonization/ Food and Drug Administration E9 Guidance documents (1998).

2 PROTOCOL SUMMARY

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to investigate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of bimekizumab (also known as UCB4940) compared with placebo in adult subjects with active ankylosing spondylitis (AS) in order to guide the selection of doses and clinical indices in the Phase 3 development program.

Eligible subjects will have active AS, determined by documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS, including symptoms for ≥3 months and age of onset <45. Furthermore, subjects will have moderate to severe active disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4 and spinal pain ≥4 [BASDAI Question 2]). Subjects must have at least 1 of the following: 1) inadequate response to nonsteroidal anti-inflammatory drug (NSAID) therapy, 2) intolerance to administration of at least 1 NSAID, or 3) contraindication(s) to NSAID therapy. Inadequate response to an NSAID is defined as lack of response for at least 4 weeks of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or the lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for at least 4 weeks total duration. Subjects may be tumor necrosis factor (TNF) inhibitor-naïve or may have received 1 prior TNF inhibitor.

An estimated 100 sites in Europe and North America will randomize 285 subjects (57 subjects per treatment arm). The enrollment of TNF inhibitor-experienced subjects will be limited to 30% of the total study population.

The study consists of a Screening Period (up to 28 days), Double-Blind Period (12 weeks), Dose-Blind Period (36 weeks) and Safety Follow-up (SFU) Period (20 weeks, only for subjects who do not enter the extension study). Therefore, the maximum duration of the study is 68 weeks.

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to assess the dose-response based on the efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) for 12 weeks in the treatment of subjects with active AS.

2.1.2 Secondary objectives

The secondary objectives of the study are as follow:

- To assess the efficacy of the individual dose regimens of bimekizumab compared to placebo

- To assess the safety and tolerability of bimekizumab
- To assess the PK of bimekizumab
- To assess the PD of bimekizumab
- To assess the immunogenicity of bimekizumab
- To assess the exposure:response relationship of bimekizumab as it related to efficacy and safety

2.1.3 Other objectives

- To assess disease activity
- To assess the impact on patient-reported quality of life (function, fatigue, sleep, and pain)
- To assess the impact on enthesitis
- To assess the impact of administration of bimekizumab on biological pathways relating to disease biology, progression, and response to therapy via biomarker analysis, and to enable genomic and related approaches for analysis of subject samples and evaluation of the potential for subject stratification approaches
- To assess the impact of bimekizumab on inflammatory changes in the spine and sacroiliac (SI) joint using magnetic resonance imaging (MRI) in a subset of subjects

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

The primary efficacy variable for this study is a follows:

- Assessment in SpondyloArthritis International Society 40% (ASAS40) response at Week 12

2.2.1.2 Secondary efficacy variables

The secondary efficacy variable for this study is as follows:

- Change from Baseline in Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) at Week 12
- Assessment in SpondyloArthritis International Society 20% (ASAS20) response at Week 12
- Assessment in SpondyloArthritis International Society 5 out of 6 response criteria (ASAS5/6) response at Week 12
- Change from Baseline in BASDAI at Week 12
- Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 12

2.2.1.3 Other efficacy variables

Other efficacy variables will be assessed as specified in Section 8.3.

- ASAS40 response (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Time to ASAS40 response

- Change from Baseline in ASDAS-CRP (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- ASDAS status (eg, inactive disease, moderate, high and very high disease activity) (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- ASAS20 response (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Time to ASAS20 response
- ASAS5/6 response (Week 4, 8, 12, 16, 24, 36, 48)
- Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- ASAS partial remission (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in BASDAI (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in BASFI (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) (Week 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in the Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index (Week 4, 12, 48)
- Physician's Global Assessment of Disease Activity (PhGADA) (Week 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in Patient's Global Assessment of Disease Activity (PGADA) (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in total and nocturnal spinal pain (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in the average of Questions 5 and 6 of the BASDAI [redacted] (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline in Physical Component Summary (PCS) and Mental Component Summary (MCS) of the Short-Form 36-Item Health Survey (SF-36) (Week 4, 12, 16, 24, 36, 48)
- Change from Baseline in Sleep quality (Medical Outcomes Study [MOS]-12 item scale) (Week 4, 12, 16, 24, 36, 48)
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) (Week 4, 8, 12, 16, 24, 36, 48)
- Change from Baseline (Week 12, 48) in:
  - Spondyloarthritis Research Consortium of Canada (SPARCC) MRI (SI Joint) score, and
  - Ankylosing Spondylitis spine MRI- activity (ASspiMRI-a) (Berlin modification) score
- Change from Baseline in Hospital Anxiety and Depression Scale - Anxiety (HADS-A) and Hospital Anxiety and Depression Scale - Depression (HADS-D) scores (Week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48)

- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores) (Week 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48)

2.2.2 Pharmacokinetic/pharmacodynamic variables

2.2.2.1 Pharmacokinetic and pharmacodynamic variables

The PK variables are plasma concentration of bimekizumab.

The PD variables are concentrations of cytokines of relevance to the interleukin (IL)-17A/F signaling pathway and AS biology, and include but are not limited to IL-17A, IL-17F, IL-23, IL-6, and tumor necrosis factor alpha (TNFα).

2.2.3 Pharmacogenomic variables

Where local regulations permit, additional blood samples will be collected from consenting subjects at specific time points and stored at -80°C for up to 20 years to allow for potential, exploratory analyses of genomic, genetic, proteomic, and metabolomic biomarkers relevant to disease biology and progression, response to therapy, and the inflammatory and immune response processes.

Analysis will include, but not be limited to genotyping of human leukocyte antigen (HLA) alleles (HLA Cw6, HLAB27, etc.).

2.2.4 Immunological variables

Immunological variables allow evaluation of immunogenicity as well as immunological biomarkers.

- Anti-bimekizumab antibody (AbAb) detection prior to and following study treatment
- Serum complement concentrations
- Flow cytometry analysis of key immune cell populations, including but not limited to CD3, CD19, CD4, CD8, and CD69 (using fluorescence activated cell sorting)
- Cytokines and other exploratory markers

2.2.5 Safety variables

Safety variables to be assessed as specified in Section 10 are as follows:

- Incidence of adverse events (AEs) and serious adverse events (SAEs)
- Withdrawal due to AEs
- Change from Baseline in vital signs (blood pressure, pulse rate) and body weight
- Standard 12-lead electrocardiogram (ECG) intervals (RR, PR, QRS, QT, and QT intervals corrected for heart rate using Bazett's and Fridericia's formulas (QTcB and QTcF), including changes from Baseline ECG variables
- Change from Baseline in clinical laboratory variables (hematology, biochemistry, and urinalysis)

2.3 Study design and conduct

To be eligible to participate in this study, subjects must meet the following key inclusion criteria:

- Subject has active AS, determined by documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS, including symptoms for ≥3 months and age of onset <45 years.
- Subject has moderate to severe active disease as defined by each of the following:
  - BASDAI score ≥4
  - Spinal pain ≥4 (from BASDAI question 2)
- Subjects must have at least 1 of the following:
  - inadequate response to NSAID therapy
  - intolerance to administration of at least 1 NSAID
  - contraindication(s) to NSAID therapy
- Subjects may be TNF inhibitor-naïve or may have received 1 prior TNF inhibitor. Subjects who have been on a TNF inhibitor previously must have:
  - experienced an inadequate response to previous treatment given for at least 12 weeks
  - been intolerant to administration (eg, had a side effect/AE that led to discontinuation)
  - lost access to TNF inhibitor for other reasons

Approximately 285 eligible subjects will be randomized to 1 of 5 treatment arms to receive treatment according to their randomized placebo or bimekizumab dose regimen until Week 12. Thereafter, subjects randomized to bimekizumab 160mg Q4W or bimekizumab 320mg Q4W will remain on their randomized dose and subjects randomized to placebo, bimekizumab 16mg Q4W, and bimekizumab 64mg Q4W, will be re-randomized in a 1:1 fashion to bimekizumab 160mg Q4W or bimekizumab 320mg Q4W. The total duration of treatment is 48 weeks.

Screening Period/ Baseline

During the Screening Period, the Investigator will assess the eligibility of subjects according to the inclusion and exclusion criteria. The Screening Period will also enable washout of any medications not permitted for use during the study and allow initiation of latent tuberculosis (TB) treatment where necessary and appropriate. The Screening Period will be up to 28 days.

Double-Blind Period

At Baseline subjects will be randomized in a 1:1:1:1:1 ratio (stratified by region and prior TNF inhibitor exposure) to receive the following blinded study treatment regimens during the Double-Blind Period:

- Placebo
- Bimekizumab 16mg administered sc Q4W
- Bimekizumab 64mg administered sc Q4W
- Bimekizumab 160mg administered sc Q4W
- Bimekizumab 320mg administered sc Q4W

The enrollment of TNF inhibitor-experienced subjects will be limited to approximately 30% of the total study population.

The investigational medicinal product (IMP) will be administered sc in the clinic at Baseline, Week 4, Week 8, and Week 12. Additional study visits in the Double-Blind Period (without dosing) will occur at Week 1 and Week 2. At Week 12, subjects will transition from the Double-Blind Period into the 36-week Dose-Blind Period.

Subjects withdrawing early from the study will undergo the Early Termination Visit assessments and will enter the SFU Period.

Dose-Blind Period

The Dose-Blind Period lasts from Week 12 to Week 48. Subjects randomized to bimekizumab 160mg Q4W or bimekizumab 320mg Q4W will remain on their randomized dose and subjects randomized to placebo, bimekizumab 16mg Q4W, and bimekizumab 64mg Q4W, will be rerandomized in a 1:1 fashion to bimekizumab 160mg Q4W or bimekizumab 320mg Q4W. The total duration of treatment is 48 weeks.

During the 36-week Dose-Blind Period, subjects will be evaluated for eligibility to rescue treatment at defined time points. Subjects who do not show an improvement in both PGADA and spinal pain compared to Baseline will be eligible to receive rescue therapy as defined in Section 6.5.

Safety Follow-Up Visit/Extension study

At the completion of the Dose-Blind Period, subjects will be given the opportunity to enter an extension study at Week 48. All subjects who complete the study and do not enter the extension study or who discontinue early, including those withdrawn from study treatment, will have a SFU Visit at 20 weeks after their last dose of IMP.

2.4 Determination of sample size

A total of 285 subjects (57 in each treatment group) are planned to be randomized in this study. The primary efficacy analysis will be based on the Full Analysis Set (FAS). While some randomized subjects may not be in the FAS, it is expected that this number will not impact the following calculations.

The sample size is calculated based on the ASAS40 response data from the Phase 3 studies in subjects with AS treated with secukinumab (MEASURE 1 and 2; Baeten et al, 2015). The ASAS40 response rates at Week 12 were reported to be 40% in both studies for the secukinumab 150mg dose while placebo response rates were 18% (MEASURE 1) and 9% (MEASURE 2).

Based on those ASAS40 response rates and preliminary information on the bimekizumab dose-response profile, ASAS40 response rates of 40.0%, 36.0%, 20.0%, 15.0%, and 12.0% at the end of a 12-week Treatment Period for bimekizumab 320mg, bimekizumab 160mg, bimekizumab 64mg, bimekizumab 16mg, and placebo have been assumed, respectively. Since the loading dose regimen of MEASURE 1 (iv) was different from MEASURE 2 (sc), the assumption for placebo response was based primarily on MEASURE 2, but with a weighting towards the higher placebo response rate of MEASURE 1.

The sample size for the primary objective of evaluating the dose-response relationship was calculated using a 2-sided test for detecting a linear trend across proportions (Nam, 1987) at a 2-

sided significance level of 0.05. Assuming 57 subjects in each treatment group, the test for detecting the overall dose response based on ASAS40 response is powered at >99% for the subjects with diagnosis of AS (ie, 57 subjects per group).

The sample size calculations were performed using the software nQuery Advisor® 7.0.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All computations and generation of outputs will be performed using SAS® Version 9.3 or later. All tables and listing will use Courier New font size 9.

All original and derived variables will be listed and described using summary statistics (number of observations [n], mean, standard deviation [SD], median, minimum and maximum, unless otherwise stated) or frequency counts (number of subjects [N] and percentages). For multiple post-Baseline assessments at a specific visit, the first non-missing measurement will be used for summary statistics or frequency counts.

Descriptive statistics will be displayed to provide an overview of the study results. For categorical variables, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. For continuous variables, descriptive statistics will include number of subjects with available measurements (n), mean, SD, median, minimum, and maximum.

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

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

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 3 decimal places. P-values less than 0.001 will be presented as "<0.001" and p-values greater than 0.999 will be presented as ">0.999". Statistical comparisons will be performed by two-sided statistical tests at the 0.050 level of significance.

The SAS output for Cochran-Mantel-Haenszel test, logistics regression, and analysis of covariance (ANCOVA), as well as multiple imputation (MI) will be provided as a separate PDF document in addition to TFLs. The SAS output will be included in the 'Documentation of Statistical Methods' section of the clinical study report.

In the Double-Blind Period the order of treatment groups to be presented in tables from left to right will be Placebo, BKZ16mg, BKZ64mg, BKZ160mg, and BKZ320mg, where BKZ is the abbreviation for bimekizumab. The general principle is to go from the lowest to highest dose when moving from left to right. Tables may also include columns for all subjects or all subjects on bimekizumab. An overview of the treatment group assignment is available in Table 12–2.

Selected tables which are specified in the TFL shells will only use data from the Dose-Blind Period. For listings and the selected tables, the label and order of treatment groups will be presented as follows: Placebo-BKZ160mg, Placebo-BKZ320mg, BKZ16mg-BKZ160mg, BKZ16mg-BKZ320mg, BKZ64mg-BKZ160mg, BKZ64mg-BKZ320mg, BKZ160mg-BKZ160mg, and BKZ320mg-BKZ320mg.

All subjects on bimekizumab will be labeled as "All BKZ" in the TFLs.

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

Unless otherwise stated, listings will be sorted by treatment, subject number within each treatment group (not randomization number), variables (if applicable) and visit (if applicable; including timing relative to dosing if applicable). For listings including nonrandomized subjects, the nonrandomized subjects will be shown first in the listing, ordered by subject number. All listings will include repeat and unscheduled measurements; such measurements will appear in chronological order together with the scheduled visits, ie, a repeated measurement will appear directly after the visit and time relative to dosing for which the repeat measurement was performed. In all the listings dates will be presented in the format "YYYY-MM-DD" and times will be presented in 24h clock format as "hh:mm".

3.2 General study level definitions

3.2.1 Relative day

Relative day will be calculated as the current date minus the date of first dose of study drug administration plus 1 for days on or after the day of first dose of study drug dose. Relative day 1 is the date of first bimekizumab administration.

Relative days before first administration of bimekizumab will have the prefix "-" and will be calculated as date of first dose of study drug administration minus the current date.

For days after the last bimekizumab administration, relative day will be calculated as the current date minus the date of last dose of study drug administration including the prefix "+".

Calculations of "Relative Day" should not include partial dates, but should be left blank in these instances.

For AEs, relative days for start and stop dates will be calculated as the number of days since the first injection of the medication. For non-treatment emergent AEs, relative day of onset will be negative if the event started and stopped before the first dose. A complete date must be established in order to correctly identify the AEs. Section 4.2.2 describes imputation rules in case of missing data for AEs.

3.2.2 Study Periods

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

- Pre-treatment period (Screening period): up to 28 days, ends with the visit date of the first dose of study medication (Visit 2)
- Double-Blind treatment period: starts with the visit date of the first dose of study medication (Visit 2), ends at Week 12 visit date

- Dose-Blind treatment period: starts at the Week 12 visit, ends at Week 48 visit
- Post-treatment period: the post-treatment period (Follow-up period) is the period after the Week 48 visit

3.3 Definition of Baseline values

The last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value. If a scheduled Baseline assessment is taken on the same day and after the first administration of study medication, it will be analyzed as the first post-Baseline assessment. If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication.

The exception of the above rule are the questionnaires collected from the vendor ERT and measurements for C-reactive protein (CRP) and high sensitivity C-reactive protein (hs-CRP). For those measurement, the last valid measurement at the same day as Visit 2 will be used as the Baseline value.

However, for some variables, assessments may be scheduled for Screening only and not for Baseline. In this case the Screening value will be utilized as Baseline value. If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead.

3.4 Protocol deviations

Important protocol deviations are defined as those deviations from the protocol likely to have a meaningful impact on the primary efficacy outcomes for an individual subject. Important protocol deviations will be identified and classified by the deviation types defined in the appropriate protocol-specific document. All protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from Per Protocol Set (PPS), Pharmacokinetics Per-Protocol Set (PK-PPS), and Pharmacodynamics Per-Protocol Set (PD-PPS). The exclusion from PPS is limited to the Double-Blind Period, ie. only subjects with important protocol deviations prior to re-randomization at Visit 7 (Week 12) will be excluded from PPS. Subjects with important protocol deviations after Visit 7 (Week 12) will not be excluded from PPS.

3.5 Mapping of assessments performed at early termination visit

Study assessments at an early termination visit where visit date matches the visit date of a scheduled visit will be summarized at the scheduled visit with the same visit date. Premature study termination visit assessments that do not have a scheduled visit with a matching date will be assigned to the next scheduled site visit following the last visit where assessments were available regardless whether or not there will be an assessment on this visit. The assessment of AbAb is an exception to this rule: AbAb will be mapped to the next visit where antibody levels are measured. For subjects who discontinue study treatment early and return for the Week 12 visits as per the protocol, the assessments collected at that visit are summarized as Week 12 assessments.

3.6 Analysis sets

The primary efficacy variable will be analyzed for all subjects in the FAS. The supportive analysis for the primary efficacy variables will be performed for Randomized Set (RS), PPS, and FAS. All other efficacy variables will be based on the FAS. Demographics tables will be performed for FAS, Safety Set (SS), and Dose-Blind Set (DBS). Safety variables will be summarized using the SS. In addition, safety analyses during the Dose-Blind Period will be conducted on all subjects in the DBS. PK variables will be analyzed for all subjects in the Pharmacokinetics Per-Protocol Set (PK-PPS). PD variables will be analyzed for all subjects in the Pharmacodynamics Per-Protocol Set (PD-PPS).

At the time of the Week 48 interim it was discovered that the Dose-Blind Responder Set (DBRS) and Escape Subject Set (ESS) were defined incorrectly from the original intent. The original intent of the ESS analysis set was to have only those subjects that were eligible to receive rescue therapy, that went on to actually receive rescue therapy, with all other subjects remaining in the DBRS. As such, two extra sets, the Corrected Dose-Blind Responder Set (cDBRS) and Corrected Escape Subject Set (cESS) have been added. These analysis sets will correctly select out those subjects that were eligible and received rescue medication. All outputs created on the DBRS and ESS will also be produced on the cDBRS and cESS to give full transparency of the difference. Further all outputs using the DBRS and ESS will be repeated on the DBS and this analysis will be used as the main analysis of the Dose-Blind Period as this analysis set is the most unbiased set.

3.6.1 Enrolled Set (ES)

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

3.6.2 Randomized Set (RS)

The RS will consist of all randomized subjects.

3.6.3 Safety Set (SS)

The SS will consist of all randomized subjects who received at least 1 dose of IMP.

3.6.4 Full Analysis Set (FAS)

The FAS will consist of all randomized subjects who received at least 1 dose of IMP and have a valid measurement of the primary efficacy variable at Baseline.

3.6.5 Per-Protocol Set (PPS)

The PPS will consist of all subjects in the FAS who had no important protocol deviation affecting the primary efficacy variable. The subjects with important protocol deviations will be predefined and evaluated during a data evaluation meeting prior to unblinding of the data.

3.6.6 Pharmacokinetics Per-Protocol Set (PK-PPS)

The PK-PPS is a subset of the FAS, consisting of those subjects who had no important protocol deviations affecting the pharmacokinetic variables, as confirmed during ongoing data cleaning meetings prior to database lock.

3.6.7 Pharmacodynamics Per-Protocol Set (PD-PPS)

The PD-PPS will consist of all randomized subjects who took at least 1 dose of IMP and provide at least 1 PD measurement postdose that is without important protocol deviation affecting that time point.

3.6.8 Dose-Blind Set (DBS)

The DBS consists of all subjects starting the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period including the dose at Week 12.

3.6.9 Escape Subject Set (ESS)

The ESS consists of all subjects starting the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have not achieved at least a 10% reduction from Baseline in PGADA and total and nocturnal spinal pain at either Week 16, Week 24, or Week 36.

3.6.10 Dose-Blind Responder Set (DBRS)

The DBRS consists of all subjects starting the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have achieved at least a 10% reduction from Baseline in PGADA and total and nocturnal spinal pain at Week 16, Week 24, and Week 36.

3.6.11 Corrected Escape Subject Set (cESS)

The cESS is a corrected version of the ESS, which was incorrectly defined previously. The cESS consists of subjects that have shown less than a 10% improvement in SJC and TJC at either Week 16, Week 24, or Week 36 and received rescue therapy.

3.6.12 Corrected Dose-Blind Responder Set (cDBRS)

The cDBRS is a corrected version of the DBRS, which was incorrectly defined previously. The cDBRS consists of subjects that have shown at least a 10% improvement in SJC or TJC at Week 16, Week 24 and Week 36. Subjects that would be in the cESS, including subjects that discontinue, that did not receive rescue therapy will be in the cDBRS.

3.7 Treatment assignment and treatment groups

It is expected that subjects receive treatment as randomized and hence safety analyses will be based on the SS, as randomized. However, if after unblinding it is determined that subjects randomized to placebo received bimekizumab at any time, then for safety analyses these subjects will be reallocated to the appropriate bimekizumab treatment group. Subjects randomized to bimekizumab will only be reallocated to the placebo treatment group if they did not receive bimekizumab at any time during the study.

Depending on the analysis sets, subjects will be summarized and listed based on the actual received treatment or according to the randomization which will be considered as planned treatment:

- All subjects screened/ES: planned treatment
- RS: planned treatment

- SS: actual treatment
- FAS: planned treatment
- PPS: planned treatment
- PK-PPS: actual treatment
- PD-PPS: actual treatment
- DBS: planned treatment (demographics, baseline characteristics, and efficacy analyses) or actual treatment
- ESS: planned treatment
- DBRS: planned treatment

3.8 Center pooling strategy

Centers will be pooled into geographic regions for analysis purposes. Centers will be grouped in the geographic regions North America, Western and Eastern Europe.

3.9 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Previous and ongoing medical history will be classified by primary system organ class and preferred term (PT).

All AEs will be classified by primary system organ class, high level term and PT. Prior and concomitant medications will be coded using version SEP2015 of the World Health Organization Drug Dictionary (WHO-DD) and will be classified by Anatomical Main Group, Pharmacological Subgroup, and PT. Medical procedures will not be coded.

3.10 Changes to protocol-defined analyses

Instead of stopping the pairwise testing of each bimekizumab dose versus placebo once it failed to reach significance at a significance level of α=0.05, the pairwise testing will continue and further pairwise comparisons are seen as non-significant.

No fixed sequence testing will be used for the secondary efficacy variables.

Time to a given response is defined as the length in weeks from Baseline until the first date when the response is achieved. In the definition the length was changed from days to weeks due to easier interpretation.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The primary efficacy analysis and secondary analysis will be adjusted for treatment, geographic region, and prior TNF inhibitor exposure (yes/no).

4.2 Handling of dropouts or missing data

4.2.1 Handling of missing data for efficacy analysis

The analysis for the binary primary, secondary, and other efficacy variables will use non-responder imputation (NRI) for handling missing data. In NRI, each subject with missing data or

who has discontinued Double-Blind study treatment prior to Week 12 will be counted as a non-responder.

Sensitivity analysis will be performed for the secondary analysis of the primary variable (ASAS40 response at Week 12) using MI assuming that missingness is missing at random (MAR). The MI method will be applied as follows:

1. Create a data set, sorted by treatment groups, of subjects with observed values and those needing estimation by multiple imputation. For the imputation step, missing values will be separated into non-monotone missing values (ie, intermittent missing values between completed assessments) and monotone missing values (ie, missing values after the patient dropped out). The procedure will sequentially estimate an imputation model for the ASAS components at each post-Baseline visit where ASAS components are collected, with geographic region, and prior TNF inhibitor exposure as covariates separated between the treatment groups.

   – For the imputation of intermediate missing values, the missing ASAS components in each data set will be filled in using the Markov-Chain Monte Carlo (MCMC) method with multiple chains and monotone imputing. A total number of imputations will be 100. The seed used for these imputations will be 2017.

     Note: All other multiple imputation procedures described in this SAP will use this same seed as well.

     Note: The imputation model based on the MCMC method will only allow continuous variables as predictors. Therefore, prior TNF inhibitor exposure and geographic region will be re-coded as numeric variables (with values of 0 or for the levels of TNF [1=prior inhibitor exposure, 0=non prior inhibitor exposure] and two binary variables for geographic region [Variable 1: 1=North America, 0=others, Variable 2: 1=Eastern Europe, 0=others] as representation of geographic region).

     Note: To avoid that imputed values are outside of the pre-defined range of values for the ASAS components (eg, PGADA [0-10]) maximum and minimum values for imputed variable values are specified. Moreover, the rounding options for imputed values are used where appropriate.

   – Once the intermediate missing data are imputed, the monotone missing data will be imputed for all patients with monotone regression including geographic region, and prior TNF inhibitor exposure as covariates. The dataset is the output dataset of the partial imputation. Since this dataset already has 100 imputed values at each visit, only one imputation will be performed.

     Note: Maximum and minimum values (and rounding where appropriate) are specified for imputed variable values to avoid values outside of the pre-defined range of values.

2. The ASAS40 response will be calculated using the complete datasets. That is, the values of the ASAS components at Week 12 based on the complete datasets will be compared to their corresponding Baseline values to calculate an ASAS40 response for each subject (as described in Section 8.1.1). Each complete data set will then be analyzed based on a logistic regression model with factors of treatment group, geographic region, and prior TNF inhibitor exposure.

3. The Week 12 results from the logistic regression analysis of each of the 100 imputed data sets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987).

Some key points to consider relative to the calculation of the odds ratios and corresponding confidence intervals are noted below:

As the estimates of the odds ratios from the logistic regression model in step 3 follow a lognormal distribution, a log transformation is needed to normalize these estimates since the procedures for combining results from multiple imputed datasets are based on the assumption that the statistics estimated from each imputed dataset are normally distributed. Therefore, the log of the odds ratio estimates from the logistic regression model are used when combining into a single inference (step 3). Additionally, the standard errors (SE) for the odds ratios are transformed as follows:

$$SE = \frac{\log(UCL) - \log(LCL)}{2Z_{\propto/2}} \quad (1)$$

where UCL and LCL are the upper and lower confidence limit, respectively, for the confidence interval of the odds ratio from the logistic regression model, and $Z_{\alpha/2}$ is the relevant critical value from the standard normal distribution (1.96 for a 95% confidence interval). The estimates of the log odds ratio for each bimekizumab dose relative to placebo and the corresponding upper and lower confidence limits will be provided. The odds ratio is estimated by exponentiating the estimate of the log odds ratio. The confidence limits of the odds ratio are then estimated as follows:

$$LCL = OR * \exp(-SE * Z_{\propto/2}) \quad (2)$$

$$UCL = OR * \exp(SE * Z_{\propto/2}) \quad (3)$$

where OR is the back-transformed estimate of the odds ratio just described, SE is the standard error of the log odds ratio and $Z\alpha/2$ is the relevant critical value from the standard normal distribution (1.96 for a 95% confidence interval). These calculations will be done such that odds ratios and corresponding confidence intervals are calculated for the odds ratio of each bimekizumab dose versus placebo. Note that the p-values presented in the tables are not impacted by the transformations described above.

The supportive analysis number 3 (analysis of the ASAS components), and all continuous secondary efficacy variables will use the same multiple imputation method as described above. Instead of using the logistic regression model the ANCOVA with treatment group, geographic region, and TNF inhibitor exposure as fixed effects and the Baseline values as covariate will be used. No log transformation is needed for the ANCOVA estimations.

Following Rubin (1987), multiple imputation estimates of descriptive statistics are computed by simply averaging the estimates from $m = 1, \ldots, M$ independent repetitions of the imputation algorithm:

$$\bar{\theta} = \frac{1}{M}\sum_{m=1}^{M}\hat{\theta}_m \quad (4)$$

where $\hat{\theta}_m$ is the estimate of θ from the completed data set $m = 1, \ldots, M$ (Berglund, 2014).

The imputation model will be applied for each treatment group separately. However, in the event there are computational challenges with the imputation model (eg, due to a standard deviation of 0 for responses of a given imputation), it is acceptable to modify the imputation model to include treatment as a variable in the model rather than running a separate model for each treatment group. It should be noted that doing so assumes that treatment does not interact with any of the other variables in the imputation model.

4.2.2 Handling of missing data for adverse events (AEs)

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

Partial AE 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 and the subject did not switch treatment during that month and year, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the month and year are specified and the subject did switch treatment during that month and year, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is not the same as the year of the start date and the subject did not switch treatment during that year, 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 only the year is specified, and the year of first dose is the same as the year the subject did switch treatment, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is the same as the year of the start date and the same as the year the subject did switch treatment, then use the date of first dose.
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.

If the date of first study medication or switch treatment is partial, then the above imputation approach will be applied:

- If only the day of first study medication or switch treatment administration is unknown, then this will be set to either the first of the month, or the day of first treatment allocation visit (excluding placebo run-in), whichever is later.
- If both the day and month of first study medication or switch treatment are unknown, then this date will be imputed to be the date of first treatment allocation visit.
- If first treatment allocation visit date is missing then the all activities events will be assumed to be treatment emergent.

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 the AE was treatment emergent, the AE will be considered treatment emergent.

If the intensity of an AE is unknown, it is considered as severe.

If the relationship to study drug is missing, it is considered as related.

The imputation rule for missing seriousness differ between the interim and final analysis. For the interim analysis no imputations rule will be applied. For the final analysis the worst case approach will be applied. If the seriousness of an AE is missing for the final analysis, it is considered as serious.

4.2.3 Handling of missing data for prior and concomitant medication

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the electronic case report form (eCRF).

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 and the subject did not switch treatment during that month and year, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the month and year are specified and the subject did switch treatment during that month and year, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is not the same as the year of the start date and the subject did not switch treatment during that year, 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 only the year is specified, and the year of first dose is the same as the year the subject did switch treatment, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is the same as the year of the start date and the same as the year the subject did switch treatment, then use the date of first dose.
- If only the year is specified and the end date is before date of first dose, then set the start date to the 1st of January of the year of the start date.
- If only the year and day are specified and month is missing, then only the year will be considered and the month and day will be imputed with the rules above
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.
- If the start date is completely unknown and the stop date is prior to the date of first dose, then set the start date to the 1st of January of the year of the end date.

If the date of first study medication or switch treatment is partial, then the below imputation approach will be applied:

- If only the day of first study medication or switch treatment administration is unknown, then this will be set to either the first of the month, or the day of first treatment allocation visit (excluding placebo run-in), whichever is later.
- If both the day and month of first study medication or switch treatment are unknown, then this date will be imputed to be the date of first treatment allocation visit.

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.

There will be no imputation of any other missing data.

4.3 Interim analyses and data monitoring

Two interim analyses are planned for the study after the subjects have completed 12 and 48 weeks.

4.3.1 Interim analysis Week 12

After all enrolled subjects have completed the 12 weeks Double-Blind Period, an interim analysis will be performed (i) to analyze the dose:exposure response for the ASAS40 response criteria to determine the optimal therapeutic dose(s) for subsequent studies, and (ii) to perform a comprehensive evaluation of all Double-Blind data of the study.

No separate SAP for the interim analysis will be provided. The interim analysis is a limited version of the final analysis and will focus on the primary and secondary efficacy analysis and comprise the results of the 12 weeks Double-Blind Period. The TFL shells for the interim and final analysis will be provided in two different documents.

The interim analysis will summarize disposition, demographics, AS history, Baseline characteristics, AS concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). Listings of AEs, hematology, biochemistry and C-SSRS data will be provided. Not all collected hematology and biochemistry laboratory variables will be displayed in the tables and listings. For the interim analysis only selected hematology and biochemistry variables will be provided as listed in Table 12–3.

For efficacy the interim analysis will include following primary and secondary variables: ASAS40,20,5/6 response at Week 12, and change from Baseline in BASDAI, ASDAS-CRP, BASFI at Week 12. The variables will be analyzed using the same methods described in Section 8.1.2 and Section 8.2 including supportive and sensitivity analyses (Section 8.1.3 and Section 8.1.4). In addition, summary tables for the primary and secondary efficacy variables, and the ASAS components will be provided. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive statistics by each visit. Time to onset of ASAS20 response and ASAS40 response will be summarized and plotted as described in Section 8.3.

PK and PD data will be analyzed in the interim analysis as described in Section 9.1 and Section 9.2. PKPD will be analyzed as part of the exposure:response modeling outside of the scope of the SAP. Biomarker data will not be analyzed in the interim analysis.

The interim analysis includes selected data up to Week 12 and in addition data up to Week 16. The data up to Week 16 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. All analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Following variables will be analyzed: ASAS40, ASAS20, ASDAS-CRP, BASDAI, PK, AbAb and TEAEs. It depends on the analysis how those additional time points will be presented in the interim analysis. Two summary tables for TEAE will be presented. The first table will include TEAEs with a relative TEAE start date less equal 84 (12*7) days by treatment group at Baseline. The second table will include TEAEs with a relative TEAE start date less equal 112 (16*7) days by the following treatment groups: bimekizumab 160mg and bimekizumab 320mg. The summary table for the other variables will present only data up to Week 12 for the Baseline treatment groups Placebo, bimekizumab 16mg, and bimekizumab 64mg. Data up to Week 16 will be presented for bimekizumab 160mg and bimekizumab 320mg. All Listings which include data up to Week 16 will use the same approach.

If an AE occurs on the same day as the treatment switch (Visit 7, Week 12) then the AE will be allocated to the Double-Blind treatment. An exception from this general rule is made for adverse drug reactions (ADRs), and AE of hypersensitivity reactions and anaphylactic reactions. If those AEs occur on the same days as the treatment switch, the AEs will be allocated to the Dose-Blind treatment and will not be presented for the interim analysis.

Exposure of study medication will not be summarized but a listing will be provided including following information: date of first dose, date of last dose, and duration of exposure. The last dose for the Double-Blind Period is planned on Visit 6 (Week 8).

For the interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The investigators and subjects will remain blind to the assigned

bimekizumab dosing regimen until the subject completes the Dose-Blind Period at Week 48. Further details are available in the AS0008 blinding plan.

Safety data will be provided to an independent Data Monitoring Committee (DMC). The DMC will review those safety data periodically. The composition and operation of the DMC will be defined in the DMC charter. The presentation and analysis of data for the DMC meetings is described within a separate DMC SAP.

4.3.1.1 Changes from interim analysis Week 12 to SAP-defined analyses

For TEAE two summary tables were presented as described in previous section with one modification: the first table was displaying all TEAE during the Double-Blind Period instead of limiting it TEAE with a relative TEAE start date less equal 84 days.

The definitions of AE of special monitoring were updated with the third SAP Amendment after the interim analysis. The interim analysis used the previous definition which is displayed in Section 4.3.1.2. The interim analysis only displayed the overall number of AE of special monitoring by treatment group.

The baseline definition for CRP and hs-CRP measurements were updated with the fifth SAP Amendment after the interim analysis. The interim analysis used the previous definition: The last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value.

4.3.1.2 Search and selection criteria for AE of special monitoring for interim analysis Week 12

Following AEs are defined as TEAEs of special monitoring:

- Fungal infectious disorder
- Opportunistic infection (including TB)
- Malignant or unspecified tumor
- Malignant tumor
- Major cardiovascular event
- Haematopoietic cytopenias
- Neuropsychiatric events
- Inflammatory bowel disease
- Hypersensitivity and anaphylactic reaction
- Hepatic events

Fungal Infectious disorder

All TEAEs which code into the High Level Group Term (HLGT) of “Fungal infectious disorders” are classified as fungal infectious disorder.

Opportunistic infection

All TEAEs identified using UCB-defined search criteria as described in Section 12.13.

Malignant or unspecified tumor

The search criteria is based on the Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)".

Malignant tumor

The search criteria is based on the SMQ="Malignant tumours (SMQ)".

Major cardiovascular events

The major cardiovascular events are identified using the following UCB-defined search criteria:

- All serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups of the following SMQs:
  - Haemorrhagic central nervous system vascular conditions (SMQ)
  - Ischaemic central nervous system vascular conditions (SMQ)
- All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to PT "Chest Pain" or "Chest discomfort"
- All serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders" as Primary SOC.

Haematopoietic cytopenias

The search criteria is based on the SMQ = "Haematopoietic cytopenias". The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Neuropsychiatric events

The search criteria is based on the SMQ = "Depression and suicide/self-injury (SMQ)". The SMQ search will include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Inflammatory bowel disease

All TEAEs which code into the HLT of "Colitis (excl infective)" are identified as inflammatory bowel disease.

Hypersensitivity reactions and anaphylactic reactions

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

a) Hypersensitivity reactions: All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, which code to a PT which contains the term "hypersensitivity" will be considered to be a hypersensitivity reaction and included in the summary table as such.

b) Anaphylactic reactions: An algorithmic approach will be used to identify TEAEs that are considered to be anaphylactic reactions. PTs are separated into the 4 distinct categories (A, B, C, D) prior to the algorithmic approach being applied.

All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, and which fulfill any of the 3 criteria described in Section 12.14 will be included in the summary table.

Hepatic events

The search criteria is based on all TEAEs in the SMQ "Drug related hepatic disorders - comprehensive search (SMQ)". Note that the following two sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps)" and "Liver neoplasms, malignant and unspecified (SMQ)".

The SMQ search should include all TEAEs (regardless of whether they have been judged as related to study medication or not) which code to a PT included in the Scope=Narrow group within each SMQ.

4.3.2 Interim analysis Week 48

After all enrolled subjects have completed the Week 48 or Early termination visit, a second interim analysis will be performed to analyze the key efficacy and safety data for the whole treatment period.

No separate SAP for that interim analysis will be provided. This interim analysis is a subset of the final analysis and will focus on the primary and secondary efficacy analysis. The TFL shells for the final analysis will be used.

The snapshot for the AS0008 interim analysis Week 48 will occur before all subjects have completed the AS0008 study. Specifically, subjects who do not enter the extension study will need to complete the SFU Visit, which occurs 20 weeks after the last dose of study treatment. The Week 48 interim database lock will be performed based on the last subject completing the Week 48 visit. It is anticipated that there will be some subjects still awaiting the SFU at that time. The number of subjects in the SFU period is expected to be low, and the minimal data to be collected from their SFU visits is not considered mandatory to evaluation of the key efficacy and safety objectives of the study.

4.3.2.1 Changes from interim analysis to SAP-defined analyses

The baseline definition for CRP and hs-CRP measurements were updated with the fifth SAP Amendment after the interim analysis. The interim analysis used the previous definition: The last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline vale.

4.3.2.2 Changes during interim analysis to SAP-defined analyses

At the time of the Week 48 interim it was discovered that the DBRS and ESS were defined incorrectly from the original intent. The original intent of the ESS analysis set was to have only those subjects that were eligible to receive rescue therapy, that went on to actually receive rescue therapy, with all other subjects remaining in the DBRS. As such, two extra sets, the cDBRS and cESS have been added. These analysis sets will correctly select out those subjects that were eligible and received rescue medication. For the final analysis, all outputs created on the DBRS and ESS will also be produced on the cDBRS and cESS to give full transparency of the difference. Further all outputs using the DBRS and ESS will be repeated on the DBS and this

analysis will be used as the main analysis of the Dose-Blind as this analysis set is the most unbiased set.

4.4 Multicenter studies

The data from all centers will be pooled for the purposes of the analysis. There will be no formal statistical evaluation of the effect of center on the results obtained.

4.5 Multiple comparisons/multiplicity

In order to control for the overall Type I error rate, the pairwise comparisons of bimekizumab will be formally evaluated for statistical significance only if the primary efficacy analysis is statistically significant at the two-sided 5% level. In addition, the pairwise comparisons will follow a sequential testing sequence and the formal evaluation of statistical significance of each comparison is dependent upon the previous comparison achieving statistical significance at the two-sided 5% level. If the sequential testing fails to reach significance at a significance level of α=0.05, then the pairwise testing will continue and the comparison are seen as non-significant. The p-values will be displayed as nominal p-values. More details can be found in Section 8.1.3.

4.6 Use of an efficacy subset of subjects

The primary dose-response analysis and pairwise comparisons will be repeated for (1) all subjects in the PPS, and (2) for all subjects in the RS as a supportive analysis. The purpose is (1) to evaluate the effect of important protocol deviations on the analysis, and (2) to evaluate the consistency of the FAS with the intent-to-treat (ITT) principle.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

The following variables for subgroup analyses will be used:

- Age (<45 years, ≥45 years)
- Gender (male, female)
- Geographic region (North America, Eastern and Western Europe)
- Treatment-emergent AbAb status (positive, negative)
- Prior TNF inhibitor exposure (yes, no)
- Current NSAIDs at Baseline (yes, no)
- BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])

Subjects will be counted to have a positive treatment-emergent AbAb status in case the first AbAb positivity occurred up to Visit 7 (Week 12). The definition of first AbAb occurrence is described in Section 9.2.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Summary tables of all subjects screened will be presented including reason for screen failures and disposition of subjects screened. The disposition of subjects screened will include the number of subjects included in each analysis set (ES, RS, SS, FAS, PPS, PK-PPS, PD-PPS, DBS, ESS, and DBRS) overall and by site.

The number and percentage of subjects who discontinued study medication, who discontinued the study, and who discontinued due to AEs will be summarized for subjects in the RS.

Study eligibility criteria will be listed and a separate listing of subjects who did not meet the eligibility criteria will be presented. Only failed criteria will be included in the former listing.

Subject disposition will be listed for all subjects screened and will include, inter alia, the following information: subject status, date of informed consent, randomization, first and last study medication, and primary reason for premature study termination. Listings of subject analysis sets, study and study medication discontinuation, and visit dates will be presented by subject including the relative study day (calculated as described in Section 3.2.1) for each visit.

5.2 Protocol deviations

Important protocol deviations will be identified and classified by the deviation types. Following different important protocol deviation types will be classified: inclusion criteria deviation, exclusion criteria deviation, withdrawal criteria deviation, prohibited concomitant medication use, incorrect treatment or dose, treatment non-compliance, and procedural non-compliance.

Summary tables of the number and percentage of subjects with an important protocol deviation will be provided including a summary of subjects excluded from the PPS, PK-PPS, and PD-PPS due to important protocol deviations. Summary tables will be presented for FAS analysis sets.

A listing of all important protocol deviations identified at the data evaluation meeting will be presented by subject for all subjects in the RS, and will include deviation type and description.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Tables with descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) and listings will be given for the demographic variables age (at time of informed consent), gender, racial group, ethnicity, weight at Screening, height at Screening, and body mass index (BMI). Age will be summarized as a continuous variable and as categorical variables based on the following categories: ≤18, 19-<65, ≥65 years (clinicaltrials.gov requirement) and 18-<65, 65-<85, ≥85 years (EudraCT requirement).

BMI in kg/m2 is calculated based on the height (in m) and the weight (in kg) using the formula:

For adults:

$$BMI = \frac{Weight}{Height^2} \quad (5)$$

Even if they are available in the database, these variables are calculated during analysis (if applicable). These calculated values are used in the statistical analysis since they are considered more accurate.

A frequency table for Lifestyle will be presented as well as a corresponding listing. Subjects of childbearing potential will only be listed.

The summary tables will be performed on the SS and repeated using the FAS, and the DBS. If the SS and FAS analysis sets are identical the summaries will not be repeated. The Listing will be provided for all subjects screened, except the Lifestyle listing will use the RS.

6.2 Other Baseline characteristics

AS history will be summarized for subjects in the FAS and SS including the time since first diagnosis of AS, time since first symptoms of AS, and age at first diagnosis date. The history will be listed for all subjects in the RS.

Time since first diagnosis of AS will be calculated as:

$$Time\ since\ first\ diagnosis\ (years) = \frac{Date\ of\ Informed\ Consent - Date\ of\ diagnosis + 1}{365.25} \quad (6)$$

If the date of diagnosis is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing).

Time since first symptoms will be calculated as:

$$Time\ since\ first\ symptoms\ (years) = \frac{Date\ of\ Informed\ Consent - Date\ of\ first\ symptoms + 1}{365.25} \quad (7)$$

Age at first diagnosis will be calculated as:

$$Age\ at\ first\ diagnosis = \frac{Date\ of\ first\ diagnosis - Date\ of\ birth}{365.25} \quad (8)$$

These formulas may result in incorrect ages after rounding if the birth day falls on the date of first diagnosis. In that case the age is calculated as the number of years between the year of birth and the year of the randomization visit. The age for individual subjects is presented with 1 decimal. The rounding is done downwards. For subjects enrolled at German sites, only the year of birth may be entered into the eCRF for this study. For these subjects age will be calculated after imputing their date of birth to be 01 Jan XXXX.

Baseline characteristics (including scores relevant for inclusion and exclusion criteria) will be summarized by treatment group and overall for FAS, SS, and DBS. Following variables will be summarized:

- BASDAI total score
- BASDAI spinal pain (question 2)

- PGADA
- Total spinal pain (question 1 of the total and nocturnal spinal pain questionnaire)
- BASFI
- hs-CRP
- Prior NSAID therapy, prior anti-TNF therapy (frequency counts)
- NSAID therapy, synthetic DMARDs, methotrexate, sulfasalazine, and hydroxychloroquine

The corresponding listings will be presented for the RS.

6.3 Medical history and concomitant diseases

Medical history and ongoing medical conditions will be summarized by MedDRA system organ class (SOC) and PT by treatment and overall including the number and percentage of subjects with each condition. The denominator for the percentages will be the number of subjects in the SS and FAS for each treatment or overall.

Medical history and ongoing medical conditions will be listed by treatment and subject including the reported term, PT, and SOC for the RS. The start date (month and year only) and end date (or ongoing if applicable) will also be included in the listing. A glossary of all medical history conditions will also be presented including the reported term, PT and SOC.

6.4 Prior and concomitant medications

Prior medications include any medications that started and ended prior to the start date of study medication. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For bimekizumab, the dosing period is typically from the date of first dose up to (but not including) one dosing interval post last dose. Thus, a concomitant medication is any medication whose start date is on or after the date of first study medication and prior to the date of last study medication administration + 28 days (1 dosing interval), or whose stop date is either missing, or on or after the date of first study medication administration.

In the case of missing data, the classification of medications as prior or concomitant will be performed as described in Section 4.2.3.

The number and percentage of subjects taking prior medications will be summarized by treatment group, overall and by anatomical therapeutic chemical (ATC) class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and PT.

The number and percentage of subjects taking concomitant medications will be summarized similarly in two tables separating between AS concomitant medications and concomitant medications. AS concomitant medications includes the following list: NSAIDS, corticosteroid, methotrexate, sulfasalazine, hydroxychloroquine. Tables for prior and concomitant medications will be presented for SS and FAS.

Prior and concomitant medications will be listed by treatment and subject for RS.

6.5 Prohibited medication and rescue medication

Prohibited medications are defined in the protocol (Section 7.8.2).

Rescue medication will be allowed for some subjects evaluated at weeks 16, 24, and 36. Further details are defined in the protocol (Section 5.1.4). The number and percentage of subjects who used rescue medication will be summarized and listed.

The SS and FAS will be used for the summary table and the RS will be used for the listing.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance will be summarized as the number of doses received relative to the number of doses scheduled:

$$Percent\ compliance = 100 * \frac{\text{Number of doses received}}{\text{Number of doses expected}} \quad (9)$$

where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes treatment 12 doses are expected (Baseline and every 4th week afterwards until Week 44). If a subject discontinues early, then the number of expected doses is based on the time of early discontinuation relative to the dosing visits. If a dose is not completely given at a specific visit (eg, subject only received one injection instead of the two planned injections), then the subject will be considered to have no compliance for the visit. In the formula above it will be counted as no dose received at this visit.

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group for the overall treatment period as well as for Double-Blind treatment period. For the Double-Blind treatment period compliance will refer to the first 12 weeks and will be presented by treatment received at baseline. For the overall treatment period, the compliance will be calculated for the following three groups: bimekizumab 160mg, bimekizumab 320mg, and all bimekizumab. Treatment compliance for the bimekizumab 160mg and 320mg group will be calculated for the time the subject receives 160mg or 320mg, eg for a subject who switches from Placebo or bimekizumab 16mg to bimekizumab 160mg at Week 12, the compliance will only be calculated for the time the subject receives bimekizumab 160mg. The all bimekizumab group will consist of all the doses of bimekizumab including bimekizumab 16mg, and will only exclude the time subjects receive Placebo.

A by-subject listing of treatment compliance will be provided, presenting percent compliance and numbers of expected and received doses for the Double-Blind Period and for treatment with any dose of bimekizumab.

8 EFFICACY ANALYSES

8.1 Statistical analysis of the primary efficacy variable

8.1.1 Derivations of ASAS score and response

The ASAS20 response is defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 numeric rating scale (NRS) in at least 3 of the 4 following domains (Anderson, 2001):

- PGADA
- Pain assessment (total spinal pain, question 1 from total and nocturnal spinal pain questionnaire)

- Function (represented by the BASFI)
- Inflammation (the mean of the BASDAI questions 5 and 6) c[redacted]

and absence of deterioration in the potential remaining domain. Deterioration is defined as a relative worsening of at least 20% and an absolute worsening of at least 1 unit.

The ASAS criteria for 40% improvement are defined as relative improvement of at least 40% and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, which includes, in addition to the 4 domains above, spinal mobility (ie, lateral spinal flexion) and hs-CRP as more objective measures (Brandt et al, 2004). If the hs-CRP value is below 2 mg/L, then it will be imputed as the constant value of 2 mg/L.

The ASAS partial remission response is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains.

For all non-missed visits, if any of the component scores are missing, then the following rules will be applied:

- If the component values are missing at Baseline, the percent improvement from Baseline to a visit for the given component will be imputed as 0%. The unit improvement will be imputed as 0.
- If the component value at a given visit is missing and the Baseline value is present, the missing component will be replaced by the last non-missing observation (LOCF) for that component.

If the Baseline value of an ASAS component is 0, then for the purposes of calculating ASAS, the percent change from Baseline will be determined as follows (zero divisor rule):

- If the post-Baseline component value is also 0, set the percent change equal to 0;
- If the post-Baseline component value is >0, then calculate the percent change as though the Baseline value were 0.1.

If all ASAS components at Baseline are missing, no Screening observation will be used and the subject will be regarded as non-responder throughout the study.

With regards to the BASFI component see Section 8.1.1.3 for calculation in case of missing values of single questionnaire items.

With regards to the BASDAI component see Section 8.1.1.4 for calculation in case of missing values of single questionnaire items.

8.1.1.1 Patient's Global Assessment of Disease Activity (PGADA)

Subjects will score their global assessment of their disease activity in response to the question "How active was your spondylitis on average during the last week?" using a NRS where 0 is "not active" and 10 is "very active" (van Tubergen et al, 2015) (Section 12.4).

8.1.1.2 Total and nocturnal spinal pain

The pain experienced by AS subjects is adequately measured by 2 separate questions: 1) total pain in the spine due to AS (ie, "How much pain of your spine due to spondylitis do you have?"); and 2) pain in the spine at night due to AS (ie, "How much pain of your spine due to spondylitis do you have at night?") (Sieper et al, 2009; van der Heijde et al, 2005; Committee for Proprietary Medicinal Product/EWP/556/95) (Section 12.5).

The arithmetic mean of both questions describes the total and nocturnal spinal pain.

8.1.1.3 Bath Ankylosing Spondylitis Functional Index (BASFI)

The BASFI contains 10 questions (Section 12.6). The first 8 questions evaluate activities related to functional anatomical limitations due to the course of this inflammatory disease. The final 2 questions evaluate the subjects' ability to cope with everyday life. An NRS ranging from 0 to 10 is used to answer the questions on the test.

The arithmetic mean of the 10 scales gives the BASFI score, which is a value between 0 and 10.

In case of missing answers to 1 or 2 of the single items within the BASFI questionnaire, the BASFI score will be calculated by imputing missing items with the mean of the completed items. Then, the BASFI score will be calculated as described above. If more than 2 of the items are missing, the BASFI score will be left missing.

8.1.1.4 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI is the most commonly used instrument to [redacted]. The BASDAI is a validated self-reported instrument which consists of 6 NRSs, each with 10 units to measure the severity of the 5 major symptoms: [redacted] over the last week. The BASDAI questionnaire is available in Section 12.7. To give each symptom equal weighting, the average of the 2 scores relating to [redacted] is taken. The resulting 0 to 50 sum score is divided by 5 to give a final BASDAI score between 0 and 10, with lower scores indicating lower disease activity.

The BASDAI is calculated as follows:

$$BASDAI = \frac{Q1 + Q2 + Q3 + Q4 + (\frac{Q5 + Q6}{2})}{5} \quad (10)$$

where Q1 – Q6 are the six question from the BASDAI questionnaire.

If 1 of the 2 [redacted] (ie, questions: [redacted] and [redacted] is missing, the other one will be used for the morning stiffness calculation. The same imputation is also applied for the calculation of the ASAS inflammation component, which is calculated as the average of the 2 [redacted] measurements.

If 1 major symptom of the BASDAI is missing, the sum score of the remaining symptoms will be divided by the number of symptoms assessed. If more than 1 major symptom is missing, the sum score will be set to missing.

8.1.2 Primary analysis of the primary efficacy variable

The primary efficacy variable (ASAS40 at Week 12) will be analyzed for all subjects in the FAS.

The dose-response relationship between treatment and ASAS40 response will be assessed with an ordered categorical analysis using a non-parametric correlation statistic of Mantel and Haenszel (Mantel and Haenszel, 1959) and modified ridit scores (Bross, 1958) with the corresponding p-value.

The analysis will include geographic region and prior TNF inhibitor exposure (yes/no) as stratification factors. Prior TNF inhibitor exposure will be used as stratification factor as it may have an impact on efficacy. The correlation between dose and ASAS40 response will be evaluated at a two-sided significance level of α=0.05. This evaluation of dose-response will constitute the primary efficacy analysis.

A table will present the responder rates for placebo, BKZ 16mg, BKZ 64mg, BKZ 160mg, BKZ 320mg, and the correlation statistic of Mantel and Haenszel (ridit score) with the corresponding p-value.

NRI will be used to account for missing data; ie, subjects with a missing ASAS40 score at Week 12 or who discontinued study treatment prior to the Week 12 visit will be considered non-responders for the primary analysis.

8.1.3 Secondary analyses of the primary efficacy variable

As the secondary analysis for the primary efficacy variable, a logistic regression model will be used to assess the effect of each individual dose versus placebo on ASAS40 response. The model will include fixed effects for treatment, geographic region, and prior TNF inhibitor exposure. To avoid the problem of the so-called monotone likelihood resulting in infinite large confidence intervals (eg, if one of the cell counts in the 2x2 table is equal to zero), a penalized maximum likelihood approach based on the modified score procedure of Firth (eg, Heinze and Schemper, 2002) will be used in the logistic models. If the logistic regression model is unable to converge, then a 2-way categorical variable for geographic region (North America and Europe) will be used. Should the logistic regression model be is unable to converge even with this restriction, then geographic region may be dropped from the model to facilitate convergence. If the logistic regression model be unable to converge after dropping the geographic region, then prior TNF inhibitor exposure may be dropped as well. Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% confidence interval, and the corresponding p-value will be calculated. If the logistic regression model is unable to converge after dropping the geographic region, then prior TNF inhibitor exposure may be dropped as well. Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% confidence interval, and the corresponding p-value will be calculated.

The pairwise comparisons of bimekizumab versus placebo will be formally evaluated for statistical significance only if the primary dose response efficacy analysis is statistically significant. Once the dose response has been established, pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose.

If the dose-response relationship fails to reach significance at a significance level of α=0.05, then the further pairwise comparisons are seen as non-significant.

A table will present the responder rates for placebo, BKZ 16mg, BKZ 64mg, BKZ 160mg, BKZ 320mg, and for each dose the odds ratios (differences to placebo), 95% confidence intervals, and corresponding p-values from the logistic regression.

NRI will be used to account for missing data; ie, subjects with a missing ASAS40 score at Week 12 or who discontinued study treatment prior to the Week 12 visit will be considered non-responders for the primary analysis.

8.1.4 Supportive analyses of the primary efficacy variable

The following supportive analyses for the primary endpoint are planned:

1. The primary dose-response analysis and pairwise comparisons will be repeated for all subjects in the PPS to evaluate the effect of important protocol deviations on the analysis.
2. The primary dose response analysis and pairwise comparisons will be repeated for all subjects in the RS to evaluate the consistency of the FAS with the ITT principle. Subjects with no valid measurement of the primary efficacy variable at Baseline will be included as non-responders. NRI will be used to account for missing data.
3. The change from Baseline in all ASAS components (ie, PGADA, total spinal pain, BASFI, and BASDAI) will be analyzed using the ANCOVA with treatment, geographic region, and prior TNF inhibitor exposure as fixed effects and the Baseline values as covariate. MI will be used for missing data (Section 4.2.1).

For the supportive analysis number 1 and 2 two tables will be displayed. One table will present the responder rates for placebo, BKZ 16mg, BKZ 64mg, BKZ 160mg, BKZ 320mg, and the correlation statistic of Mantel and Haenszel (ridit score) with the corresponding p-value. The other table will present the responder rates, and for each dose the odds ratios (differences to placebo), 95% confidence intervals, and corresponding p-values from the logistic regression.

For the supportive analysis number 3 tables will present the least-square means and standard error for placebo and bimekizumab dose for the ANCOVA models. For the pairwise comparison between placebo and bimekizumab dose the least-square means, standard error, corresponding p-values, and 95% confidence intervals for the contrasts will be provided.

8.1.5 Sensitivity analyses of the primary efficacy variable

Two sensitivity analyses will be performed for the primary dose response analysis and for the supportive analysis number 3:

1. This analysis evaluates the effectiveness of the treatment (de facto hypothesis) and will be based on the ordered categorical analysis to evaluate dose-response as specified in the primary analysis. In an attempt to prevent missing data during the study, efforts will be made to collect data from subjects that withdraw early from the study. An analysis will be performed in which all available data at Week 12 will be considered. In this case, subjects will be analyzed according to their randomized treatment, even if they discontinued prior to Week 12 and were no longer on the randomized study treatment when the assessment was performed at Week 12. If Week 12 data for the ASAS response are not collected, the subject will be assumed to be a non-responder. It should be noted that this measures something

different from the primary analysis and could be confounded by placebo subjects who withdraw and are subsequently on another active medication at the time of the Week 12 assessment.

2. An additional sensitivity analysis will be based on observed data only for subjects who are still on the initially randomized treatment at Week 12. Subjects with missing data or who have prematurely discontinued study treatment will be excluded from the analysis. The same procedure described for the primary efficacy analysis of dose response will be used.

The following sensitivity analyses will be performed for the secondary analysis for the primary efficacy variable (pairwise comparison analysis of the primary efficacy variable) in order to assess the missing data assumptions:

1. Missing data will be imputed using MI. In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by monotone regression for monotone missing data to evaluate the effect of the method for handling missing data on the analysis. The ASAS components will be imputed individually and then the ASAS response will be calculated using the complete datasets. The multiply imputed data sets will be analyzed using a logistic regression model with fixed effects fixed effects for treatment, region, and prior TNF inhibitor exposure. Finally, the results will be combined into a single inference using Rubin's rule (Carpenter and Kenward, 2013). This procedure assumes a MAR pattern of missingness and corresponds to an estimand of what has been called the difference in outcome improvement if all subjects tolerated or adhered to treatment (Mallinckrodt et al, 2012). More details are available in Section 4.2.1.

2. The logistic regression model will be applied where all available data at Week 12 will be considered, as described in sensitivity analysis (1) for the primary efficacy variable.

3. The logistic regression model will be applied where only observed data for subjects still on the initially randomized treatment at Week 12 will be considered, as described in sensitivity analysis (2) for the primary efficacy variable.

The same tables as used for the primary and secondary efficacy analysis for the primary efficacy variable and for the supportive analysis number 3 with the different imputation analysis will be presented.

8.2 Statistical analysis of the secondary efficacy variables

The secondary efficacy variables will be analyzed for all subjects in the FAS.

All categorical variables (ie, ASAS20 response and ASAS5/6) will be analyzed for treatment effects using pairwise comparisons based on the same method as that for the primary efficacy variable.

All continuous variables (ie, ASDAS-CRP, BASDAI, and BASFI) will be analyzed for treatment effects using pairwise comparisons based on an ANCOVA model with treatment, geographic region, and prior TNF inhibitor exposure as fixed effects and the Baseline value as covariate.

For the categorical variables the responder rates for placebo, BKZ 16mg, BKZ 64mg, BKZ 160mg, BKZ 320mg, and for each dose the odds ratios (differences to placebo), 95% confidence intervals, and corresponding p-values from the logistic regression will be provided.

For the continuous variables the least-square means and standard error for placebo and bimekizumab dose for the ANCOVA models will be displayed. To pairwise compare placebo and bimekizumab dose the least-square means, standard error, corresponding p-values, and 95% confidence intervals for the contrasts will be provided. The ANCOVA model results for BASFI will be located in the supportive analysis section for the ASAS component and not in the secondary analysis section.

All categorical efficacy variables will be analyzed using observed cases as treated and imputed with NRI and all continuous variables will be analyzed using the MI.

8.2.1 Derivations of ASDAS-CRP, ASDAS-MI, and ASDAS Status

The ASDAS consists of a number of assessments which are scored by the subject and physician and multiplied by a proven formula (van der Heijde et al, 2009) as shown below:

- 0.121 x [redacted] (BASDAI question 2 result)
- 0.058 x [redacted] (BASDAI question 6 result)
- 0.110 x PGADA
- 0.073 x [redacted] (BASDAI question 3 result)
- 0.579 x (natural logarithm of the (hs-CRP [mg/L] + 1))

[redacted], PGADA, [redacted] are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009).

The sum of these weighted components gives the ASDAS-CRP.

If one component for the ASDAS-CRP is missing at a given visit, that component will be imputed by carrying the last observation forward, and the ASDAS-CRP will be calculated accordingly. If no value is available for that component before the missing time point, the next observation may be carried backwards. If more than one component for the ASDAS-CRP is missing, ASDAS-CRP will be treated as missing.

If the hs-CRP value is below 2 mg/L, then it will be imputed as the constant value of 2 mg/L (Machado et al, 2015).

ASDAS Status in defined in four disease activity categories based on ASDAS-CRP as follows:

- Inactive Disease: ASDAS-CRP <1.3
- Moderate Disease Activity: ASDAS-CRP >=1.3 to <2.1
- High Disease Activity: ASDAS-CRP >=2.1 to <=3.5
- Very High Disease Activity: ASDAS-CRP >3.5

ASDAS-MI is defined as ASDAS-CRP reduction (improvement) of ≥ 2.0 relative to Baseline.

8.3 Statistical analysis of other efficacy variables

Other efficacy variables will be analyzed for all subjects in the FAS, DBRS, ESS, cDBRS, cESS, and DBS.

All categorical variables will be presented using frequency tables by each visit. All continuous variables will be summarized using descriptive statistics by each visit.

The Hospital Anxiety and Depression Scale (HADS) will be analyzed separately for HADS-A and HADS-D. The summary statistics for HADS-A and HADS-D will be presented in two different tables.

Times series plots will be provided for the response rate or change from Baseline for the primary and secondary efficacy variables. The plots will show the weekly response rate over the first 12 weeks.

The MRI of the spine and sacroiliac joints will be performed in a substudy with subjects who were classified as MRI-positive at Baseline as per ASAS-Outcome Measures in Rheumatology Clinical Trials (OMERACT) criteria.

A subset of the FAS will be used for the analyses of MASES. The MASES Score will only be analyzed for subjects with enthesitis at Baseline (MASES > 0).

Time to onset of ASAS20 response and ASAS40 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates. Subjects who discontinue study prior to achieving a response will be censored at the date of study discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

The median time to response including the 2-sided 95% confidence interval will be calculated for each treatment. Between groups differences (each bimekizumab dose versus placebo) will be analyzed using a log-rank test stratified by geographic region and prior TNF inhibitor exposure. Missing response data will be imputed with NRI.

Summary tables will be presented for the time to onset of ASAS20 response and ASAS40 response including following information: number of subjects achieving ASAS20/ASAS40 response, number of subjects censored, descriptive statistics (minimum, 25th percentile, median, 75th percentile, maximum) for the Kaplan-Meier estimates including the p-value (difference to placebo). Additional Kaplan-Meier Plots will be provided.

All other efficacy variables will be analyzed using observed cases as treated and imputed with NRI for binary variables and MI for continuous variables.

Subjects in the ESS who discontinue with bimekizumab treatment during the Dose-Blind Period will be treated as missing and categorical/continuous variables will be imputed.

In order to assess the potential bias of the potentially unblinded subjects based on data, the results of the final analysis will be utilized. Results of the ASAS40 response of the rerandomized 320mg and 160mg treatment group at Week 48 will be compared to the potentially unblinded, randomized 320mg and 160mg treatment groups. If the percentage of ASAS40 responders is

comparable as assessed by overlapping 95% confidence intervals, the potential bias is estimated to be at minimum.

8.3.1 Bath Ankylosing Spondylitis Metrology Index (BASMI)

The BASMI characterizes the spinal mobility of a subject with AS and consists of 5 clinical measures to reflect axial status: cervical rotation; tragus-to- wall distance; lateral lumbar flexion; lumbar flexion (modified Schober); intermalleolar distance. Each of the 5 movements is scored according the linear BASMI definition (see bullet points below). The mean of the 5 scores provides the BASMI score. The higher the BASMI score, the more severe is the patient's limitation of movement due to their AS.

BASMI linear definition (S=score, A=assessment):

- Lateral lumbar flexion (mean right/left): S = (21.1 cm –A) / 2.1 cm
- Tragus-to-wall distance (mean right/left): S = (A – 8 cm) / 3 cm
- Lumbar flexion (modified Schober): S = (7.4 cm – A) /0.7 cm
- Intermalleolar distance: S = (124.5 cm – A) / 10 cm
- Cervical rotation (mean right/left): S = (89.3° - A) / 8.5°

The points above have all the additional condition $0 \leq S \leq 10$.

For cervical rotation, tragus-to-wall distance and lumbar flexion, take the mean of the left and right measurements, if both are available. Otherwise, the available measurement will be used.

For the lumbar flexion (modified Schober), values greater than 9.0 cm (Maksymowych, 2006) will be flagged as invalid and treated as if they were missing values. The below imputation rules apply for BASMI.

If 1 or 2 clinical measures for the BASMI are missing at one visit, the missing measure will be imputed by carrying the last observation forward, and the BASMI will be calculated accordingly. If no value is available for the clinical measure before the missing time point, the next observation may be carried backwards. If more than 2 items are missing, the BASMI score will be treated as missing.

8.3.2 Physician's Global Assessment of Disease Activity (PhGADA)

The Investigator will assess the overall status of the subject with respect to their AS signs and symptoms and functional capacity (considering both joint and skin components) using an NRS in which 0=very good, asymptomatic and no limitations of normal activities and 10=very poor, very severe symptoms which are intolerable and inability to carry out normal activities.

8.3.3 Short Form – 36 Items Health Survey

The SF-36 measures the following 8 health domains as rated by the subjects over the past four weeks: Physical Functioning, role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The questionnaire is available in Section 12.8. The classification of the questionnaire items to the health domains is shown in Section 12.9.

The SF-36 PCS and MCS are used to measure the two broad components, or aspects, of health-physical and mental. PCS and MCS are based on the aggregate of 8 health concepts described

above and all of the eight health domain scales are used to score both components summary measures.

One additional item asks respondents about health change over the past year.

The SF-36 will be used using QualityMetric's Health Outcomes™ Scoring Software. The software uses updates 2009 U.S. population norms and applies a Full Missing Score Estimation method as follows:

- A health domain score (except the physical functioning domain) will be estimated provided that at least one non-missing response is available within that domain.
- For the physical functioning domain item response theory will be used to develop a model for estimates of the missing score.
- Regression methods are then applied to estimate the PCS and the MCS on the basis of the available domains.

8.3.4 Medical Outcomes Study (MOS) Sleep Scale

The MOS Sleep Scale is a validated generic self-administered scale measuring specific aspects of sleep. The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 6-point scale ranging from "none of the time" to "all of the time", except sleep quantity, which is reported in hours. All scores are transformed linearly to range from 0 to 100, again with the exception of the sleep quantity subscale, which is scored in hours. Higher scores indicate more of the attribute implied by the scale name (eg, more sleep disturbance, more adequate sleep, or greater sleep quantity). The questionnaire is available in Section 12.10.

The item scores (1, and 3 through 12) are used to derive 7 different scale scores. In addition, the average number of hours slept over the past 4 weeks (Item 2) is used to create a raw and a dichotomized measure of sleep. The scale scores are created by averaging the respective rescaled item scores. Scales with at least 1 item answered can be used to generate a scale score. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Scores represent the average for all items in the scale that the respondent answered. The domains of interest for this study are the Sleep Disturbance and the Sleep Problems Index II domains. The table below describes which items are used for both sleep scales.

Table 8–1: MOS Sleep Scale Scores

Scale description (Short name)	Item score
Sleep disturbance (SLPD4)	1, 3 (R), 7 (R), 8 (R)
Sleep problems Index II (SLP9)	1, 3 (R), 4, 5 (R), 6 (R), 7 (R), 8 (R), 9 (R), 12

(R) refers to a reversed item.

Prior to averaging, the item score is re-scaled as shown in the following table.

Table 8–2: MOS Sleep Scale recoding of items

Item numbers	Original response category	Re-coded value (not reversed)	Re-coded value (reversed)
1	<1 1 2 3 4 5 >5	. 0 25 50 75 100 .	 -- N/A --
3, 5, 6, 7, 8, 9, 10, 11	<1 1 2 3 4 5 6 >6	 -- N/A 	. 100 80 60 40 20 0 .
4, 12	<1 1 2 3 4 5 6 >6	. 0 20 40 60 80 100 .	. 100 80 60 40 20 0 .

N/A=not applicable.

8.3.5 Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL consists of 18 items, each with a score of 0 = no or 1 = yes, so that the sum score ranges from 0 to 18, with higher scores indicating worse quality of life. The questionnaire is available in Section 12.11.

If 3 or fewer items are missing, the missing responses will be imputed with the mean of the available responses from that visit to calculate a total score. If more than 3 items are missing, the total score will be left missing.

8.3.6 Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index

The MASES Index comprises 13 items (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest and proximal insertion of the achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each

scored as 0 = yes or 1 = no and then summed for a possible score of 0 to 13, with higher scores indicating worse enthesitis. The questionnaire is available in Section 12.12.

If 7 or more items are available, MASES will be imputed by dividing the sum score with the number of assessments and multiplying the result with 13. If less than 7 times are available, MASES will be treated as missing.

Presence of enthesitis at Baseline should be defined as a Baseline MASES score >0.

8.3.7 MRI assessment

An MRI of the spine and sacroiliac joints will be performed in a substudy with approximately 20 subjects per treatment group at Baseline. A central reader will assess Baseline MRIs to identify MRI-positive subjects as per the ASAS OMERACT criteria. An MRI at Week 12 and Week 48 will be performed for those subjects who were MRI-positive at Baseline. The Baseline MRI should be performed after confirmation of eligibility based on screening assessments for the study and before the first bimekizumab injection. Magnetic resonance imaging at Week 12 and Week 48 should be performed as close to the Week12/Week 48 Visit as possible. Additional details for standardized performance and processing of MRIs will be provided in an MRI manual. The MRIs will be read centrally by readers who are blinded to treatment assignment and chronological order of the MRIs according to a charter for independent imaging assessment.

The following 2 different scoring systems will be utilized to determine changes from Screening.

SPARCC MRI (SI joint) score

The SPARCC MRI (SI joint) scoring method for lesions found on the MRI is based on an abnormal increased signal on the short-tau-inversion recovery (STIR) sequence, representing bone marrow edema (defined as an increased signal in bone marrow on a T2-weighted sequence, reflecting an increased concentration of "free water" related to a bone lesion). Each SI joint is divided into 4 quadrants: upper iliac, lower iliac, upper sacral, and lower sacral. The presence of increased signal on STIR in each of these 4 quadrants are scored on a dichotomous basis, where 1 = increased signal and 0 = normal signal. Joints that include a lesion exhibiting intense signal are each given an additional score of 1 per slice that demonstrated this feature. Similarly, each joint that included a lesion demonstrating continuous increased signal of depth greater or equal 1 cm from the articular surface is also given an additional score of 1. The scoring is repeated in each of 6 consecutive coronal slices. Total SI joint SPARCC scores can range from 0 to 72.

ASspiMRI-a (Berlin modification) score

The Berlin modification of the ASspiMRI-a is a scoring system with a concentration on STIR sequences without other fat saturation techniques. This scoring method quantifies active changes in 23 vertebral units (VU) of the spine (from C2 to S1). A VU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of bone marrow edema from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular VU. Total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69.

The following imputation rules should be used for calculating the total for both SPARCC MRI (SI joint) scores and ASspiMRI-a (Berlin modification) score:

- If all scores are NA at a visit, the imputed total is blank for that visit.

- Treat NA as 0 when computing the total score.
- If ALL the Baseline scores are NA, then do not carry forward the Baseline scores. Treat the subsequent visit as a surrogate Baseline.
- Carry the NA score from the Baseline visit forward to all follow-up visits unless all scores at Baseline are NA.
- Carry the numeric score from the last visit with non-NA score forward if a score is NA at a follow-up visit (unless all scores are NA at follow-up).

8.3.8 Hospital Anxiety and Depression Scale (HADS)

The Hospital Anxiety and Depression Scale (HADS) was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with chronic plaque psoriasis (Langley et al, 2010; Dauden et al, 2009). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal whereas a score of 15 and above is considered severe (Snaith and Zigmond, 1994).

8.3.9 C-reactive protein (CRP) and high-sensitivity C-reactive protein (CRP)

Blood will be collected for measurement of CRP and hs-CRP. CRP and hs-CRP are indicators for inflammation and are measured in the blood. Hs-CRP is a component of composite efficacy variables, and in addition is also summarized and analyzed as individual variables. For hs-CRP the summary statistics should contain n, geometric mean, geometric CV, median, first and third quartile (Q1 and Q3), minimum, and maximum, where the geometric CV (%) is calculated using:

$$CV = \sqrt{e^{SD_{ln}^2} - 1} \qquad (11)$$

with SD_{ln} – the standard deviation of the ln-transformed hs-CRP values.

For descriptive statistics, the observed values and ratio to Baseline values will be displayed.

hs-CRP and CRP values below the limit of quantification should be set to half the limit of quantification for the calculations. The limit of quantification for hs-CRP is 0.16 mg/L and 0.4 mg/dL = 4.00 mg/L for CRP.

8.4 Subgroup analysis

Subgroup analyses will be performed on the primary and secondary efficacy variables. The variables for subgroup analyses are defined in Section 4.8.

Subjects will be counted to have a positive treatment-emergent AbAb status in case the first AbAb positivity occurred up to Visit 7 (Week 12). The definition of first AbAb occurrence is described in Section 9.2.

All subgroup analyses are based on imputed data and will be summarized using descriptive statistics only.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit using the PK-PPS, and using a subset of the DBS which includes subjects that belong to both analysis sets, the DBS and the PK-PPS.

If bimekizumab plasma concentration measurements are deemed to be below the level of quantification (BLQ), then for calculation of the derived statistics this sample result will be set to half the LLOQ. The subjects with at least 1 result that is defined as BLQ will also be listed within the respective analysis table. Descriptive statistics will be calculated if at least 2/3 of the values are above the LLOQ. If this is not the case, only median, minimum, and maximum will be presented.

In addition geometric mean bimekizumab plasma concentration time curves will be plotted by treatment group.

The bimekizumab concentrations will also be listed.

9.2 Pharmacodynamics and Immunogenicity

The biomarker data will be separated between LGC assays, mulitplex proinflammatory cytokine and chemokine analysis, flow cytometry - TBNK panel, and flow cytometry - Th1/Th2/Th17/Th22 panel. Biomarker variables will be summarized and listed for each treatment at each scheduled visit using the PD-PPS, and using a subset of the DBS which includes subjects that belong to both analysis sets, the DBS and the PK-PPS.

In addition to the PD variables, whole blood will be stored to isolate deoxyribonucleic acid which may be used to examine genetic and epigenetic changes. The blood samples for genetic and epigenetic, and genomic, proteomic/metabolomics will not be analyzed in the interim or final analysis. Variables will be analyzed in a separate analysis as ad-hoc analysis.

The AbAb status will be determined for each visit where samples are taken for drug concentration measures. A cut point will be determined by the bioanalytical laboratory and will be used to determine the AbAb status as “above the cut point” (ACP) or “below the cut point” (BCP). For any AbAb levels that are ACP, a further confirmatory assay will be performed, the results of which will be determined as either “confirmed positive” (CP) or “not confirmed positive” (NCP). For samples that are CP, a further titre assay will be performed and the AbAb titre will be reported.

At each visit:

- Samples that are either BCP or ACP and NCP are defined as AbAb-
- Samples that are ACP and CP are defined as AbAb+

In addition, overall AbAb status should be determined:

- Subject AbAb positivity is defined as having with AbAb+ at any time in the treatment period. This does not include Baseline/pre-treatment
- Subject AbAb negativity is defined with AbAb- at any time in the treatment period. This does also include AbAb+ at Baseline/pre-treatment

- If there is AbAb+ at Baseline/pretreatment and there is a 4-fold increase in titre at least at one visit during the treatment period, then the subject has also an overall AbAb positivity status.

The visit of the first occurrence of AbAb positivity is defined as the visit when a subject is AbAb+ for the first time during treatment period excluding Baseline/pre-treatment. If there is AbAb+ at Baseline/pre-treatment and there is a 4-fold increase in titre at least at one visit during the treatment period, then the subject's first occurrence visit is the Baseline Visit.

The number and percentage of subjects with AbAb levels above the specified cut point will be summarized.

In addition, the time point of the first occurrence of AbAb positivity during the Double-Blind Period, and the entire treatment period (excluding Baseline and pre-treatment) will be summarized for each treatment group.

All individual subject-level AbAb results will be listed including the screening assay, confirmatory assay, and titres if applicable. Note, that titre results will only be available, if the confirmatory assay is positive.

Immunogenicity data will be summarized and listed using the PK-PPS analysis set.

10 SAFETY ANALYSES

All safety summaries and listings will be performed using all subjects in the SS.

10.1 Extent of exposure

The duration of exposure and time at risk will be summarized for the Double-Blind Period and the entire treatment period. For the entire treatment period the duration of exposure and time at risk will be calculated for bimekizumab 160mg, bimekizumab 320mg, and all bimekizumab. The calculation of exposure duration and time at risk for the all bimekizumab group is different from that of the other two groups. For all bimekizumab the duration of exposure and time at risk will include the time a subject received any dose of bimekizumab (including 16mg or 64mg) while for the other two treatment groups only the time a subject received 160mg, or 320mg will be included into the calculation.

Duration of exposure Double-Blind Period

The duration of exposure (in days) during the Double-Blind Period will be calculated as:

$$\begin{aligned} &Duration\ of\ exposure \\ &\quad = Date\ of\ last\ injection\ (double-blind\ period) \\ &\quad - Date\ of\ first\ injection\ (double-blind\ period) + 28 \end{aligned} \qquad (12)$$

28 days refer to one half-life of bimekizumab.

Note: If the date of last injection (Double-Blind Period) + 28 extends to a date beyond the date of first injection (Dose-Blind Period), then this calculation reverts to

$$Duration\ of\ exposure = Date\ of\ first\ injection\ (dose - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (13)$$

For subjects who die during the Double-Blind Period, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection\ (double - blind\ Period) + 1 \quad (14)$$

Duration of exposure entire treatment period

For subjects who do not switch study treatments, or who receive bimekizumab 16mg or 64mg will be summarized under all bimekizumab group:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (15)$$

Note: If the date of last injection +28 extends to a date beyond the final visit date (not including SFU), then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection + 1 \quad (16)$$

For subjects who die, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection + 1 \quad (17)$$

For subjects who receive Placebo or bimekizumab 16mg or 64mg in the Double-Blind Period and will be summarized under their Dose-Blind treatment in the overall table group bimekizumab 160mg or 320mg, or subjects who received Placebo and will be summarized in the overall table under their Dose-Blind treatment:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 28 \quad (18)$$

Note: If the date of last dose +28 extends to a date beyond the final visit date (not including SFU), then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (19)$$

For subjects who die during the Dose-Blind Period, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (20)$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose in Double-Blind Period, the date of first and last dose in Dose-Blind Period and the duration of exposure during Double-Blind Period and under bimekizumab treatment (any dose of bimekizumab) will be performed.

Time at risk Double-Blind Period

For subjects who complete the final visit of the Double-Blind Period and continue to the Dose-Blind Period:

$$Time\ at\ risk = Date\ of\ first\ injection\ (dose - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (21)$$

For subjects who discontinue on or prior to the final visit of the Double-Blind Period, use the minimum of the following:

$$Date\ of\ last\ injection\ (double - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 140 \quad (22)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (23)$$

$$Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (24)$$

where 140 days refers to 5*half-life of bimekizumab.

For subjects who die during the Double-Blind Period, then this calculation reverts to:

$$Date\ of\ death - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (25)$$

Time at risk entire treatment period

For subjects who do not switch study treatments, or who receive bimekizumab 16mg or 64mg and will be summarized under all bimekizumab group:

For subjects who complete the Dose-Blind Period and enter the extension study:

$$Time\ at\ risk = Date\ of\ Visit\ 16\ (Week\ 48) - Date\ of\ first\ injection + 1 \quad (26)$$

For subjects who die prior to the final visit:

$$Time\ at\ risk = Date\ of\ death - Date\ of\ first\ injection + 1 \quad (27)$$

For all other subjects, use the minimum of the following:

$$Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (28)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection + 1 \quad (29)$$

For subjects who receive Placebo or bimekizumab 16mg or 64mg in the Double-Blind Period and will be summarized under their Dose-Blind treatment in the overall table group bimekizumab 160mg or 320mg, or subjects who received Placebo and will be summarized in the overall table under their Dose-Blind treatment:

For subjects who complete the Dose-Blind Period and enter the extension study:

$$Time\ at\ risk = Date\ of\ Visit\ 16\ (Week\ 48) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (30)$$

For subjects who die during the Dose-Blind Period:

$$Time\ at\ risk = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (31)$$

For all other subjects, use the minimum of the following:

$$Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 140 \quad (32)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (33)$$

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \end{aligned} \quad (34)$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose\ + 1 \end{aligned} \quad (35)$$

10.2 Adverse events (AEs)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs (including serious AEs) are characterized as either non-treatment or treatment emergent according to the following criteria:

- Non-treatment emergent are the events with onset date and time prior to the very first administration of study medication (bimekizumab or placebo) or after a 140-day period after the final drug administration.
- Treatment-emergent AEs (TEAE) are those with onset date at or after the very first administration of study medication. The events that emerge within 140 days after the final drug administration, will also be considered as treatment emergent (eg, in the case of premature discontinuation or during the SFU period).

All AEs occurring during the study (i.e., after signature of the informed consent document) will be recorded in the eCRF. For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was classified as a SAE, as an AE of special interest, intensity, relationship to study medication, action taken with study medication, other action taken, outcome, date of outcome, and whether the AE led to study drug discontinuation or to study discontinuation.

ADRs are defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. Any AE that is considered "Related" to study treatment will be classed as an ADR.

If an AE occurs on the same day as the treatment switch (Visit 7, Week 12) then the AE will be allocated to the Double-Blind treatment. An exception from this general rule is made for adverse drug reactions (ADRs), and AE of hypersensitivity reactions and anaphylactic reactions. If those AEs occur on the same days as the treatment switch, the AEs will be allocated to the Dose-Blind treatment.

The incidence of TEAEs will be summarized by MedDRA SOC, high level term, and PT. Tables with incidences of classified TEAEs by maximum intensity, by relationship, and by subject number will be provided. The incidence of non TEAEs, non-serious TEAEs above the reporting threshold of 5% of subjects and relationship will be summarized. Furthermore the incidence of all TEAEs, serious TEAEs, non-serious TEAEs, and TEAEs leading to study discontinuation and/or permanent withdrawal of study medication, adverse drug reactions, fungal infectious disorder TEAEs, opportunistic infection (including tuberculosis) TEAEs, malignant or unspecified tumor TEAEs, malignant tumor TEAEs, major cardiovascular event TEAEs, haematopoietic cytopenias TEAEs, neuropsychiatric events TEAEs, inflammatory bowel disease TEAEs, hypersensitivity and anaphylactic Reaction TEAEs, hepatic events TEAEs, and TEAEs by timing of onset relative to AbAb Status will be summarized. In addition, an overall summary table will be provided.

The tables will be split into the Double-Blind Period and the complete treatment period (exception non TEAE table and TEAEs by timing of onset relative to AbAb Status). Presentations for the Double-Blind Period will summarize AEs that start prior to or at Visit 7 (see details given above) by treatment group as randomized for the Double-Blind Period. Presentations for the complete treatment period will only summarize AEs that occur under treatment with bimekizumab, irrespective of the treatment period. For summaries of the bimekizumab 160mg, and bimekizumab 320mg treatment groups, patients randomized to Placebo, bimekizumab 16mg or 64mg at Baseline will only be included with AEs that start in the Dose-Blind Period. The all bimekizumab treatment group will also present AEs occurring under bimekizumab 16mg or 64mg treatment in the Double-Blind Period. AEs for each subject will be summarized based on the treatment actually received at the onset of each particular AE.

Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER) will only be calculated for the complete treatment period for following tables in the final analysis: all TEAEs, serious TEAEs, TEAEs leading to study discontinuation and/or permanent withdrawal, adverse drug reactions, fungal infectious disorder TEAEs, opportunistic infection (including tuberculosis) TEAEs, malignant or unspecified tumor TEAEs, malignant tumor TEAEs, major cardiovascular event TEAEs, haematopoietic cytopenias TEAEs, neuropsychiatric events TEAEs, inflammatory bowel disease TEAEs, hypersensitivity and anaphylactic Reaction TEAEs, hepatic events TEAEs, and TEAEs by timing of onset relative to AbAb Status.

10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (36)$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2 and Table 12–1.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - date\ of\ first\ dose + 1 \quad (37)$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$\begin{aligned} &Time\ since\ most\ recent\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset \\ &\quad - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \end{aligned} \tag{38}$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (37 and 38) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

10.2.2 Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)

The EAIR is defined as the number of subjects (n_{AE}) with a specific AE adjusted for the exposure and will be scaled to 100 patient-years:

$$EAIR = 100 * \frac{n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \tag{39}$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [36] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (Section 10.1).

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (Section 10.1) in years is used. As indicated above, exposure-adjusted incidence rates will only be calculated for the overall treatment period. These presentations do not include AEs that occur under Placebo treatment. Therefore, a subject's exposure time will only start at the first dose of bimekizumab in the Dose-Blind Period for subjects randomized to Placebo at Baseline. Also, for subject's randomized to bimekizumab 16mg or 64mg at Baseline, exposure time will only be considered from the start of Dose-Blind Period, when presenting AEs for the bimekizumab 160mg, or bimekizumab 320mg groups. All exposure time on any bimekizumab dose is considered for the all bimekizumab column.

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

$$LCL = \frac{\chi^2_{2n_{AE},\frac{\alpha}{2}}}{2} \tag{40}$$

$$UCL = \frac{\chi^2_{2(n_{AE}+1),1-\alpha/2}}{2} \tag{41}$$

$$CI_{Lower} = 100 * \frac{LCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (42)$$

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (43)$$

where n_{AE} is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [36] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (Section 10.1).

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (44)$$

where N_{AE} is the total number of AEs, $T_{Risk,j}$ is a subject's total time at risk in years and n_{All} the number of subjects.

No confidence interval will be computed for EAER.

10.2.3 AE of Special Interest and AE of Special Monitoring

AE of special interest is any AE which meets the Hy's Law criteria, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

AE of special monitoring for this study include:

- Infections (serious, opportunistic, fungal and TB)
- Malignancies, including lymphoma
- Major cardiovascular events
- Neutropenia
- Neuropsychiatric events (in particular depression and suicide)
- Inflammatory bowel disease
- Anaphylactic reaction
- Hepatic events

For the definitions of AE of special monitoring the Bimekizumab Safety Topics of Interest (Version date 19Feb2018) will be used.

The incidence of TEAEs of special monitoring will be summarized by MedDRA system organ class, high level term, and PT. EAIR with associated 95% CI and the EAER will be included in the summary tables. Serious infections are also classified as AE of special monitoring but no separate table will be produced.

The output table for the search criteria Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)" will include two different overall rows:

- The first overall incidence row will summarize "Any malignancies (including unspecified)" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.
- The second overall incidence row will summarize "Any malignancy (including unspecified, excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

The output table for the search criteria SMQ="Malignant tumours (SMQ)" will include two different overall rows:

- The first overall incidence row will summarize "Any malignancies" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.
- The second overall incidence row will summarize "Any malignancy (excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

The output table for Anaphylactic reaction will include three different overall rows:

- The first row within the body of the table will be labeled "Any hypersensitivity/anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction or at least one anaphylactic reaction.
- The second row within the body of the table will be labeled "Any hypersensitivity reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction.
- The third row within the body of the table will be labeled "Any anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one anaphylactic reaction.

10.3 Clinical laboratory evaluations

The routine clinical laboratory evaluations specified in Table 10–1 and will be summarized. If any additional analytes are also recorded then these will be listed only.

Different summary tables for hematology and biochemistry variables will be provided, based on data from scheduled visits: observed values and change from Baseline, shift from Baseline to

maximum post-Baseline value (in Double-Blind Period), shift from Baseline to maximum post-Baseline value (in Dose-Blind Period), shift from Baseline to minimum post-Baseline value (in Double-Blind Period), shift from Baseline to minimum post-Baseline value (in Dose-Blind Period), shift from Baseline to end of treatment (in Double-Blind Period), shift from Baseline to end of treatment (in Dose-Blind Period), and markedly abnormal laboratory data.

End of treatment (in Double-Blind Period) will be defined as the last visit in the Double-Blind Period or the early termination assessment depending if the subject discontinued in the Double-Blind Period.

End of treatment (in Dose-Blind Period) will be defined as the Week 48 visit or the early termination assessment depending if the subject discontinued early or not.

In addition, number of subjects who meet the Hy's Law criteria (Section 10.2) will be described using frequencies.

All laboratory data will be listed by treatment, subject and visit including changes from Baseline for numeric variables, flags for measurements outside the normal ranges, the relative study day, a flag for whether the test was not done and a flag for whether the subject was fasting.

Additional listings will be presented for Hepatitis B and C, human immunodeficiency virus (HIV), genomic proteomic/metabolomics, and genetic/epigenetic tests. CRP and hs-CRP will be tabulated and listed separately in the efficacy section.

Table 10–1: Laboratory measurements

Hematology	**Biochemistry**	**Urinalysis**
Basophils	Calcium	Bacteria
Eosinophils	Chloride	Crystals
Lymphocytes	Magnesium	Glucose
Monocytes	Potassium	pH
Neutrophils	Sodium	RBC
Hematocrit	Glucose	WBC
Hemoglobin	BUN	Urine dipstick for pregnancy testing[a]
MCH	Creatinine	
MCHC	AST	
MCV	ALT	
Platelet count	ALP	
RBC count	GGT	
WBC count	Total bilirubin	
	LDH	
	Uric acid	
	Total cholesterol	

Table 10–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
	Albumin	
	Serum pregnancy testing[a]	
	CRP[b]	
	hs-CRP[b]	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=gamma glutamyltransferase; hs-CRP=high sensitivity C-reactive protein; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SFU=Safety Follow-up; WBC=white blood cell

[a] A serum pregnancy test will be performed at Screening for all women of childbearing potential. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles and women during menopause. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause (International Menopause Society, 2015). A urine pregnancy test is also required at the Baseline, Week 48, ET, and at SFU visits. A urine pregnancy test will also be performed at any study visit where there has been a delay in menses. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles. Pregnancy test results must be negative prior to administering IMP.

[b] Both CRP and hs-CRP will be tested at specified visits per Protocol Table 5.1.

Markedly abnormal values for biochemistry and hematology will be defined as laboratory values graded 3 or 4 according to the Rheumatology Common Toxicity Criteria (RCTC). Definitions of the markedly abnormal values are given in Table 10–2 and Table 10–3 and are based on the RCTC units. All units in the tables below will be converted to the standard international units based on Clinical Data Interchange Standards Consortium (CDISC) standards.

Values that are below the lower limit of the reference range will be flagged as “L” (low) and values that are above the upper limit of the reference range will be flagged as “H” (high) and listed as well.

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. In the case where laboratory values are below the lower limit of quantification, then these will be set to the midpoint between 0 and the lower limit of quantification for the purpose of summarizing the data.

Table 10–2: Definitions of Markedly Abnormal Biochemistry Values

Variable (RCTC units)	Markedly abnormal definition	
	Low	High
ALP	N/A	>3 x ULN
ALT	N/A	>3 x ULN
AST	N/A	>3 x ULN
Calcium (mg/dL)	<7.0	>12.5

Table 10–2: Definitions of Markedly Abnormal Biochemistry Values

Variable (RCTC units)	Markedly abnormal definition	
	Low	High
Creatinine (mg/dL)	N/A	>1.8 x ULN
Glucose (mg/dL)	<40	>250
Potassium (mmol/L)	<3.0	>6.4
Sodium (mmol/L)	<125	N/A
Total bilirubin	N/A	≥2 x ULN
Uric acid	N/A	≥3 x ULN

ALP=alkaline phosphatase; AST=aspartate aminotransferase; N/A=Not applicable; RCTC= Rheumatology Common Toxicity Criteria; ULN=upper limit of normal.

Table 10–3: Definitions of Markedly Abnormal Hematology Values

Variable (RCTC units)	Markedly abnormal definition	
	Low	High
Hemoglobin (g/dL)	<LLN AND >2.0 decrease from Baseline	N/A
Hemoglobin (g/dL)	<8.0	N/A
Leukocytes (total x 1000)	<2.0	N/A
Lymphocytes (x 1000)	<0.5	N/A
Neutrophils (x 1000)	<1.0	N/A
Platelets (x 1000)	<50	N/A

LLN=lower limit of normal; N/A = not applicable; RCTC= Rheumatology Common Toxicity Criteria.

10.4 Potential drug-induced liver injury (PDILI) assessment

All potential drug-induced liver injury (PDILI) events require immediate action, testing, and monitoring. The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are included but not limited to those listed in Table 10–4 (additional information) and Table 10–5 (laboratory measurements).

PDILI laboratory results and additional PDILI information will only be listed by treatment group and subject. If specific PDILI information collected separately is matching to the entries in the standard eCRF pages collected for all subjects, the specific PDILI information will be added to the corresponding listing for the standard eCRF information (eg, lifestyle information is collected for all study subjects, the additional PDILI information for alcohol and illicit drug use will be included in the listings for lifestyle). For information collected on top (eg, family history of PDILI) a new listing will be generated.

Table 10–4: Additional PDILI information

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) • Recent travel Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

Table 10–5: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophil antibody or monospot testing)

Table 10–5: PDILI laboratory measurements

Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen[a]
Chemistry	Amylase
	ALT, AST
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[b]
	Serum pregnancy test
	PK sample

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; HBcAb-IgM=hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; LDH=lactate dehydrogenase; PDILI=potential drug-induced liver injury; PK=pharmacokinetic; RNA=ribonucleic acid; ULN=upper limit of normal

[a] For detecting substances (ie, amphetamines, benzodiazepines, opioids, marijuana, cocaine, phencyclidine, and tricyclic antidepressants), additional tests may be performed based on the Investigator's medical judgment and patient's history.

[b] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

10.5 Vital signs, physical findings, and other observations related to safety

10.5.1 Vital signs

The following vital signs measurements will be assessed:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (C)

Vital signs measurements (absolute values and changes from Baseline) will be summarized and listed by visit and timing relative to dosing including changes from Baseline. The listing will also include details to abnormal values as defined in Table 10–6. Temperature will only be listed and not summarized in a table.

Table 10–6: Definitions of markedly abnormal blood pressure values

Variable (Unit)	Markedly abnormal low	Markedly abnormal high
Systolic blood pressure (mmHg)	<90 and a decrease from Baseline of ≥20	>180 and an increase from Baseline of ≥20
Diastolic blood pressure (mmHg)	<50 and a decrease from Baseline of ≥15	>105 and an increase from Baseline of ≥15

10.5.2 Electrocardiograms

The following ECG variables will be assessed:

- PR interval (ms)
- RR interval (ms)
- QRS duration (ms)
- QT interval (ms)
- QTcF interval (ms)
- QTcB interval (ms)

The date and time of the ECG will be recorded in the eCRF together with the Investigator interpretation and details of any abnormalities.

A summary of the number and percentage of subjects with normal, abnormal not clinically significant and abnormal clinically significant ECG results at all applicable visits will be presented.

All ECG variables will be summarized (absolute values and change from Baseline) and listed by visit.

10.5.3 Other safety variables

Physical Examination

Abnormal results of the physical examination together with details of abnormalities will be listed by treatment group, subject, and visit.

Assessment of Tuberculosis

Listings of history of latent TB, TB test results and 'Evaluation of signs and symptoms of tuberculosis' questionnaire data will be provided by treatment and subject.

Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

The eC-SSRS is an assessment tool that evaluates suicidal ideation and behavior. The eC-SSRS contains 9 categories with binary responses (yes/no):

- Category 1 – [redacted]
- Category 2 – [redacted]
- Category 3 – [redacted]

- Category 4 – [redacted]
- Category 5 – [redacted]
- Category 6 – [redacted]
- Category 7 – [redacted]
- Category 8 – [redacted]
- Category 9 – [redacted]

Following composite endpoints based on the above categories are defined as:

- Suicidal ideation: A "yes" answer at any time during treatment to any one of the five suicidal ideation questions (Categories 1-5).
- Suicidal behavior: A "yes" answer at any time during treatment to any one of the five suicidal behavior questions (Categories 6-9).
- Suicidal ideation or behavior: A "yes" answer at any time during treatment to any one of the ten suicidal ideation and behavior questions (Categories 1-9).

The incidence of subjects with suicidal ideation, behavior and injuries including the composite endpoints will be summarized by treatment group and visit. A by-subject listing of the eC-SSRS data will be provided.

Self-injurious behavior without suicidal intent is defined as event in the category non-suicidal self-injurious behavior.

11 REFERENCES

Anderson JJ, Baron G, van der Heijde D, Felson DT, Dougados M. Ankylsoing spondylitis assessment group preliminary definition of short-term improvement in ankylosing spondylitis. Arthritis Rheum. 2001 Aug;44(8):1876-86.

Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med. 2015;373:2534-48.

Berglund P, Heeringa S. Multiple imputation of missing data using SAS®. Cary, NC: SAS Institute Inc. 2014.

Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNFa treatment in ankylosing spondylitis. Ann Rheum Dis. 2004;63:1438-44.

Bross I. D. J. How to use ridit analysis. Biometrics. 1958;14 (1):18-38.

Carpenter JR, Kenward MG. Multiple imputation and its application. Chichester: John Wiley & Sons Ltd; 2013.CPMP/EWP/556/95. Points to consider on the clinical investigation of medicinal products other than NSAIDS for the treatment of RA. June 2004.

Committee for Proprietary Medicinal Product/ICH/135/95. Note for guidance on good clinical practice. July 2002.

Daudén E, Griffiths CE, Ortonne JP, Kragballe K, Molta CT, Robertson D, et al. Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. J Eur Acad Dermatol Venereol. 2009;23(12), 1374-82.

Fay MP, Feuer EJ. Confidence intervals for directly standardized rates: a method based on the Gamma distribution. Statistics in Medicine. 1997;16, 791-801.

Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewé R, van der Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis. 2003;62:127-32.

International Conference on Harmonization/ Food and Drug Administration E9 Guidance documents; 1998.
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf

International Menopause Society. Cornwall, UK: Menopause Terminology; c2015.
http://www.imsociety.org/menopause_terminology.php. Accessed 25 Jan 2016.

Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, Hsu MC, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebocontrolled phase III trial. J Am Acad Dermatol. 2010;63(3):457-65.

Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:18-24.

Machado P, Navarro-Compan V, Landewe R, van Gaalen VA, Roux C, van der Heijde D. Calculating the Ankylosing Spondylitis Disease Activity Score If the Conventional C-Reactive Protein Level Is Below the Limit of Detection or If High-Sensitivity C-Reactive Protein Is Used: An Analysis in the DESIR Cohort. Arthritis Rheum. 2015 Feb;67(2):408-13.

Maksymowych WP, Mallon C, Richardson R, et al. Development and Validation of the Edmonton Ankylosing Spondylitis Metrology Index. Arthritis Rheum. 2006;55:575-82.

Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharm Stat. 2012;11:456-61.

Mantel N, Haenszel W. Statistical aspects of the Analysis of Data From Retrospective Studies of Disease. J Natl Cancer Inst. 1959; 22:719-48.

Nam, JM. A simple approximation for calculating sample sizes for detecting linear trend in proportions. Biometrics. 1987;43(3):701-5.

Rubin D.B. 1987. Muliple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons.

Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68(Supple 2):ii1-44.

Snaith RP, Zigmond AS. The hospital anxiety and depression scale, with the irritabilitydepression-anxiety scale and the Leeds situational anxiety scale manual. 1994.

Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology. 1990;131, 373-375.

van der Heijde D, Dougados M, Davis J, Weisman MH, Maksymowych W, Braun J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. Arthritis Rheum. 2005;52:386-94.

van der Heijde D, Schiff MH, Sieper J, Kivitz AJ, Wong RL, Kupper H, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis. 2009;68:922-9.

12 APPENDICES

12.1 Calculation rules for duration of adverse events

The calculation rules for duration of AEs are presented in Table 12–1. AE duration is computed and reported in day.

Table 12–1: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Complete data	D1	D2	Duration = D2 – D1 + 1
Start date missing	-	D2	Duration = < D2 – D0 +1 Where, for a subject in the SS, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day
End date missing	D1	-	Duration = > Final contact date – D1 + 1 For resolved and ongoing AE Duration
Start and end date missing	-	-	Duration = > Final contact date – D0 + 1 For resolved and ongoing AE Duration Where, for subjects in the SS, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day

12.2 Treatment group assignment for tables and figures

Table 12–2 displays the treatment group labels for each data type. This overview clarifies what kind of treatment groups will be used for producing the tables and figures separated between the different table types.

Table 12–2: Treatment group assignment for tables and figures

	Placebo	BKZ 16mg/ BKZ64mg/ BKZ 160mg/ BKZ 320mg	All BKZ	All subjects
Subject disposition	X	X		X
Important protocol deviation	X	X		X
Demographics/Lifestyle	X	X		X
Ankylosing spondylitis history	X	X		X
Baseline characteristics	X	X		X
TB testing	X	X		X
Previous and ongoing medical history	X	X		X

Table 12–2: Treatment group assignment for tables and figures

	Placebo	BKZ 16mg/ BKZ64mg/ BKZ 160mg/ BKZ 320mg	All BKZ	All subjects
Prior and concomitant medication	X	X		X
Rescue and prohibited medication	X	X		X
Bimekizumab compliance	X	X	X	
Extent of exposure	X	X	X	
Efficacy analysis	X	X		
Plasma/Bimekizumab concentration	X	X		
Pharmacokinetic variables/Biomarker data/AbAb	X	X		
AEs	X	X	X	
Safety laboratory tests	X	X	X	
Vital signs/Body weight/ECG/ Physical examination	X	X	X	
eC-SSRS	X	X	X	

AbAb=Anti-bimekizumab antibody; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale.

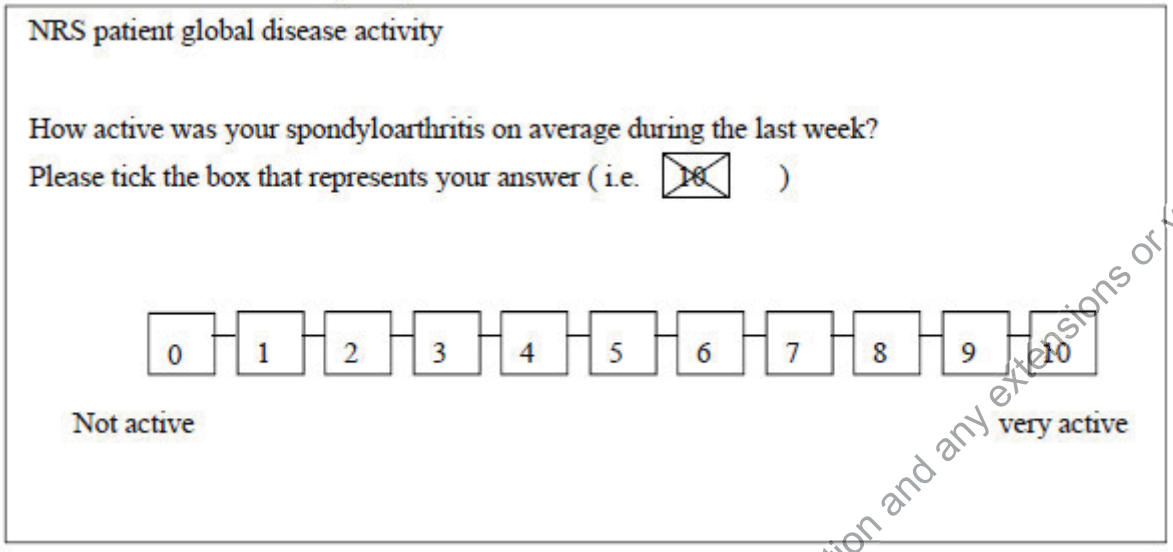
12.3 Hematology and biochemistry variables for the interim analysis

Table 12–3: Selected hematology and biochemistry variables for the interim analysis

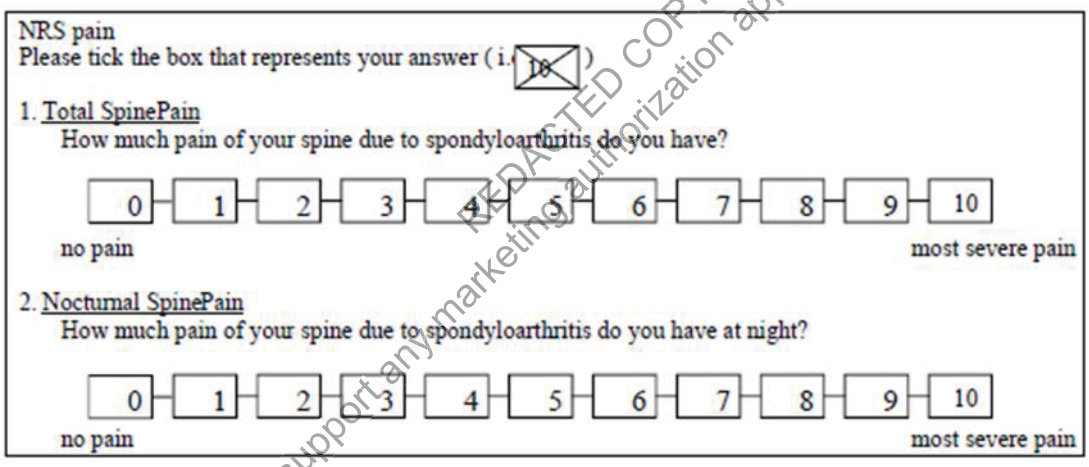
Hematology	Biochemistry
Lymphocytes	AST
Neutrophils	ALT
Hematocrit	Total bilirubin
Hemoglobin	
Platelet count	

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

12.4 Physician's Global Assessment of Disease Activity (PGADA) questionnaire



12.5 Total and nocturnal spinal pain questionnaire



The following information (eg, questionnaire) is copyrighted and UCB does not have permission to disclose the contents.

12.12 Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) questionnaire

Tendon Insertion Site	Score	
	Right Side	Left Side
Costochondral 1	☐0 Not tender ☐1 Tender	☐0 Not tender ☐1 Tender
Costochondral 7	☐0 Not tender ☐1 Tender	☐0 Not tender ☐1 Tender
Anterior superior iliac spine	☐0 Not tender ☐1 Tender	☐0 Not tender ☐1 Tender
Iliac crest	☐0 Not tender ☐1 Tender	☐0 Not tender ☐1 Tender
Posterior iliac spine	☐0 Not tender ☐1 Tender	☐0 Not tender ☐1 Tender
L5 spinous process	☐0 Not tender ☐1 Tender	NA
Achilles tendon, proximal insertion	☐0 Not tender ☐1 Tender	☐0 Not tender ☐1 Tender

12.13 Identification of Opportunistic infections

Opportunistic infections are identified in two steps:

Step 1: Refer to column B of the spreadsheet (Opportunistic infections MedDRA v 19.xlsx) which identifies the PTs to be classified as opportunistic infections using either a single "x" or a double "xx".

- TEAEs which code to a PT flagged with a single "x" need to also be serious in order to be considered an opportunistic infection.
- All TEAEs which code to a PT flagged with a double "xx" are considered to be an opportunistic infection, regardless of seriousness.

All serious TEAEs in the study database which code to a PT flagged with a single "x" and all TEAEs in the study database which code to a PT flagged with a double "x" will be summarized as an opportunistic infection in the stand-alone table.

Step 2: Refer to column C of the spreadsheet which identifies the PTs that need to be evaluated on a case-by-case basis by the study physician in order to determine whether it is a true opportunistic infection or not. The process for physician review is as follows:

1. Study programming team creates a spreadsheet which lists all of the subjects with a TEAE present in the database which codes to a PT identified as case-by-case. Information from the AE dataset to be included in the spreadsheet: Subject ID, AE verbatim term, SOC, High Level Term, Lower Level Term, PT, AE start date, AE end date, seriousness, severity, relationship to study medication, action taken. Additionally, a column will be included where the study physician can document their decision on the case.
2. Study physician reviews the cases in the spreadsheet and indicates in the additional column which AEs are confirmed to be opportunistic infections via a single "x".
3. Study programming team incorporates these decisions into the AE dataset by merging the study physician decisions for individual subjects / PTs and flagging the confirmed opportunistic infections as such in the dataset.

All subjects with a case-by-case PT reported that has been confirmed by the study physician to be an opportunistic infection will be summarized as such in the stand-alone table, along with all of the events identified in Step 1 of this process.

The timing and frequency of Step 2 should be outlines and agreed to by the study team at the beginning of the study. It is suggested that this process be executed multiple times throughout the course of the study, more frequently in the weeks leading up to database lock, and one final time immediately prior to database lock.

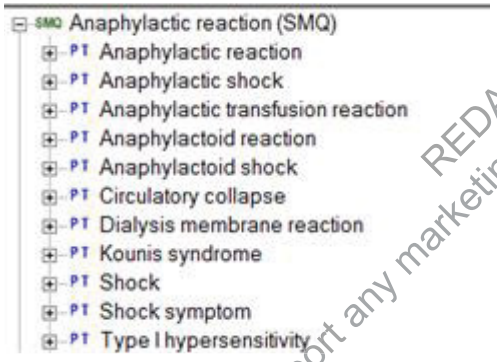
Following the initial physician review of case-by-case events, subsequent reviews will be based on the cumulative set of case-by-case events present in the database at each time point of spreadsheet creation. Physician decisions from previous runs should be retained in each subsequent run. The final run of the spreadsheet, with all study physician decisions on the full set of case-by-case events, will be archived at the conclusion of the study.

12.14 MedDRA algorithmic approach to anaphylaxis

The SMQ Anaphylactic reaction consists of three parts:

- A narrow search: If a subject reports any TEAE which codes to a PT included in Category A, then the event will be flagged as an anaphylactic reaction and summarized as such in the table.

  Category A



- A broad search: If a subject reports any TEAE which codes to a PT included in Category B AND reports any TEAE which codes to a PT included in Category C, and both TEAEs have the same start date, then both events will be flagged as anaphylactic reactions and summarized as such in the table.

  Category B

- Acute respiratory failure
- Asthma
- Bronchial oedema
- Bronchospasm
- Cardio-respiratory distress
- Chest discomfort
- Choking
- Choking sensation
- Circumoral oedema
- Cough
- Cyanosis
- Dyspnoea
- Hyperventilation
- Irregular breathing
- Laryngeal dyspnoea
- Laryngeal oedema
- Laryngospasm
- Laryngotracheal oedema
- Mouth swelling
- Nasal obstruction
- Oedema mouth
- Oropharyngeal spasm
- Oropharyngeal swelling
- Respiratory arrest
- Respiratory distress
- Respiratory dyskinesia
- Respiratory failure
- Reversible airways obstruction
- Sensation of foreign body
- Sneezing
- Stridor
- Swollen tongue
- Tachypnoea
- Throat tightness
- Tongue oedema
- Tracheal obstruction
- Tracheal oedema
- Upper airway obstruction
- Wheezing

Category C

- Allergic oedema
- Angioedema
- Erythema
- Eye oedema
- Eye pruritus
- Eye swelling
- Eyelid oedema
- Face oedema
- Flushing
- Generalised erythema
- Injection site urticaria
- Lip oedema
- Lip swelling
- Nodular rash
- Ocular hyperaemia
- Oedema
- Periorbital oedema
- Pruritus
- Pruritus allergic
- Pruritus generalised
- Rash
- Rash erythematous
- Rash generalised
- Rash pruritic
- Skin swelling
- Swelling
- Swelling face
- Urticaria
- Urticaria papular

Category D

- Blood pressure decreased
- Blood pressure diastolic decreased
- Blood pressure systolic decreased
- Cardiac arrest
- Cardio-respiratory arrest
- Cardiovascular insufficiency
- Diastolic hypotension
- Hypotension

- An algorithmic approach: If a subject reports any TEAE which codes to a PT included in Category D AND reports (either a TEAE which codes to a PT included in Category B OR a TEAE which codes to a PT included in Category C), and both TEAEs have the same start date, then both events will be flagged as anaphylactic reactions and summarized as such in the table.

13 AMENDMENT TO THE STATISTICIAL ANALYSIS PLAN

13.1 Amendment 1

13.1.1 Rationale for the amendment

The main objectives of this SAP amendment are to provide more consistency between AS0008 and the PA0008 study. The SAP has been amended to:

- Update the AbAb analysis
- Remove SAS notations from the multiple imputation text
- Re-structure the AE section for a better overview
- Add more information for the interim analysis

13.1.2 Modifications and changes

Change # 1

LIST OF ABBREVIATIONS

…	
AbAb	Anti-bimekizumab antibody
AE	Adverse event
…	
BASMI	Bath Ankylosing Spondylitis Metrology Index
BKZ	Bimekizumab
…	
BUN	Blood urea nitrogen
CPK	Creatine phosphokinase
…	
n	Number of observations
NRI	Non-responder imputation

Has been changed to

…	
AbAb	Anti-bimekizumab antibody
ACP	**Above the cut point**
ADR	**Adverse drug reaction**
AE	Adverse event
…	

BASMI	Bath Ankylosing Spondylitis Metrology Index
BCP	**Below the cut point**
BKZ	Bimekizumab
…	
BUN	Blood urea nitrogen
CP	**Confirmed positive**
CPK	Creatine phosphokinase
…	
n	Number of observations
NCP	**Not confirmed positive**
NRI	Non-responder imputation
…	

Change # 2

Section 3.4 Protocol deviations

Important protocol deviations are defined as those deviations from the protocol likely to have a meaningful impact on the primary efficacy outcomes for an individual subject. Important protocol deviations will be identified and classified by the deviation types defined in the appropriate protocol-specific document. All protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from Per Protocol Set (PPS). The exclusion from PPS is limited to the double-blind period, ie. only subjects with important protocol deviations prior to re-randomization at Visit 7 (Week 12) will be excluded from PPS. Subjects with important protocol deviations after Visit 7 (Week 12) will not be excluded from PPS.

Has been changed to

Important protocol deviations are defined as those deviations from the protocol likely to have a meaningful impact on the primary efficacy outcomes for an individual subject. Important protocol deviations will be identified and classified by the deviation types defined in the appropriate protocol-specific document. All protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from Per Protocol Set (PPS)**, Pharmacokinetics Per-Protocol Set (PK-PPS), and Pharmacodynamics Per-Protocol Set (PD-PPS)**. The exclusion from PPS is limited to the double-blind period, ie. only subjects with important protocol deviations prior to re-randomization at Visit 7 (Week 12) will be excluded from PPS. Subjects with important protocol deviations after Visit 7 (Week 12) will not be excluded from PPS.

Change # 3

3.10 Changes to protocol-defined analyses

There have been no changes to the protocol-defined analyses.

Has been changed to

~~There have been no changes to the protocol-defined analyses.~~

Instead of stopping the pairwise testing of each bimekizumab dose versus placebo once it failed to reach significance at a significance level of α=0.05, the pairwise testing will continue and further pairwise comparisons are seen as non-significant.

No fixed sequence testing will be used for the secondary efficacy variables.

Time to a given response is defined as the length in weeks from Baseline until the first date when the response is achieved. In the definition the length was changed from days to weeks due to easier interpretation.

Change # 4

Section 4.2.1 Handling of missing data for efficacy analysis

The analysis for the binary primary, secondary, and other efficacy variables will use non-responder imputation (NRI) for handling missing data. In NRI, each subject with missing data or who has discontinued double-blind study treatment prior to Week 12 will be counted as a non-responder.

Sensitivity analysis will be performed for the secondary analysis of the primary variable (ASAS40 response at Week 12) using MI assuming that missingness is missing at random (MAR). The MI method will be applied as follows:

1. Create a data set, sorted by treatment groups, of subjects with observed values and those needing estimation by multiple imputation. For the imputation step, missing values will be separated into non-monotone missing values (ie, intermittent missing values between completed assessments) and monotone missing values (ie, missing values after the patient dropped out). The procedure will sequentially estimate an imputation model for the ASAS components at each post-Baseline visit where ASAS components are collected, with geographic region, and prior TNF inhibitor exposure as covariates separated between the treatment groups.
   - For the imputation of intermediate missing values, the missing ASAS components in each data set will be filled in using the Markov-Chain Monte Carlo (MCMC) method in PROC MI with multiple chains and monotone imputing. To perform separate multiple imputation analyses for the treatment groups the BY statement in PROC MI will be used. A total number of imputations will be 100. The seed used for these imputations will be 2017.

     Note: All other multiple imputation procedures described in this SAP will use this same seed as well.

     Note: The imputation model based on the MCMC method will only allow continuous variables as predictors. Therefore, prior TNF inhibitor exposure and geographic region will be re-coded as indicator variables (with values of 0 or 1 for each level of the variable).

Note: To avoid that imputed values are outside of the pre-defined range of values for the ASAS components (eg, PGADA [0-10]) the MAXIMUM and MINIMUM options in PROC MI will be used.

– If the intermediate missing data are imputed, the monotone missing data will be imputed for all patients with monotone missing data (eg, patients that discontinued the studies). The multiple imputation will be done with the monotone regression option in PROC MI including geographic region, and prior TNF inhibitor exposure as covariates. The dataset is the output dataset of the partial imputation. Since this dataset already has 100 imputed values at each visit, only one imputation will be performed.

  Note: MAXIMUM and MINIMUM options will be used as well to avoid values outside of the pre-defined range of values.

2. The ASAS40 response will be calculated using the complete datasets. That is, the values of the ASAS components at Week 12 based on the complete datasets will be compared to their corresponding Baseline values to calculate an ASAS40 response for each subject (as described in Section 8.1.1). Each complete data set will then be analyzed based on a logistic regression model with factors of treatment group, geographic region, and prior TNF inhibitor exposure.
3. The Week 12 results from the logistic regression analysis of each of the 100 imputed data sets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). This will be done using SAS PROC MIANALYZE.

Some key points to consider relative to the calculation of the odds ratios and corresponding confidence intervals are noted below:

As the estimates of the odds ratios from the logistic regression model in step 3 follow a lognormal distribution, a log transformation is needed to normalize these estimates since the procedures for combining results from multiple imputed datasets are based on the assumption that the statistics estimated from each imputed dataset are normally distributed. Therefore, the log of the odds ratio estimates from the logistic regression model are used when combining into a single inference (the use of PROC MIANALYZE in step 3). Additionally, the standard errors (SE) for the odds ratios are transformed as follows:

$$SE = \frac{\log(UCL) - \log(LCL)}{2Z_{\propto/2}} \quad (1)$$

where UCL and LCL are the upper and lower confidence limit, respectively, for the confidence interval of the odds ratio from the logistic regression model, and $Z_{\alpha/2}$ is the relevant critical value from the standard normal distribution (1.96 for a 95% confidence interval). The estimates of the log odds ratio for each bimekizumab dose relative to placebo and the corresponding upper and lower confidence limits will be provided. The odds ratio is estimated by exponentiating the estimate of the log odds ratio. The confidence limits of the odds ratio are then estimated as follows:

$$LCL = OR * \exp(-SE * Z_{\propto/2}) \quad (2)$$

$$UCL = OR * \exp(SE * Z_{\propto/2}) \quad (3)$$

where OR is the back-transformed estimate of the odds ratio just described, SE is the standard error of the log odds ratio derived in PROC MIANALYZE and Zα/2 is the relevant critical value from the standard normal distribution (1.96 for a 95% confidence interval). These calculations will be done such that odds ratios and corresponding confidence intervals are calculated for the odds ratio of each bimekizumab dose versus placebo. Note that the p-values presented in the tables will be the ones provided initially by PROC MIANALYZE and are not impacted by the transformations described above.

The supportive analysis number 3 (analysis of the ASAS components), and all continuous secondary efficacy variables will use the same multiple imputation method as described above. Instead of using the logistic regression model the ANCOVA with treatment group, geographic region, and TNF inhibitor exposure as fixed effects and the Baseline values as covariate will be used. No log transformation is needed for the ANCOVA estimations.

The mean and standard error of the continuous other efficacy variables will be computed using SAS PROC UNIVARIATE. The imputed means and their standard errors will be summarized using PROC MIANALYZE as described above. Following Rubin (1987), multiple imputation estimates of descriptive statistics are computed by simply averaging the estimates from $m = 1, \ldots, M$ independent repetitions of the imputation algorithm:

$$\bar{\theta} = \frac{1}{M}\sum_{m=1}^{M}\hat{\theta}_m \quad (4)$$

where $\hat{\theta}_m$ is the estimate of θ from the completed data set $m = 1, \ldots, M$ (Berglund, 2014).

Has been changed to

The analysis for the binary primary, secondary, and other efficacy variables will use non-responder imputation (NRI) for handling missing data. In NRI, each subject with missing data or who has discontinued double-blind study treatment prior to Week 12 will be counted as a non-responder.

Sensitivity analysis will be performed for the secondary analysis of the primary variable (ASAS40 response at Week 12) using MI assuming that missingness is missing at random (MAR). The MI method will be applied as follows:

1. Create a data set, sorted by treatment groups, of subjects with observed values and those needing estimation by multiple imputation. For the imputation step, missing values will be separated into non-monotone missing values (ie, intermittent missing values between completed assessments) and monotone missing values (ie, missing values after the patient dropped out). The procedure will sequentially estimate an imputation model for the ASAS components at each post-Baseline visit where ASAS components are collected, with geographic region, and prior TNF inhibitor exposure as covariates separated between the treatment groups.
   - For the imputation of intermediate missing values, the missing ASAS components in each data set will be filled in using the Markov-Chain Monte Carlo (MCMC) method ~~in~~

~~PROC MI~~ with multiple chains and monotone imputing. ~~To perform separate multiple imputation analyses for the treatment groups the BY statement in PROC MI will be used.~~ A total number of imputations will be 100. The seed used for these imputations will be 2017.

Note: All other multiple imputation procedures described in this SAP will use this same seed as well.

Note: The imputation model based on the MCMC method will only allow continuous variables as predictors. Therefore, prior TNF inhibitor exposure and geographic region will be re-coded as indicator variables (with values of 0 or 1 for each level of the variable).

Note: To avoid that imputed values are outside of the pre-defined range of values for the ASAS components (eg, PGADA [0-10]) **maximum and minimum values for imputed variable values are specified.** ~~the MAXIMUM and MINIMUM options in PROC MI will be used.~~

– If the intermediate missing data are imputed, the monotone missing data will be imputed for all patients with monotone **regression including geographic region, and prior TNF inhibitor exposure as covariates.** ~~missing data (eg, patients that discontinued the studies). The multiple imputation will be done with the monotone regression option in PROC MI including geographic region, and prior TNF inhibitor exposure as covariates~~. The dataset is the output dataset of the partial imputation. Since this dataset already has 100 imputed values at each visit, only one imputation will be performed.

Note: ~~MAXIMUM and MINIMUM options will be used as well~~ **Maximum and minimum values are specified for imputed variable values** to avoid values outside of the pre-defined range of values.

2. The ASAS40 response will be calculated using the complete datasets. That is, the values of the ASAS components at Week 12 based on the complete datasets will be compared to their corresponding Baseline values to calculate an ASAS40 response for each subject (as described in Section 8.1.1). Each complete data set will then be analyzed based on a logistic regression model with factors of treatment group, geographic region, and prior TNF inhibitor exposure.
3. The Week 12 results from the logistic regression analysis of each of the 100 imputed data sets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). ~~This will be done using SAS PROC MIANALYZE.~~

Some key points to consider relative to the calculation of the odds ratios and corresponding confidence intervals are noted below:

As the estimates of the odds ratios from the logistic regression model in step 3 follow a lognormal distribution, a log transformation is needed to normalize these estimates since the procedures for combining results from multiple imputed datasets are based on the assumption that the statistics estimated from each imputed dataset are normally distributed. Therefore, the log of the odds ratio estimates from the logistic regression model are used when combining into a

single inference (~~the use of PROC MIANALYZE in~~ step 3). Additionally, the standard errors (SE) for the odds ratios are transformed as follows:

$$SE = \frac{\log(UCL) - \log(LCL)}{2Z_{\propto/2}} \quad (1)$$

where UCL and LCL are the upper and lower confidence limit, respectively, for the confidence interval of the odds ratio from the logistic regression model, and $Z_{\alpha/2}$ is the relevant critical value from the standard normal distribution (1.96 for a 95% confidence interval). The estimates of the log odds ratio for each bimekizumab dose relative to placebo and the corresponding upper and lower confidence limits will be provided. The odds ratio is estimated by exponentiating the estimate of the log odds ratio. The confidence limits of the odds ratio are then estimated as follows:

$$LCL = OR * \exp(-SE * Z_{\propto/2}) \quad (2)$$

$$UCL = OR * \exp(SE * Z_{\propto/2}) \quad (3)$$

where OR is the back-transformed estimate of the odds ratio just described, SE is the standard error of the log odds ratio ~~derived in PROC MIANALYZE~~ and Zα/2 is the relevant critical value from the standard normal distribution (1.96 for a 95% confidence interval). These calculations will be done such that odds ratios and corresponding confidence intervals are calculated for the odds ratio of each bimekizumab dose versus placebo. Note that the p-values presented in the tables ~~will be the ones provided initially by PROC MIANALYZE and~~ are not impacted by the transformations described above.

The supportive analysis number 3 (analysis of the ASAS components), and all continuous secondary efficacy variables will use the same multiple imputation method as described above. Instead of using the logistic regression model the ANCOVA with treatment group, geographic region, and TNF inhibitor exposure as fixed effects and the Baseline values as covariate will be used. No log transformation is needed for the ANCOVA estimations.

~~The mean and standard error of the continuous other efficacy variables will be computed using SAS PROC UNIVARIATE. The imputed means and their standard errors will be summarized using PROC MIANALYZE as described above.~~ Following Rubin (1987), multiple imputation estimates of descriptive statistics are computed by simply averaging the estimates from $m = 1, \ldots, M$ independent repetitions of the imputation algorithm:

$$\bar{\theta} = \frac{1}{M}\sum_{m=1}^{M}\hat{\theta}_m \quad (4)$$

where $\hat{\theta}_m$ is the estimate of θ from the completed data set $m = 1, \ldots, M$ (Berglund, 2014).

Change # 5

Section 4.2.2 Handling of missing data for adverse events (AEs)

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In the event of ambiguity or incomplete data which makes it impossible to determine whether the AE was treatment emergent, the AE will be considered treatment emergent.

Has been changed to

…

In the event of ambiguity or incomplete data which makes it impossible to determine whether the AE was treatment emergent, the AE will be considered treatment emergent.

If the intensity of an AE is unknown, it is considered as severe.

If the relationship to study drug is missing, it is considered as related.

The imputation rule for missing seriousness differ between the interim and final analysis. For the interim analysis no imputations rule will be applied. For the final analysis the worst case approach will be applied. If the seriousness of an AE is missing for the final analysis, it is considered as serious.

Change # 6

Section 4.3 Interim analysis and data monitoring

After all enrolled subjects have completed the 12 weeks Double-Blind Period, an interim analysis will be performed (i) to analyze the dose:exposure response for the ASAS response criteria to determine the optimal therapeutic dose(s) for subsequent studies, and (ii) to perform a comprehensive evaluation of all double-blind data of the study.

No separate SAP for the interim analysis will be provided. The interim analysis is a limited version of the final analysis and will focus on specific topics, eg, primary and secondary efficacy analysis and comprise the results of the 12 weeks Double-Blind Period only. The TFL shells for the interim and final analysis will be provided in two different documents.

The interim analysis will summarize disposition, demographics, AS history, Baseline characteristics, AS concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). Corresponding listings will be provided. Not all collected hematology and biochemistry laboratory variables will be summarized and listed. For the interim analysis only selected variables will be provided as listed in Table Table 12–3.

The interim efficacy analysis will focus on the primary and secondary efficacy analyses including supportive and sensitivity analyses. In addition, summary tables for the primary and secondary efficacy variables, and the ASAS components will be provided. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive statistics by each visit. Time to onset of ASAS20 response and ASAS40 response will be summarized and plotted as described in Section 8.3.

PK and PD data will not be analyzed in the interim analysis. A separate PKPD analysis including separate SAP will be performed after Week 12.

For the interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The investigators and subjects will remain blind to the assigned bimekizumab dosing regimen until the subject completes the Dose-Blind Period at Week 48.

Safety data will be provided to an independent Data Monitoring Committee (DMC). The DMC will review those safety data periodically. The composition and operation of the DMC will be defined in the DMC charter. The presentation and analysis of data for the DMC meetings is described within a separate DMC SAP.

Has been changed to

After all enrolled subjects have completed the 12 weeks Double-Blind Period, an interim analysis will be performed (i) to analyze the dose:exposure response for the ASAS**40** response criteria to determine the optimal therapeutic dose(s) for subsequent studies, and (ii) to perform a comprehensive evaluation of all double-blind data of the study.

No separate SAP for the interim analysis will be provided. The interim analysis is a limited version of the final analysis and will focus on ~~specific topics, eg,~~ **the** primary and secondary efficacy analysis and comprise the results of the 12 weeks Double-Blind Period ~~only~~. The TFL shells for the interim and final analysis will be provided in two different documents.

The interim analysis will summarize disposition, demographics, AS history, Baseline characteristics, AS concomitant medication, efficacy analysis, **AEs and treatment-emergent AEs (derivation Section 10.2)**, hematology and biochemistry laboratory data, and **Electronic Columbia-Suicide Severity Rating Scale** (eC-SSRS). ~~Corresponding listings will be provided.~~ Not all collected hematology and biochemistry laboratory variables will be summarized ~~and listed~~. For the interim analysis only selected **hematology and biochemistry** variables will be provided as listed in Table 12–3. **Listings of AEs, hematology, biochemistry and C-SSRS data will be provided.**

The interim efficacy analysis will ~~focus on the primary and secondary efficacy analyses including supportive and sensitivity analyses~~ **include following primary and secondary variables: ASAS40,20,5/6 response at Week 12, and change from Baseline in BASDAI, ASDAS-CRP, BASFI at Week 12. The variables will be analyzed using the same methods described in** Section 8.1.2 **and** Section 8.2 **including supportive and sensitivity analyses (**Section 8.1.3 **and** Section 8.1.4). In addition, summary tables for the primary and secondary efficacy variables, and the ASAS components will be provided. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive statistics by each visit. Time to onset of ASAS20 response and ASAS40 response will be summarized and plotted as described in Section 8.3.

PK and PD data will ~~not~~ be analyzed in the interim analysis **as described in** Section 9.1 **and** Section 9.2. ~~A separate PKPD analysis including separate SAP will be performed after Week 12.~~ **PKPD will be analyzed as part of the exposure:response modeling outside of the scope of the SAP. Biomarker data will not be analyzed in the interim analysis.**

The interim analysis includes selected data up to Week 12 and in addition data up to Week 16. The data up to Week 16 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. All analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Following variables will be analyzed: ASAS40, ASAS20, ASDAS-CRP, BASDAI, PK, AbAb and TEAEs. It depends on the analysis how those additional time points will be presented in the interim analysis. Two summary tables for TEAE will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 16 by following treatment groups: bimekizumab 160mg and bimekizumab 320mg. The summary table for the other variables will present only data up to Week 12 for the Baseline treatment groups Placebo, bimekizumab 16mg, and bimekizumab 64mg. Data up to Week 16 will be presented for bimekizumab 160mg and bimekizumab 320mg. All Listings which include data up to Week 16 will use the same approach.

If an AE occurs on the same day as the treatment switch (Visit 7, Week 12) then the AE will be allocated to the Double-Blind treatment. An exception from this general rule is made for adverse drug reactions (ADRs), and AE of hypersensitivity reactions and anaphylactic reactions. If those AEs occur on the same days as the treatment switch, the AEs will be allocated to the Dose-Blind treatment and will not be presented for the interim analysis.

Exposure of study medication will not be summarized but a listing will be provided including following information: date of first dose, date of last dose, and duration of exposure. The last dose for the Double-Blind Period is planned on Visit 6 (Week 8). For subject who completed the Double-Blind Period the Week 8 date is the date of the last dose. If a subject discontinued within the Double-Blind Period, the discontinuation date will be presented for the date of last dose.

For the interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The investigators and subjects will remain blind to the assigned bimekizumab dosing regimen until the subject completes the Dose-Blind Period at Week 48.

Safety data will be provided to an independent Data Monitoring Committee (DMC). The DMC will review those safety data periodically. The composition and operation of the DMC will be defined in the DMC charter. The presentation and analysis of data for the DMC meetings is described within a separate DMC SAP.

Change # 7

Section 4.5 Multiple comparisons/multiplicity

In order to control for the overall Type I error rate, the pairwise comparisons of bimekizumab will be formally evaluated for statistical significance only if the primary efficacy analysis is statistically significant at the two-sided 5% level. In addition, the pairwise comparisons will follow a sequential testing sequence and the formal evaluation of statistical significance of each comparison is dependent upon the previous comparison achieving statistical significance at the two-sided 5% level. More details can be found in Section 8.1.3.

Has been changed to

In order to control for the overall Type I error rate, the pairwise comparisons of bimekizumab will be formally evaluated for statistical significance only if the primary efficacy analysis is statistically significant at the two-sided 5% level. In addition, the pairwise comparisons will follow a sequential testing sequence and the formal evaluation of statistical significance of each comparison is dependent upon the previous comparison achieving statistical significance at the two-sided 5% level. **If the sequential testing fails to reach significance at a significance level of α=0.05, then the pairwise testing will continue and the comparison are seen as non-significant. The p-values will be displayed as nominal p-values.** More details can be found in Section 8.1.3.

Change # 8

Section 8.1.1 Derivations of ASAS score and response

The ASAS20 response is defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 numeric rating scale (NRS) in at least 3 of the 4 following domains (Anderson, 2001):

- PGADA
- Pain assessment (total spinal pain, question 1 from total and nocturnal spinal pain questionnaire)
- Function (represented by the BASFI)
- Inflammation (the mean of the BASDAI questions 5 and 6) concerning [redacted]

and absence of deterioration in the potential remaining domain. Deterioration is defined as a relative worsening of at least 20% and an absolute worsening of at least 1 unit.

The ASAS criteria for 40% improvement are defined as relative improvement of at least 40% and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, which includes, in addition to the 4 domains above, spinal mobility (ie, lateral spinal flexion) and high sensitivity C-reactive protein (hs-CRP) as more objective measures (Brandt et al, 2004). If the hs-CRP value is below the lower limit of quantification (LLOQ), then it will be imputed as the midpoint between 0 and the LLOQ.

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Has been changed to

The ASAS20 response is defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 numeric rating scale (NRS) in at least 3 of the 4 following domains (Anderson, 2001):

- PGADA
- Pain assessment (total spinal pain, question 1 from total and nocturnal spinal pain questionnaire)
- Function (represented by the BASFI)

- Inflammation (the mean of the BASDAI questions 5 and 6) concerning [redacted]

and absence of deterioration in the potential remaining domain. Deterioration is defined as a relative worsening of at least 20% and an absolute worsening of at least 1 unit.

The ASAS criteria for 40% improvement are defined as relative improvement of at least 40% and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains and no worsening at all in the remaining domain.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, which includes, in addition to the 4 domains above, spinal mobility (ie, lateral spinal flexion) and high sensitivity C-reactive protein (hs-CRP) as more objective measures (Brandt et al, 2004). ~~If the hs-CRP value is below the lower limit of quantification (LLOQ), then it will be imputed as the midpoint between 0 and the LLOQ.~~ **If the hs-CRP value is below 2 mg/L, then it will be imputed as the constant value of 2 mg/L.**

…

Change # 9

Section 8.1.3 Secondary analysis of the primary efficacy variable

As the secondary analysis for the primary efficacy variable, a logistic regression model will be used to assess the effect of each individual dose versus placebo on ASAS40 response. The model will include fixed effects for treatment, geographic region, and prior TNF inhibitor exposure. If the logistic regression model is unable to converge, then region may be dropped from the model to facilitate convergence. Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% confidence interval, and the corresponding p-value will be calculated.

The pairwise comparisons of bimekizumab versus placebo will be formally evaluated for statistical significance only if the primary dose response efficacy analysis is statistically significant. Once the dose response has been established, pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose. Each test will only be conducted if the previous test reaches significance at a 2-sided significance level of α=0.05. This procedure will control the overall Type I error rate. If the dose response relationship fails to reach significance at a significance level of α=0.05, then no further testing will be conducted and the pairwise comparisons are seen as non-significant.

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Has been changed to

As the secondary analysis for the primary efficacy variable, a logistic regression model will be used to assess the effect of each individual dose versus placebo on ASAS40 response. The model will include fixed effects for treatment, geographic region, and prior TNF inhibitor exposure. **To avoid the problem of the so-called monotone likelihood resulting in infinite large confidence intervals (eg, if one of the cell counts in the 2x2 table is equal to zero), a penalized maximum likelihood approach based on the modified score procedure of Firth (eg, Heinze and Schemper, 2002) will be used in the logistic models.** If the logistic regression model is

unable to converge, then geographic region may be dropped from the model to facilitate convergence. **If the logistic regression model is unable to converge after dropping the geographic region, then prior TNF inhibitor exposure may be dropped as well.** Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% confidence interval, and the corresponding p-value will be calculated.

The pairwise comparisons of bimekizumab versus placebo will be formally evaluated for statistical significance only if the primary dose response efficacy analysis is statistically significant. Once the dose response has been established, pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose. ~~Each test will only be conducted if the previous test reaches significance at a 2-sided significance level of α=0.05. This procedure will control the overall Type I error rate. If the dose response relationship fails to reach significance at a significance level of α=0.05, then no further testing will be conducted and the pairwise comparisons are seen as non-significant.~~ **If the dose-response relationship fails to reach significance at a significance level of α=0.05, then the further pairwise comparisons are seen as non-significant.**

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Change # 10

8.2 Statistical analysis of the secondary efficacy variables

The secondary efficacy variables will be analyzed for all subjects in the FAS.

All categorical variables (ie, ASAS20 response and ASAS5/6) will be analyzed for treatment effects using pairwise comparisons based on the same method as that for the primary efficacy variable.

All continuous variables (ie, ASDAS-CRP, BASDAI, and BASFI) will be analyzed for treatment effects using pairwise comparisons based on an ANCOVA model with treatment, geographic region, and prior TNF inhibitor exposure as fixed effects and the Baseline value as covariate.

Pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose as described in Section 8.1.3.

For the categorical variables the responder rates for placebo, BKZ 16mg, BKZ 64mg, BKZ 160mg, BKZ 320mg, and for each dose the odds ratios (differences to placebo), 95% confidence intervals, and corresponding p-values from the logistic regression will be provided.

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Has been changed to

The secondary efficacy variables will be analyzed for all subjects in the FAS.

All categorical variables (ie, ASAS20 response and ASAS5/6) will be analyzed for treatment effects using pairwise comparisons based on the same method as that for the primary efficacy variable.

All continuous variables (ie, ASDAS-CRP, BASDAI, and BASFI) will be analyzed for treatment effects using pairwise comparisons based on an ANCOVA model with treatment, geographic region, and prior TNF inhibitor exposure as fixed effects and the Baseline value as covariate.

~~Pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose as described in Section 8.1.3.~~

For the categorical variables the responder rates for placebo, BKZ 16mg, BKZ 64mg, BKZ 160mg, BKZ 320mg, and for each dose the odds ratios (differences to placebo), 95% confidence intervals, and corresponding p-values from the logistic regression will be provided.

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Change # 11

Section 8.2.1 Derivations of ASDAS-CRP, ASDAS-MI, and ASDAS Status

The ASDAS consists of a number of assessments which are scored by the subject and physician and multiplied by a proven formula (van der Heijde et al, 2009) as shown below:

- 0.121 x [redacted] (BASDAI question 2 result)
- 0.058 x [redacted] (BASDAI question 6 result)
- 0.110 x PGADA
- 0.073 x [redacted] (BASDAI question 3 result)
- 0.579 x (natural logarithm of the (hs-CRP [mg/L] + 1))

[redacted], PGADA, [redacted] are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009).

The sum of these weighted components gives the ASDAS-CRP.

If one component for the ASDAS-CRP is missing at a given visit, that component will be imputed by carrying the last observation forward, and the ASDAS-CRP will be calculated accordingly. If no value is available for that component before the missing time point, the next observation may be carried backwards. If more than one component for the ASDAS-CRP is missing, ASDAS-CRP will be treated as missing.

If the hs-CRP value is below the LLOQ, then it will be imputed as the midpoint between 0 and the LLOQ.

…

Has been changed to

The ASDAS consists of a number of assessments which are scored by the subject and physician and multiplied by a proven formula (van der Heijde et al, 2009) as shown below:

- 0.121 x [redacted] (BASDAI question 2 result)
- 0.058 x [redacted] (BASDAI question 6 result)
- 0.110 x PGADA

- 0.073 x [redacted] (BASDAI question 3 result)
- 0.579 x (natural logarithm of the (hs-CRP [mg/L] + 1))

[redacted], PGADA, [redacted] are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009).

The sum of these weighted components gives the ASDAS-CRP.

If one component for the ASDAS-CRP is missing at a given visit, that component will be imputed by carrying the last observation forward, and the ASDAS-CRP will be calculated accordingly. If no value is available for that component before the missing time point, the next observation may be carried backwards. If more than one component for the ASDAS-CRP is missing, ASDAS-CRP will be treated as missing.

~~If the hs-CRP value is below the LLOQ, then it will be imputed as the midpoint between 0 and the LLOQ.~~ **If the hs-CRP value is below 2 mg/L, then it will be imputed as the constant value of 2 mg/L (Machado et al, 2015).**

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Change # 12

8.3 Statistical analysis of other efficacy variables

All other efficacy variables in the Double-Blind Period will be analyzed for all subjects in the FAS. For the Dose-Blind Period, other efficacy variables will be analyzed for all subjects in the DBRS, and ESS.

All categorical variables will be presented using frequency tables by each visit. All continuous variables will be summarized using descriptive statistics by each visit.

The Hospital Anxiety and Depression Scale (HADS) will be analyzed separately for HADS-A and HADS-D. The summary statistics for HADS-A and HADS-D will be presented in two different tables.

Figures for the response rate or change from Baseline will be provided for the primary and secondary efficacy variables.

The MRI of the spine and sacroiliac joints will be performed in a substudy with subjects who were classified as MRI-positive at Baseline as per ASAS-Outcome Measures in Rheumatology Clinical Trials (OMERACT) criteria.

Time to onset of ASAS20 response and ASAS40 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in days from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

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Has been changed to

All other efficacy variables in the Double-Blind Period will be analyzed for all subjects in the FAS. For the Dose-Blind Period, other efficacy variables will be analyzed for all subjects in the DBRS, and ESS.

All categorical variables will be presented using frequency tables by each visit. All continuous variables will be summarized using descriptive statistics by each visit.

The Hospital Anxiety and Depression Scale (HADS) will be analyzed separately for HADS-A and HADS-D. The summary statistics for HADS-A and HADS-D will be presented in two different tables.

~~Figures for the response rate or change from Baseline will be provided for the primary and secondary efficacy variables.~~ **Times series plots will be provided for the response rate or change from Baseline for the primary and secondary efficacy variables. The plots will show the weekly response rate over the first 12 weeks.**

The MRI of the spine and sacroiliac joints will be performed in a substudy with subjects who were classified as MRI-positive at Baseline as per ASAS-Outcome Measures in Rheumatology Clinical Trials (OMERACT) criteria.

Time to onset of ASAS20 response and ASAS40 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in ~~days~~ **weeks** from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

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Change # 13

Section 8.3 Analysis of the other efficacy variables

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All other efficacy variables will be analyzed using observed cases as treated and imputed with NRI for binary variables and MI for continuous variables.

Subjects in the ESS who discontinue with bimekizumab treatment during the Dose-Blind Period will be treated as missing and categorical/continuous variables will be imputed.

Has been changed to

…

All other efficacy variables will be analyzed using observed cases as treated and imputed with NRI for binary variables and MI for continuous variables.

Subjects in the ESS who discontinue with bimekizumab treatment during the Dose-Blind Period will be treated as missing and categorical/continuous variables will be imputed.

In order to assess the potential bias of the potentially unblinded subjects based on data, the results of the final analysis will be utilized. Results of the ASAS40 response of the rerandomized 320mg and 160mg treatment group at Week 48 will be compared to the

potentially unblinded, randomized 320mg and 160mg treatment groups. If the percentage of ASAS40 responders is comparable as assessed by overlapping 95% confidence intervals, the potential bias is estimated to be at minimum.

Change # 14

Section 8.3.9 C-reactive protein (CRP) and high-sensitivity C-reactive protein (CRP)

…

The values of hs-CRP values will be rounded to integers prior to calculating ratio to Baseline and values below the limit of quantification should be set to should be set to half the limit of quantification for the calculations.

CRP values will not be summarized and only presented in listings.

Has been changed to

…

The values of hs-CRP **and CRP** ~~values~~ will be rounded to integers prior to calculating ratio to Baseline and values below the limit of quantification should be set to should be set to half the limit of quantification for the calculations.

~~CRP values will not be summarized and only presented in listings.~~

Change # 15

Section 9.1 Pharmacokinetics

….

In addition geometric mean bimekizumab plasma concentration time curves will be plotted by treatment group, and by cumulative antibody status (ie, positive, negative) for subjects randomized to bimekizumab.

The bimekizumab concentrations will also be listed.

Has been changed to

…

In addition geometric mean bimekizumab plasma concentration time curves will be plotted by treatment group, and by cumulative antibody status (ie, positive, negative) for subjects randomized to bimekizumab **as well as individual time curves of DAS28(CRP), bimekizumab concentration, and AbAb.**

The bimekizumab concentrations will also be listed.

Change # 16

Section 9.2 Pharmacodynamics and Immunogenicity

The biomarker data will be separated between LGC assays, mulitplex proinflammatory cytokine and chemokine analysis, flow cytometry - TBNK panel, and flow cytometry - Th1/Th2/Th17/Th22 panel. Biomarker variables will be summarized and listed for each treatment at each scheduled visit using the PD-PPS analysis set.

In addition to the PD variables, whole blood will be stored to isolate deoxyribonucleic acid which may be used to examine genetic and epigenetic changes. The blood samples for genetic and epigenetic, and genomic, proteomic/metabolomics will not be analyzed in the interim or final analysis. Variables will be analyzed in a separate analysis as ad-hoc analysis.

The AbAb status will be determined for each visit where samples are taken for drug concentration measures. At each visit:

- Values ≤ predefined cut point are defined as AbAb-
- Values > predefined cut point are defined as AbAb+

In addition, overall AbAb status should be determined:

- Subject AbAb positivity is defined as having a value > predefined cut point at any time in the treatment period. This does not include Baseline/pre-treatment
- Subject AbAb positivity at Baseline is defined as having a value > predefined cut point at Baseline
- Treatment-emergent AbAb positivity is defined when a subject is having a value > predefined cut point for the first time during treatment period excluding Baseline/pre-treatment.
- AbAb- is defined as having no values > predefined cut point during the treatment period.

The cut point for determining whether the AbAb level is sufficiently high to be considered AbAb positive is not yet known. However, this will be determined prior to the database lock of the PK and AbAb data.

…

All individual subject-level AbAb results will be listed.

Immunogenicity data will be summarized and listed using the PK-PPS analysis set.

Has been changed to:

The biomarker data will be separated between LGC assays, mulitplex proinflammatory cytokine and chemokine analysis, flow cytometry - TBNK panel, and flow cytometry - Th1/Th2/Th17/Th22 panel. Biomarker variables will be summarized and listed for each treatment at each scheduled visit using the PD-PPS analysis set.

In addition to the PD variables, whole blood will be stored to isolate deoxyribonucleic acid which may be used to examine genetic and epigenetic changes. The blood samples for genetic and epigenetic, and genomic, proteomic/metabolomics will not be analyzed in the interim or final analysis. Variables will be analyzed in a separate analysis as ad-hoc analysis.

The AbAb status will be determined for each visit where samples are taken for drug concentration measures. **A cut point will be determined by the bioanalytical laboratory and will be used to determine the AbAb status as "above the cut point" (ACP) or "below the cut point" (BCP). For any AbAb levels that are ACP, a further confirmatory assay will be performed, the results of which will be determined as either "confirmed positive" (CP) or "not confirmed positive" (NCP). For samples that are CP, a further titre assay will be performed and the AbAb titre will be reported.**

At each visit:

- **Samples that are either BCP or ACP and NCP are defined as AbAb-**
- **Samples that are ACP and CP are defined as AbAb+**

In addition, overall AbAb status should be determined:

- Subject AbAb positivity is defined as having **with AbAb+ at any time in the treatment period. This does not include Baseline/pre-treatment**
- **Subject AbAb negativity is defined with AbAb- at any time in the treatment period. This does also include AbAb+ at Baseline/pre-treatment**
- Treatment-emergent AbAb positivity is defined when a subject is **AbAb+** for the first time during treatment period excluding Baseline/pre-treatment. **If there is AbAb+ at Baseline/pretreatment and there is a pre-defined fold increase in titre at least at one visit during the treatment period, then the subject has also a treatment-emergent AbAb positivity status.**

Note: The fold increase from Baseline required will be defined with the development of the assay prior to database lock.

…

All individual subject-level AbAb results will be listed **including the screening assay, confirmatory assay, and titres if applicable. Note, that titre results will only be available, if the confirmatory assay is positive.**

Immunogenicity data will be summarized and listed using the PK-PPS analysis set.

Change # 17

Section 10.1 Extent of exposure

The duration of exposure (in days) will be calculated as:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (12)$$

28 days refer to one half-life of bimekizumab. If a change of treatment occurs prior to completion of the dosing interval, duration of exposure to study medication will be calculated as:

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ injection \quad (13)$$

For subjects who have died the exposure will be as follows:

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ injection + 1 \quad (14)$$

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose and the duration of exposure will be performed.

Time at risk is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (15)$$

where 140 days refers to 5*half-life of bimekizumab.

Has been changed to

The duration of exposure (in days) will be calculated as:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (12)$$

28 days refer to one half-life of bimekizumab. If a change of treatment occurs prior to completion of the dosing interval, duration of exposure to study medication will be calculated as:

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ injection \quad (13)$$

For subjects who have died the exposure will be as follows:

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ injection + 1 \quad (14)$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose and the duration of exposure will be performed.

Time at risk **(in days)** is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (15)$$

where 140 days refers to 5*half-life of bimekizumab.

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

Change # 18

Section 10.2 Adverse events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs (including serious AEs) are characterized as either pretreatment or treatment emergent according to the following criteria:

- Pretreatment AEs are the events with onset date and time prior to the very first administration of study medication (bimekizumab or placebo).
- Treatment-emergent AEs (TEAE) are those with onset date at or after the very first administration of study medication. The events that emerge within 140 days after the final drug administration, will also be considered as treatment emergent (eg, in the case of premature discontinuation or during the SFU period).

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

If the intensity of an AE is unknown, it is considered as severe.

If the relationship to study drug is missing, it is considered as related.

All AEs occurring during the study (i.e., after signature of the informed consent document) will be recorded in the eCRF. For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was classified as a SAE, as an AE of special interest, intensity, relationship to study medication, action taken with study medication, other action taken, outcome, date of outcome, and whether the AE led to study drug discontinuation or to study discontinuation.

The following code lists will be used for AE recording:

- Pattern of event: intermittent or continuous
- Intensity of event: mild, moderate or severe
- Relationship: related or not related
- Action taken with IMP: dose not changed, dose reduced, dose increased, drug temporarily, interrupted, drug permanently withdrawn or not applicable
- Outcome: resolving, not resolved, resolved, resolved with sequelae, worsened, fatal or unknown

For all TEAEs the following variables will be calculated:

- Duration
- Time since first dose
- Time to last/latest dose

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ if\ outcome - Date\ of\ onset \quad (16)$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - date\ of\ first\ dose \quad (17)$$

Time to first dose will not be calculated for pretreatment AEs.

The time to last dose for each AE will be calculated as follows for all TEAEs:

$$Time\ to\ last\ dose\ (days) = Date\ of\ last\ dose - date\ of\ AE\ onset \quad (18)$$

The incidence of TEAEs will be summarized by MedDRA system organ class, high level term, and PT. Tables with incidences of classified TEAEs by maximum intensity, by relationship, and by subject number will be provided. The incidence of non-serious TEAEs above the reporting threshold of 5% of subjects and relationship will be summarized. Furthermore the incidence of all TEAEs, serious TEAEs, non-serious TEAEs, and TEAEs leading to study discontinuation and/or permanent withdrawal of study medication will be summarized. In addition an overall summary table will be provided.

AE of Special Interest and AE of Special Monitoring

AE of special interest is any AE which meets the Hy's Law criteria, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

AEs of special monitoring for this study include: serious infections (including opportunistic infections and TB), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the electronic Columbia-Suicide Severity Rating Scale [eC-SSRS]), depression and anxiety (assessed using the HADS), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin), malignancies, and inflammatory bowel diseases.

The incidence of TEAEs of special interest will be summarized by MedDRA system organ class, high level term, and PT. In addition, for some TEAEs and special monitoring separate incidence summary tables including exposure adjusted incidence rate (EAIR) with associated 95% CI, and the exposure adjusted event rate (EAER) will be provided:

- Fungal infectious disorder
- Opportunistic infection (including TB)
- Malignant or unspecified tumor
- Malignant tumor
- Major cardiovascular event
- Haematopoietic cytopenias
- Neuropsychiatric events
- Inflammatory bowel disease
- Hypersensitivity and anaphylactic reaction
- Hepatic events

Fungal Infectious disorder

Fungal infections will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs which code into the High Level Group Term (HLGT) of "Fungal infectious disorders".

…

Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (19)$$

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

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (20)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (21)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (22)$$

where N_{AE} is the total number of AEs.

No confidence interval will be computed for EAER.

Has been changed to

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs (including serious AEs) are characterized as either **non-**treatment or treatment emergent according to the following criteria:

- **Non-**treatment **emergent** are the events with onset date and time prior to the very first administration of study medication (bimekizumab or placebo) **or after a 140-day period after the final drug administration**.
- Treatment-emergent AEs (TEAE) are those with onset date at or after the very first administration of study medication. The events that emerge within 140 days after the final drug administration, will also be considered as treatment emergent (eg, in the case of premature discontinuation or during the SFU period).

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

~~If the intensity of an AE is unknown, it is considered as severe.~~

~~If the relationship to study drug is missing, it is considered as related.~~

All AEs occurring during the study (i.e., after signature of the informed consent document) will be recorded in the eCRF. For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was classified as a SAE, as an AE of special interest, intensity, relationship to study medication, action taken with study medication, other action taken, outcome, date of outcome, and whether the AE led to study drug discontinuation or to study discontinuation.

The following code lists will be used for AE recording:

- Pattern of event: intermittent or continuous
- Intensity of event: mild, moderate or severe
- Relationship: related or not related
- Action taken with IMP: dose not changed, dose reduced, dose increased, drug temporarily, interrupted, drug permanently withdrawn or not applicable
- Outcome: resolving, not resolved, resolved, resolved with sequelae, worsened, fatal or unknown

For all TEAEs the following variables will be calculated:

- Duration
- Time since first dose
- ~~Time to last/latest dose~~

~~The duration of each AE will be calculated as follows:~~

$$\textit{Duration (days)} = \textit{Date if outcome} - \textit{Date of onset} \quad (16)$$

~~For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2.~~

~~The time to first dose for each AE will be calculated as follows for all TEAEs:~~

$$\textit{Time since first dose (days)} = \textit{Date of AE onset} - \textit{date of first dose} \quad (17)$$

~~Time to first dose will not be calculated for pretreatment AEs.~~

~~The time to last dose for each AE will be calculated as follows for all TEAEs:~~

$$~~Time\ to\ last\ dose\ (days) = Date\ of\ last\ dose - date\ of\ AE\ onset~~ \quad (18)$$

Adverse drug reactions (ADRs) are defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. Any AE that is considered "Related" to study treatment will be classed as an ADR.

The incidence of TEAEs will be summarized by MedDRA system organ class, high level term, and PT. Tables with incidences of classified TEAEs by maximum intensity, by relationship, and by subject number will be provided. The incidence of non-serious TEAEs above the reporting threshold of 5% of subjects and relationship will be summarized. Furthermore the incidence of all TEAEs, serious TEAEs, non-serious TEAEs, and TEAEs leading to study discontinuation and/or permanent withdrawal of study medication will be summarized. In addition an overall summary table will be provided.

Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER) will be calculated for following tables in the final analysis: all TEAEs, serious TEAEs, TEAEs leading to study discontinuation and/or permanent withdrawal, ADRs, fungal infectious disorder TEAEs, opportunistic infection (including tuberculosis) TEAEs, malignant or unspecified tumor TEAEs, malignant tumor TEAEs, major cardiovascular event TEAEs, haematopoietic cytopenias TEAEs, neuropsychiatric events TEAEs, inflammatory bowel disease TEAEs, hypersensitivity and anaphylactic Reaction TEAEs, hepatic events TEAEs, and TEAEs by timing of onset relative to AbAb Status.

10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$\boldsymbol{Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1} \quad \textbf{(16)}$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2**.**

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$\boldsymbol{Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1} \quad \textbf{(17)}$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$\boldsymbol{Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1} \quad \textbf{(18)}$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (17 and 18) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$\begin{aligned}&\textit{Days on treatment}\\&\quad=\textit{Date of last/latest dose}\\&\quad-\textit{Date of first placebo or bimekizumab dose}+1\end{aligned} \tag{19}$$

$$\begin{aligned}&\textit{Days on bimekizumab treatment}\\&\quad=\textit{Date of last/latest dose}\\&\quad-\textit{Date of first bimekizumab dose}+1\end{aligned} \tag{20}$$

10.2.2 10.2.2 Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \tag{21}$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest.

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

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \tag{23}$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \tag{23}$$

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

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

$$\underline{\boldsymbol{EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}}}} \qquad \underline{\textbf{(24)}}$$

where N_{AE} is the total number of AEs and $T_{Risk,i}$ is a subject's total time at risk in years.

No CI will be computed for EAER.

AE of Special Interest and AE of Special Monitoring

AE of special interest is any AE which meets the Hy's Law criteria, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

AEs of special monitoring for this study include: serious infections (including opportunistic infections and TB), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the electronic Columbia-Suicide Severity Rating Scale [eC-SSRS]), depression and anxiety (assessed using the HADS), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin), malignancies, and inflammatory bowel diseases.

The incidence of TEAEs of special monitoring will be summarized by MedDRA system organ class, high level term, and PT. EAIR with associated 95% CI, and the EAER will be included in the summary tables for following TEAEs of special monitoring:

~~The incidence of TEAEs of special interest will be summarized by MedDRA system organ class, high level term, and PT. In addition, for some TEAEs and special monitoring separate incidence summary tables including exposure adjusted incidence rate (EAIR) with associated 95% CI, and the exposure adjusted event rate (EAER) will be provided:~~

- Fungal infectious disorder
- Opportunistic infection (including TB)
- Malignant or unspecified tumor
- Malignant tumor
- Major cardiovascular event
- Haematopoietic cytopenias
- Neuropsychiatric events
- Inflammatory bowel disease
- Hypersensitivity and anaphylactic reaction
- Hepatic events

Fungal Infectious disorder

Fungal infections will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs which code into the High Level Group Term (HLGT) of "Fungal infectious disorders".

…

Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (19)$$

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

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (20)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (21)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (22)$$

where N_{AE} is the total number of AEs.

No confidence interval will be computed for EAER.

Change # 19

Section 11 References

…

Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:18-24.

Maksymowych WP, Mallon C, Richardson R, et al. Development and Validation of the Edmonton Ankylosing Spondylitis Metrology Index. Arthritis Rheum. 2006;55:575-82.

…

Has been changed to

…

Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:18-24.

Machado P, Navarro-Compan V, Landewe R, van Gaalen VA, Roux C, van der Heijde D. Calculating the Ankylosing Spondylitis Disease Activity Score If the Conventional C-Reactive Protein Level Is Below the Limit of Detection or If High-Sensitivity C-Reactive Protein Is Used: An Analysis in the DESIR Cohort. Arthritis Rheum. 2015 Feb;67(2):408-13.

Maksymowych WP, Mallon C, Richardson R, et al. Development and Validation of the Edmonton Ankylosing Spondylitis Metrology Index. Arthritis Rheum. 2006;55:575-82.

…

Change # 20

Section 12.2 12.2 Treatment group assignment for tables and figures

Table 12–2 displays the treatment group labels for each data type. This overview clarifies what kind of treatment groups will be used for producing the tables and figures separated between the different table types.

Table 12–2: Treatment group assignment for tables and figures

	Placebo	BKZ 16mg/ BKZ64mg/ BKZ 64mg/ BKZ 320mg	All BKZ	All subjects
Subject disposition	X	X		X
Important protocol deviation	X	X		X
Demographics/Lifestyle	X	X		X
Ankylosing spondylitis history	X	X		X
Baseline characteristics	X	X		X
TB testing	X	X		X
Previous and ongoing medical history	X	X		X
Prior and concomitant medication	X	X		X
Rescue and prohibited medication	X	X		X
Bimekizumab compliance	X	X	X	
Extent of exposure	X	X	X	
Efficacy analysis	X	X		
Plasma/Bimekizumab concentration	X	X		

Table 12–2: Treatment group assignment for tables and figures

	Placebo	BKZ 16mg/ BKZ64mg/ BKZ 64mg/ BKZ 320mg	All BKZ	All subjects
Pharmacokinetic variables/Biomarker data/AbAb	X	X		
AEs	X	X	X	
Safety laboratory tests	X	X		
Vital signs/Body weight/ECG/ Physical examination	X	X		
eC-SSRS	X	X		

AbAb=Anti-bimekizumab antibody; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale.

Has been changed to

Table 12–2 displays the treatment group labels for each data type. This overview clarifies what kind of treatment groups will be used for producing the tables and figures separated between the different table types.

Table 12–2: Treatment group assignment for tables and figures

	Placebo	BKZ 16mg/ BKZ64mg/ BKZ 160mg/ BKZ 320mg	All BKZ	All subjects
Subject disposition	X	X		X
Important protocol deviation	X	X		X
Demographics/Lifestyle	X	X		X
Ankylosing spondylitis history	X	X		X
Baseline characteristics	X	X		X
TB testing	X	X		X
Previous and ongoing medical history	X	X		X
Prior and concomitant medication	X	X		X
Rescue and prohibited medication	X	X		X
Bimekizumab compliance	X	X	X	
Extent of exposure	X	X	X	
Efficacy analysis	X	X		
Plasma/Bimekizumab concentration	X	X		

Table 12–2: Treatment group assignment for tables and figures

	Placebo	BKZ 16mg/ BKZ64mg/ BKZ 160mg/ BKZ 320mg	All BKZ	All subjects
Pharmacokinetic variables/Biomarker data/AbAb	X	X		
AEs	X	X	X	
Safety laboratory tests	X	X	X	
Vital signs/Body weight/ECG/ Physical examination	X	X	X	
eC-SSRS	X	X	X	

AbAb=Anti-bimekizumab antibody; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale.

13.2 Amendment 2

13.2.1 Rationale for the amendment

The SAP has been amended to:

- Group the geographic region in North America, Western and Eastern Europe
- Remove subgroup synthetic disease-modifying antirheumatic drugs (DMARDs) and add subgroup current NSAIDs at Baseline
- Correct inflammatory bowel disease coding
- Add rule for handling missing data for prior and concomitant medication
- Modify Section 10

13.2.2 Modifications and changes

Section 3.8 Center pooling strategy

Centers will be pooled into geographic regions for analysis purposes. Centers will be grouped in the geographic regions North America and Europe.

Has been changed to

Centers will be pooled into geographic regions for analysis purposes. Centers will be grouped in the geographic regions North America**, Western and Eastern** Europe.

Section 4.2.1 Handling of missing data for efficacy analysis

The analysis for the binary primary, secondary, and other efficacy variables will use non-responder imputation (NRI) for handling missing data. In NRI, each subject with missing data or who has discontinued double-blind study treatment prior to Week 12 will be counted as a non-responder.

Sensitivity analysis will be performed for the secondary analysis of the primary variable (ASAS40 response at Week 12) using MI assuming that missingness is missing at random (MAR). The MI method will be applied as follows:

1. Create a data set, sorted by treatment groups, of subjects with observed values and those needing estimation by multiple imputation. For the imputation step, missing values will be separated into non-monotone missing values (ie, intermittent missing values between completed assessments) and monotone missing values (ie, missing values after the patient dropped out). The procedure will sequentially estimate an imputation model for the ASAS components at each post-Baseline visit where ASAS components are collected, with geographic region, and prior TNF inhibitor exposure as covariates separated between the treatment groups.
   - For the imputation of intermediate missing values, the missing ASAS components in each data set will be filled in using the Markov-Chain Monte Carlo (MCMC) method with multiple chains and monotone imputing. A total number of imputations will be 100. The seed used for these imputations will be 2017.

     Note: All other multiple imputation procedures described in this SAP will use this same seed as well.

Note: The imputation model based on the MCMC method will only allow continuous variables as predictors. Therefore, prior TNF inhibitor exposure and geographic region will be re-coded as indicator variables (with values of 0 or 1 for each level of the variable).

Note: To avoid that imputed values are outside of the pre-defined range of values for the ASAS components (eg, PGADA [0-10]) maximum and minimum values for imputed variable values are specified.

– If the intermediate missing data are imputed, the monotone missing data will be imputed for all patients with monotone regression including geographic region, and prior TNF inhibitor exposure as covariates. The dataset is the output dataset of the partial imputation. Since this dataset already has 100 imputed values at each visit, only one imputation will be performed.

  Note: Maximum and minimum values are specified for imputed variable values to avoid values outside of the pre-defined range of values.

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Has been changed to

The analysis for the binary primary, secondary, and other efficacy variables will use non-responder imputation (NRI) for handling missing data. In NRI, each subject with missing data or who has discontinued double-blind study treatment prior to Week 12 will be counted as a non-responder.

Sensitivity analysis will be performed for the secondary analysis of the primary variable (ASAS40 response at Week 12) using MI assuming that missingness is missing at random (MAR). The MI method will be applied as follows:

1. Create a data set, sorted by treatment groups, of subjects with observed values and those needing estimation by multiple imputation. For the imputation step, missing values will be separated into non-monotone missing values (ie, intermittent missing values between completed assessments) and monotone missing values (ie, missing values after the patient dropped out). The procedure will sequentially estimate an imputation model for the ASAS components at each post-Baseline visit where ASAS components are collected, with geographic region, and prior TNF inhibitor exposure as covariates separated between the treatment groups.

   – For the imputation of intermediate missing values, the missing ASAS components in each data set will be filled in using the Markov-Chain Monte Carlo (MCMC) method with multiple chains and monotone imputing. A total number of imputations will be 100. The seed used for these imputations will be 2017.

     Note: All other multiple imputation procedures described in this SAP will use this same seed as well.

     Note: The imputation model based on the MCMC method will only allow continuous variables as predictors. Therefore, prior TNF inhibitor exposure and geographic region will be re-coded as ~~indicator~~ **numeric** variables **(with values of 0 or for the levels of TNF [1=prior inhibitor exposure, 0=non prior inhibitor exposure] and two binary**

variables for geographic region [Variable 1: 1=North America, 0=others, Variable 2: 1=Eastern Europe, 0=others] as representation of geographic region).

Note: To avoid that imputed values are outside of the pre-defined range of values for the ASAS components (eg, PGADA [0-10]) maximum and minimum values for imputed variable values are specified**. Moreover, the rounding options for imputed values are used where appropriate.**

– **Once** the intermediate missing data are imputed, the monotone missing data will be imputed for all patients with monotone regression including geographic region, and prior TNF inhibitor exposure as covariates. The dataset is the output dataset of the partial imputation. Since this dataset already has 100 imputed values at each visit, only one imputation will be performed.

Note: Maximum and minimum values **(and rounding where appropriate)** are specified for imputed variable values to avoid values outside of the pre-defined range of values.

…

Section 4.2.3 Handling of missing data for prior and concomitant medication

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the electronic case report form (eCRF).

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 and the subject did not switch treatment during that month and year, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the month and year are specified and the subject did switch treatment during that month and year, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is not the same as the year of the start date and the subject did not switch treatment during that year, 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 only the year is specified, and the year of first dose is the same as the year the subject did switch treatment, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is the same as the year of the start date and the same as the year the subject did switch treatment, 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.

…

Has been changed to

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days. Such imputations will only be performed for these classifications and calculations; in the listings all data will be shown as recorded on the electronic case report form (eCRF).

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 and the subject did not switch treatment during that month and year, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the month and year are specified and the subject did switch treatment during that month and year, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is not the same as the year of the start date and the subject did not switch treatment during that year, 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 only the year is specified, and the year of first dose is the same as the year the subject did switch treatment, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is the same as the year of the start date and the same as the year the subject did switch treatment, 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.
- **<u>If the start date is completely unknown and the stop date is prior to the date of first dose, then set the start date to the 1st of January of the year of the end date.</u>**

…

Section 4.3 Interim analyses and data monitoring

After all enrolled subjects have completed the 12 weeks Double-Blind Period, an interim analysis will be performed (i) to analyze the dose:exposure response for the ASAS40 response criteria to determine the optimal therapeutic dose(s) for subsequent studies, and (ii) to perform a comprehensive evaluation of all double-blind data of the study.

No separate SAP for the interim analysis will be provided. The interim analysis is a limited version of the final analysis and will focus on the primary and secondary efficacy analysis and comprise the results of the 12 weeks Double-Blind Period. The TFL shells for the interim and final analysis will be provided in two different documents.

The interim analysis will summarize disposition, demographics, AS history, Baseline characteristics, AS concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic

Columbia-Suicide Severity Rating Scale (eC-SSRS). Corresponding listings will be provided. Not all collected hematology and biochemistry laboratory variables will be summarized and listed. For the interim analysis only selected variables will be provided as listed in Table 12–3.

The interim analysis will summarize disposition, demographics, AS history, Baseline characteristics, AS concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). Not all collected hematology and biochemistry laboratory variables will be summarized. For the interim analysis only selected hematology and biochemistry variables will be provided as listed in Table 12–3. Listings of AEs, hematology, biochemistry and C-SSRS data will be provided.

The interim efficacy analysis will include following primary and secondary variables: ASAS40,20,5/6 response at Week 12, and change from Baseline in BASDAI, ASDAS-CRP, BASFI at Week 12. The variables will be analyzed using the same methods described in Section 8.1.2 and Section 8.2 including supportive and sensitivity analyses (Section 8.1.3 and Section 8.1.4). In addition, summary tables for the primary and secondary efficacy variables, and the ASAS components will be provided. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive statistics by each visit. Time to onset of ASAS20 response and ASAS40 response will be summarized and plotted as described in Section 8.3.

PK and PD data will be analyzed in the interim analysis as described in Section 9.1 and Section 9.2. PKPD will be analyzed as part of the exposure:response modeling outside of the scope of the SAP. Biomarker data will not be analyzed in the interim analysis.

The interim analysis includes selected data up to Week 12 and in addition data up to Week 16. The data up to Week 16 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. All analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Following variables will be analyzed: ASAS40, ASAS20, ASDAS-CRP, BASDAI, PK, AbAb and TEAEs. It depends on the analysis how those additional time points will be presented in the interim analysis. Two summary tables for TEAE will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 16 by following treatment groups: bimekizumab 160mg and bimekizumab 320mg. The summary table for the other variables will present only data up to Week 12 for the Baseline treatment groups Placebo, bimekizumab 16mg, and bimekizumab 64mg. Data up to Week 16 will be presented for bimekizumab 160mg and bimekizumab 320mg. All Listings which include data up to Week 16 will use the same approach.

If an AE occurs on the same day as the treatment switch (Visit 7, Week 12) then the AE will be allocated to the Double-Blind treatment. An exception from this general rule is made for adverse drug reactions (ADRs), and AE of hypersensitivity reactions and anaphylactic reactions. If those AEs occur on the same days as the treatment switch, the AEs will be allocated to the Dose-Blind treatment and will not be presented for the interim analysis.

Exposure of study medication will not be summarized but a listing will be provided including following information: date of first dose, date of last dose, and duration of exposure. The last dose for the Double-Blind Period is planned on Visit 6 (Week 8). For subject who completed the

Double-Blind Period the Week 8 date is the date of the last dose. If a subject discontinued within the Double-Blind Period, the discontinuation date will be presented for the date of last dose.

For the interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The investigators and subjects will remain blind to the assigned bimekizumab dosing regimen until the subject completes the Dose-Blind Period at Week 48.

Safety data will be provided to an independent Data Monitoring Committee (DMC). The DMC will review those safety data periodically. The composition and operation of the DMC will be defined in the DMC charter. The presentation and analysis of data for the DMC meetings is described within a separate DMC SAP.

Has been changed to

After all enrolled subjects have completed the 12 weeks Double-Blind Period, an interim analysis will be performed (i) to analyze the dose:exposure response for the ASAS40 response criteria to determine the optimal therapeutic dose(s) for subsequent studies, and (ii) to perform a comprehensive evaluation of all double-blind data of the study.

No separate SAP for the interim analysis will be provided. The interim analysis is a limited version of the final analysis and will focus on the primary and secondary efficacy analysis and comprise the results of the 12 weeks Double-Blind Period. The TFL shells for the interim and final analysis will be provided in two different documents.

~~The interim analysis will summarize disposition, demographics, AS history, Baseline characteristics, AS concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). Corresponding listings will be provided. Not all collected hematology and biochemistry laboratory variables will be summarized and listed. For the interim analysis only selected variables will be provided as listed in Table Table 12–3.~~

The interim analysis will summarize disposition, demographics, AS history, Baseline characteristics, AS concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). Listings of AEs, hematology, biochemistry and C-SSRS data will be provided. Not all collected hematology and biochemistry laboratory variables will be ~~summarized~~ **displayed in the tables and listings**. For the interim analysis only selected hematology and biochemistry variables will be provided as listed in Table 12–3.

~~The interim efficacy analysis will include following primary and secondary variables:~~ **For efficacy the interim analysis will include following primary and secondary variables:** ASAS40,20,5/6 response at Week 12, and change from Baseline in BASDAI, ASDAS-CRP, BASFI at Week 12. The variables will be analyzed using the same methods described in Section 8.1.2 and Section 8.2 including supportive and sensitivity analyses (Section 8.1.3 and Section 8.1.4). In addition, summary tables for the primary and secondary efficacy variables, and the ASAS components will be provided. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive

statistics by each visit. Time to onset of ASAS20 response and ASAS40 response will be summarized and plotted as described in Section 8.3.

PK and PD data will be analyzed in the interim analysis as described in Section 9.1 and Section 9.2. PKPD will be analyzed as part of the exposure:response modeling outside of the scope of the SAP. Biomarker data will not be analyzed in the interim analysis.

The interim analysis includes selected data up to Week 12 and in addition data up to Week 16. The data up to Week 16 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. All analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Following variables will be analyzed: ASAS40, ASAS20, ASDAS-CRP, BASDAI, PK, AbAb and TEAEs. It depends on the analysis how those additional time points will be presented in the interim analysis. **Two summary tables for TEAE will be presented. The first table will include TEAEs with a relative TEAE start date less equal 84 (12*7) days by treatment group at Baseline. The second table will include TEAEs with a relative TEAE start date less equal 112 (16*7) days by the following treatment groups: bimekizumab 160mg and bimekizumab 320mg.** The summary table for the other variables will present only data up to Week 12 for the Baseline treatment groups Placebo, bimekizumab 16mg, and bimekizumab 64mg. Data up to Week 16 will be presented for bimekizumab 160mg and bimekizumab 320mg. All Listings which include data up to Week 16 will use the same approach.

If an AE occurs on the same day as the treatment switch (Visit 7, Week 12) then the AE will be allocated to the Double-Blind treatment. An exception from this general rule is made for adverse drug reactions (ADRs), and AE of hypersensitivity reactions and anaphylactic reactions. If those AEs occur on the same days as the treatment switch, the AEs will be allocated to the Dose-Blind treatment and will not be presented for the interim analysis.

Exposure of study medication will not be summarized but a listing will be provided including following information: date of first dose, date of last dose, and duration of exposure. The last dose for the Double-Blind Period is planned on Visit 6 (Week 8). For subject who completed the Double-Blind Period the Week 8 date is the date of the last dose. If a subject discontinued within the Double-Blind Period, the discontinuation date will be presented for the date of last dose.

For the interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The investigators and subjects will remain blind to the assigned bimekizumab dosing regimen until the subject completes the Dose-Blind Period at Week 48. **Further details are available in the AS0008 blinding plan.**

Safety data will be provided to an independent Data Monitoring Committee (DMC). The DMC will review those safety data periodically. The composition and operation of the DMC will be defined in the DMC charter. The presentation and analysis of data for the DMC meetings is described within a separate DMC SAP.

Section 4.8 Examination of subgroups

The following variables for subgroup analyses will be used:

- Age (<45 years, ≥45 years)

- Gender (male, female)
- Geographic region (North America, Europe)
- Treatment-emergent AbAb status (positive, negative)
- TNF inhibitor exposure (yes, no)
- Synthetic disease-modifying antirheumatic drugs (DMARDs) (concomitant, non concomitant)
- BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

Has been changed to

The following variables for subgroup analyses will be used:

- Age (<45 years, ≥45 years)
- Gender (male, female)
- Geographic region (North America, **Eastern and Western** Europe)
- Treatment-emergent AbAb status (positive, negative)
- Prior TNF inhibitor exposure (yes, no)
- ~~Synthetic disease-modifying antirheumatic drugs (DMARDs) (concomitant, non concomitant)~~
- **Current NSAIDs at Baseline (yes, no)**
- BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

Section 6.2 Other Baseline characteristics

AS history will be summarized for subjects in the FAS and SS including the time since first diagnosis of AS, time since first symptoms of AS, and age at first diagnosis date. The history will be listed for all subjects in the RS.

Time since first diagnosis of AS will be calculated as:

$$Time\ since\ first\ diagnosis = Date\ of\ diagnosis - Date\ of\ Informed\ Consent \quad (6)$$

If the date of diagnosis is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing).

Time since first symptoms will be calculated as:

$$Time\ since\ first\ symptoms = Date\ of\ first\ symptoms - Date\ of\ Informed\ Consent \quad (7)$$

…

Has been changed to

AS history will be summarized for subjects in the FAS and SS including the time since first diagnosis of AS, time since first symptoms of AS, and age at first diagnosis date. The history will be listed for all subjects in the RS.

Time since first diagnosis of AS will be calculated as:

$$Time\ since\ first\ diagnosis = Date\ of\ diagnosis - Date\ of\ Informed\ Consent \quad (6)$$

If the date of diagnosis is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing).

Time since first symptoms will be calculated as:

$$Time\ since\ first\ symptoms = Date\ of\ first\ symptoms - Date\ of\ Informed\ Consent \quad (7)$$

The absolute values of the formulas (6) and (7) will be used to display positive values.

Section 8.1.1 Derivations of ASAS score and response

…

For all non-missed visits, if any of the component scores are missing, then the following rules will be applied:

- If all the component values are missing from Baseline through the visit being considered, the percent improvement from Baseline to that visit for the given component will be imputed as 0%. The unit improvement will be imputed as 0.
- If the component value at a given visit is missing and the Baseline value is present, the missing component will be replaced by the last non-missing observation (LOCF) for that component.

If the Baseline value of an ASAS component is 0, then for the purposes of calculating ASAS, the percent change from Baseline will be determined as follows (zero divisor rule):

- If the post-Baseline component value is also 0, set the percent change equal to 0;
- If the post-Baseline component value is >0, then calculate the percent change as though the Baseline value were 0.1.

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Has been changed to

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For all non-missed visits, if any of the component scores are missing, then the following rules will be applied:

- ~~If all the component values are missing from Baseline through the visit being considered, the percent improvement from Baseline to that visit for the given component will be imputed as 0%. The unit improvement will be imputed as 0.~~
- **If the component values are missing at Baseline, the percent improvement from Baseline to a visit for the given component will be imputed as 0%. The unit improvement will be imputed as 0.**
- If the component value at a given visit is missing and the Baseline value is present, the missing component will be replaced by the last non-missing observation (LOCF) for that component.

If the Baseline value of an ASAS component is 0, then for the purposes of calculating ASAS, the percent change from Baseline will be determined as follows (zero divisor rule):

- If the post-Baseline component value is also 0, set the percent change equal to 0;
- If the post-Baseline component value is >0, then calculate the percent change as though the Baseline value were 0.1.

…

Section 8.1.3 Secondary analyses of the primary efficacy variable

As the secondary analysis for the primary efficacy variable, a logistic regression model will be used to assess the effect of each individual dose versus placebo on ASAS40 response. The model will include fixed effects for treatment, geographic region, and prior TNF inhibitor exposure. To avoid the problem of the so-called monotone likelihood resulting in infinite large confidence intervals (eg, if one of the cell counts in the 2x2 table is equal to zero), a penalized maximum likelihood approach based on the modified score procedure of Firth (eg, Heinze and Schemper, 2002) will be used in the logistic models. If the logistic regression model is unable to converge, then geographic region may be dropped from the model to facilitate convergence. If the logistic regression model is unable to converge after dropping the geographic region, then prior TNF inhibitor exposure may be dropped as well. Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% confidence interval, and the corresponding p-value will be calculated.

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Has been changed to

As the secondary analysis for the primary efficacy variable, a logistic regression model will be used to assess the effect of each individual dose versus placebo on ASAS40 response. The model will include fixed effects for treatment, geographic region, and prior TNF inhibitor exposure. To avoid the problem of the so-called monotone likelihood resulting in infinite large confidence intervals (eg, if one of the cell counts in the 2x2 table is equal to zero), a penalized maximum likelihood approach based on the modified score procedure of Firth (eg, Heinze and Schemper, 2002) will be used in the logistic models. **If the logistic regression model is unable to**

converge, then a 2-way categorical variable for geographic region (North America and Europe) will be used. Should the logistic regression **model be** unable to converge **even with this restriction**, then geographic region may be dropped from the model to facilitate convergence. If the logistic regression model is unable to converge after dropping the geographic region, then prior TNF inhibitor exposure may be dropped as well. Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% confidence interval, and the corresponding p-value will be calculated.

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Section 8.3 Statistical analysis of other efficacy variables

Time to onset of ASAS20 response and ASAS40 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

Has been changed to

Time to onset of ASAS20 response and ASAS40 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. **Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates.** Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

Section 8.4 Subgroup analysis

Subgroup analyses will be performed on the primary and secondary efficacy variables. The following variables for subgroup analyses will be defined:

- Age (<45 years, ≥45 years)
- Gender (male, female)
- Geographic region (North America, Europe)
- Treatment-emergent AbAb status (positive, negative)
- TNF inhibitor exposure (yes, no)
- Synthetic DMARDs (concomitant, non concomitant)
- BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

All subgroup analyses are based on imputed data and will be summarized using descriptive statistics only.

Has been changed to

Subgroup analyses will be performed on the primary and secondary efficacy variables. The ~~following~~ variables for subgroup analyses **are defined in Section 4.8.** ~~be defined:~~

- ~~Age (<45 years, ≥45 years)~~
- ~~Gender (male, female)~~
- ~~Geographic region (North America, **Eastern and Western** Europe)~~
- ~~Treatment-emergent AbAb status (positive, negative)~~
- ~~Prior TNF-inhibitor exposure (yes, no)~~
- ~~Synthetic DMARDs (concomitant, non-concomitant)~~
- ~~**Current NSAIDs at Baseline (yes, no)**~~
- ~~BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])~~

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

All subgroup analyses are based on imputed data and will be summarized using descriptive statistics only.

Section 10.1 Extent of exposure

The duration of exposure (in days) will be calculated as:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (12)$$

28 days refer to one half-life of bimekizumab. If a change of treatment occurs prior to completion of the dosing interval, duration of exposure to study medication will be calculated as:

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ injection \quad (13)$$

For subjects who have died the exposure will be as follows:

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ injection + 1 \quad (14)$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose and the duration of exposure will be performed.

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (15)$$

where 140 days refers to 5*half-life of bimekizumab.

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

Has been changed to

The duration of exposure (in days) will be calculated as:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (12)$$

28 days refer to one half-life of bimekizumab. If a change of treatment occurs prior to completion of the dosing interval, duration of exposure to study medication will be calculated as:

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ injection \quad (13)$$

For subjects who have died the exposure will be as follows:

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ injection + 1 \quad (14)$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose and the duration of exposure will be performed.

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (15)$$

where 140 days refers to 5*half-life of bimekizumab.

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$\boldsymbol{Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose + 1} \quad \textbf{(16)}$$

$$\boldsymbol{Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose + 1} \quad \textbf{(17)}$$

Section 10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (16)$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$\begin{aligned} &Time\ since\ first\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset - date\ of\ first\ dose + 1 \end{aligned} \quad (17)$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$\begin{aligned} &Time\ since\ most\ recent\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset \\ &\quad - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \end{aligned} \quad (18)$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (17 and 18) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \end{aligned} \quad (19)$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose\ + 1 \end{aligned} \quad (20)$$

Has been changed to

The duration of each AE will be calculated as follows:

$$AE\ Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (1\underline{\mathbf{8}})$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - date\ of\ first\ dose + 1 \quad (19)$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (20)$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (17 and 18) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

~~The days on treatment and days on bimekizumab treatment will be calculated as follows:~~

~~$$Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose + 1 \quad (19)$$~~

~~$$Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose + 1 \quad (20)$$~~

Section 10.2.2 Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (21)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest.

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

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (22)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (23)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (24)$$

where N_{AE} is the total number of AEs.

No confidence interval will be computed for EAER.

Has been changed to

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (21)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest **(equation [18] in years)** **at the level of coding evaluated**.

If a subject has multiple events **at the level of coding evaluated**, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk **(15)** is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (22)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (23)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (24)$$

where N_{AE} is the total number of AEs.

No confidence interval will be computed for EAER.

Section 10.2.3 AE of Special Monitoring

…

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLGT of "Colitis excl infective".

…

Has been changed to

…

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLGT of "Colitis excl infective".

…

13.3 Amendment 3

13.3.1 Rationale for the amendment

The SAP has been amended to:

- Add Section with changes from interim analysis to SAP-defined analyses
- Change definition of AE of special monitoring for final analysis
- Analyze the MASES Score on a subset of the FAS
- Change the missing item rule for ASQoL
- Add limit of quantification for CRP and hs-CRP
- Update AE section to apply the interim rules to the final analysis
- Update markedly abnormal laboratory units and add the RCTC reference
- Update AbAb Section to clarify the overall AbAb status and the first occurrence of AbAb positivity
- Change subgroup analysis sections to change the definitions of treatment-emergent AbAb status
- Remove rounding information for BMI, hs-CRP, and CRP
- Update prohibited medication section to remove the rule that efficacy results should be set to missing after receiving prohibited medication
- Update pharmacokinetics section to be aligned with TFLs shells

13.3.2 Modifications and changes

List of abbreviation

…

BUN	Blood urea nitrogen
CP	Confirmed positive

…

RBC	Red blood cell
RNA	Ribonucleic acid

…

Has been changed to

…

BUN	Blood urea nitrogen
CDISC	**Clinical Data Interchange Standards Consortium**

CP	Confirmed positive
…	
RBC	Red blood cell
RCTC	**Rheumatology Common Toxicity Criteria**
RNA	Ribonucleic acid
…	

Section 4.3.1 has been added

Section 4.3.1 Changes from interim analysis to SAP-defined analyses

For TEAE two summary tables were presented as described in previous section with one modification: the first table was displaying all TEAE during the Double-Blind Period instead of limiting it TEAE with a relative TEAE start date less equal 84 days.

The definitions of AE of special monitoring were updated with the third SAP Amendment after the interim analysis. The interim analysis used the previous definition which is displayed in Section 4.3.1.2. The interim analysis only displayed the overall number of AE of special monitoring by treatment group.

The definitions of time since first diagnosis of AS and time since first symptoms were updated with the third SAP Amendment after the interim analysis. In the previous definitions the date of informed consent was subtracted from the date of diagnosis or first symptoms which results in negative values. For the interim analysis following calculations were used:

$$\textit{Time since first diagnosis (years)} = \frac{\textit{Date of Informed Consent} - \textit{Date of diagnosis}}{365.25}$$

$$\textit{Time since first symptoms (years)} = \frac{\textit{Date of Informed Consent} - \textit{Date of first symptoms}}{365.25}$$

Section 4.3.2 has been added

Section 4.3.2 Search and selection criteria for AE of special monitoring for interim analysis

Following AEs are defined as TEAEs of special monitoring:

- **Fungal infectious disorder**
- **Opportunistic infection (including TB)**
- **Malignant or unspecified tumor**
- **Malignant tumor**
- **Major cardiovascular event**

- **Haematopoietic cytopenias**
- **Neuropsychiatric events**
- **Inflammatory bowel disease**
- **Hypersensitivity and anaphylactic reaction**
- **Hepatic events**

Fungal Infectious disorder

All TEAEs which code into the High Level Group Term (HLGT) of "Fungal infectious disorders".

Opportunistic infection

All TEAEs identified using UCB-defined search criteria as described in Section 12.13.

Malignant or unspecified tumor

The search criteria is based on the criteria Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)".

Malignant tumor

The search criteria is based on the criteria SMQ="Malignant tumours (SMQ)".

Major cardiovascular events

The major cardiovascular events are identified using the following UCB-defined search criteria:

- **All serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups of the following SMQs:**
  - **Haemorrhagic central nervous system vascular conditions (SMQ)**
  - **Ischaemic central nervous system vascular conditions (SMQ)**
- **All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to PT "Chest Pain" or "Chest discomfort"**
- **All serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders" as Primary SOC.**

Haematopoietic cytopenias

The search criteria is based on the SMQ = "Haematopoietic cytopenias". The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Neuropsychiatric events

The search criteria is based on the SMQ = "Depression and suicide/self-injury (SMQ)". The SMQ search will include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Inflammatory bowel disease

All TEAEs which code into the HLT of "Colitis (excl infective)".

Hypersensitivity reactions and anaphylactic reactions

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

c) **Hypersensitivity reactions: All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, which code to a PT which contains the term "hypersensitivity" will be considered to be a hypersensitivity reaction and included in the summary table as such.**

d) **Anaphylactic reactions: An algorithmic approach will be used to identify TEAEs that are considered to be anaphylactic reactions. PTs are separated into the 4 distinct categories (A, B, C, D) prior to the algorithmic approach being applied.**

All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, and which fulfill any of the 3 criteria described in Section 12.14 will be included in the summary table.

Hepatic events

The search criteria is based on all TEAEs in the SMQ "Drug related hepatic disorders - comprehensive search (SMQ)". Note that the following two sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps)" and "Liver neoplasms, malignant and unspecified (SMQ)".

The SMQ search should include all TEAEs (regardless of whether they have been judged as related to study medication or not) which code to a PT included in the Scope=Narrow group within each SMQ.

Section 4.8 Examination of subgroups

…

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

Has been changed to

…

Subjects will be counted to have a positive treatment-emergent AbAb status in case the **first** AbAb positivity occurred **up to** ~~between the first dose and~~ Visit 7 (Week 12). **The definition of first AbAb occurrence is described in** Section 9.2.

Section 6.1 Demographics

…

BMI in kg/m2 is calculated based on the height (in m) and the weight (in kg) using the formula:

For adults:

$$BMI = \frac{Weight}{Height^2} \quad (5)$$

Even if they are available in the database, these variables are calculated during analysis (if applicable). These calculated values are used in the statistical analysis since they are considered more accurate. BMI is rounded to 1 decimal.

…

Has been changed to

…

BMI in kg/m2 is calculated based on the height (in m) and the weight (in kg) using the formula:

For adults:

$$BMI = \frac{Weight}{Height^2} \quad (5)$$

Even if they are available in the database, these variables are calculated during analysis (if applicable). These calculated values are used in the statistical analysis since they are considered more accurate. ~~BMI is rounded to 1 decimal.~~

…

Section 6.2 Other Baseline characteristics

…

Time since first diagnosis of AS will be calculated as:

$$Time\ since\ first\ diagnosis = Date\ of\ diagnosis - Date\ of\ Informed\ Consent \quad (6)$$

If the date of diagnosis is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing).

Time since first symptoms will be calculated as:

$$Time\ since\ first\ symptoms = Date\ of\ first\ symptoms - Date\ of\ Informed\ Consent \quad (7)$$

Age at first diagnosis will be calculated as:

$$Age\ at\ first\ diagnosis = \frac{Date\ of\ first\ diagnosis - Date\ of\ birth}{365.25} \quad (8)$$

The absolute values of the formulas (6) and (7) will be used to display positive values.

…

Has been changed to

…

Time since first diagnosis of AS will be calculated as:

$$Time\ since\ first\ diagnosis\ (\boldsymbol{years}) = \frac{\boldsymbol{Date\ of\ Informed\ Consent - \ Date\ of\ diagnosis + 1}}{\boldsymbol{365.25}} \quad (6)$$

If the date of diagnosis is partial, it should be imputed to the most recent feasible date (ie, last day of the month if only day is missing, or the last day of the year if day and month are missing).

Time since first symptoms will be calculated as:

$$Time\ since\ first\ symptoms\ (\boldsymbol{years}) = \frac{\boldsymbol{Date\ of\ Informed\ Consent - \ Date\ of\ first\ symptoms + 1}}{\boldsymbol{365.25}} \quad (7)$$

Age at first diagnosis will be calculated as:

$$Age\ at\ first\ diagnosis = \frac{Date\ of\ first\ diagnosis - Date\ of\ birth}{365.25} \quad (8)$$

~~The absolute values of the formulas (6) and (7) will be used to display positive values.~~

…

Section 6.5 Prohibited medication and rescue medication

Prohibited medications are defined in the protocol (Section 7.8.2). All efficacy data collected at assessments after the use of prohibited medications should be treated as missing. Prohibited medication use and date of first usage should be determined and documented during the data evaluation meeting (DEM) prior to the database lock.

…

Has been changed to

Prohibited medications are defined in the protocol (Section 7.8.2). ~~All efficacy data collected at assessments after the use of prohibited medications should be treated as missing. Prohibited medication use and date of first usage should be determined and documented during the data evaluation meeting (DEM) prior to the database lock.~~

…

Section 8.3 Statistical analysis of other efficacy variables

All other efficacy variables in the Double-Blind Period will be analyzed for all subjects in the FAS. For the Dose-Blind Period, other efficacy variables will be analyzed for all subjects in the DBRS, and ESS.

All categorical variables will be presented using frequency tables by each visit. All continuous variables will be summarized using descriptive statistics by each visit.

The Hospital Anxiety and Depression Scale (HADS) will be analyzed separately for HADS-A and HADS-D. The summary statistics for HADS-A and HADS-D will be presented in two different tables.

Times series plots will be provided for the response rate or change from Baseline for the primary and secondary efficacy variables. The plots will show the weekly response rate over the first 12 weeks.

The MRI of the spine and sacroiliac joints will be performed in a substudy with subjects who were classified as MRI-positive at Baseline as per ASAS-Outcome Measures in Rheumatology Clinical Trials (OMERACT) criteria.

…

Has been changed to

All other efficacy variables in the Double-Blind Period will be analyzed for all subjects in the FAS. For the Dose-Blind Period, other efficacy variables will be analyzed for all subjects in the DBRS, and ESS.

All categorical variables will be presented using frequency tables by each visit. All continuous variables will be summarized using descriptive statistics by each visit.

The Hospital Anxiety and Depression Scale (HADS) will be analyzed separately for HADS-A and HADS-D. The summary statistics for HADS-A and HADS-D will be presented in two different tables.

Times series plots will be provided for the response rate or change from Baseline for the primary and secondary efficacy variables. The plots will show the weekly response rate over the first 12 weeks.

The MRI of the spine and sacroiliac joints will be performed in a substudy with subjects who were classified as MRI-positive at Baseline as per ASAS-Outcome Measures in Rheumatology Clinical Trials (OMERACT) criteria.

A subset of the FAS will be used for the analyses of MASES. The MASES Score will only be analyzed for subjects with enthesitis at Baseline (MASES > 0).

…

Section 8.3.5 Ankylosing Spondylitis Quality of Life (ASQoL)

The ASQoL consists of 18 items, each with a score of 0 = no or 1 = yes, so that the sum score ranges from 0 to 18, with higher scores indicating worse quality of life. The questionnaire is available in Section 12.11.

If 6 or fewer items are missing, the missing responses will be imputed with the mean of the available responses from that visit to calculate a total score. If more than 6 items are missing, the total score will be left missing.

Has been changed to

The ASQoL consists of 18 items, each with a score of 0 = no or 1 = yes, so that the sum score ranges from 0 to 18, with higher scores indicating worse quality of life. The questionnaire is available in Section 12.11.

If ~~6~~**3** or fewer items are missing, the missing responses will be imputed with the mean of the available responses from that visit to calculate a total score. If more than ~~6~~**3** items are missing, the total score will be left missing

Section 8.3.9 C-reactive protein (CRP) and high-sensitivity C-reactive protein (CRP)

…

The values of hs-CRP and CRP will be rounded to integers prior to calculating ratio to Baseline and values below the limit of quantification should be set to should be set to half the limit of quantification for the calculations.

Has been changed to

…

~~The values of hs-CRP and CRP will be rounded to integers prior to calculating ratio to Baseline and~~ **hs-CRP and CRP** values below the limit of quantification should be set to ~~should be set to~~ half the limit of quantification for the calculations. **The limit of quantification for hs-CRP is 0.16 mg/L and 0.4 mg/dL = 4.00 mg/L for CRP.**

Section 8.4 Subgroup analysis

…

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

…

Has been changed to

…

Subjects will be counted to have a positive treatment-emergent AbAb status in case the **first** AbAb positivity occurred **up to** ~~between the first dose and~~ Visit 7 (Week 12). **The definition of first AbAb occurrence is described in** Section 9.2.

…

Section 9.1 Pharmacokinetics

…

In addition geometric mean bimekizumab plasma concentration time curves will be plotted by treatment group, and by cumulative antibody status (ie, positive, negative) for subjects randomized to bimekizumab as well as individual time curves of DAS28(CRP), bimekizumab concentration, and AbAb.

…

Has been changed to

…

In addition geometric mean bimekizumab plasma concentration time curves will be plotted by treatment group~~, and by cumulative antibody status (ie, positive, negative) for subjects randomized to bimekizumab as well as individual time curves of DAS28(CRP), bimekizumab concentration, and AbAb~~.

…

Section 9.2 Pharmacodynamics and Immunogenicity

…

In addition, overall AbAb status should be determined:

- Subject AbAb positivity is defined as having with AbAb+ at any time in the treatment period. This does not include Baseline/pre-treatment
- Subject AbAb negativity is defined with AbAb- at any time in the treatment period. This does also include AbAb+ at Baseline/pre-treatment
- Treatment-emergent AbAb positivity is defined when a subject is AbAb+ for the first time during treatment period excluding Baseline/pre-treatment. If there is AbAb+ at Baseline/pretreatment and there is a pre-defined fold increase in titre at least at one visit during the treatment period, then the subject has also a treatment-emergent AbAb positivity status.

Note: The fold increase from Baseline required will be defined with the development of the assay prior to database lock.

…

Has been changed to

…

In addition, overall AbAb status should be determined:

- Subject AbAb positivity is defined as having with AbAb+ at any time in the treatment period. This does not include Baseline/pre-treatment
- Subject AbAb negativity is defined with AbAb- at any time in the treatment period. This does also include AbAb+ at Baseline/pre-treatment
- ~~Treatment-emergent AbAb positivity is defined when a subject is AbAb+ for the first time during treatment period excluding Baseline/pre-treatment.~~ If there is AbAb+ at Baseline/pretreatment and there is a ~~pre-defined~~ **4-**fold increase in titre at least at one visit during the treatment period, then the subject has also a**n** ~~treatment-emergent~~ **overall** AbAb positivity status.

~~Note: The fold increase from Baseline required will be defined with the development of the assay prior to database lock.~~

The visit of the first occurrence of AbAb positivity is defined as the visit when a subject is AbAb+ for the first time during treatment period excluding Baseline/pre-treatment. If there is AbAb+ at Baseline/pre-treatment and there is a 4-fold increase in titre at least at one visit during the treatment period, then the subject's first occurrence visit is the Baseline Visit.

…

Section 10.2 Adverse events (AEs)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs (including serious AEs) are characterized as either non-treatment or treatment emergent according to the following criteria:

- Non-treatment emergent are the events with onset date and time prior to the very first administration of study medication (bimekizumab or placebo) or after a 140-day period after the final drug administration.
- Treatment-emergent AEs (TEAE) are those with onset date at or after the very first administration of study medication. The events that emerge within 140 days after the final drug administration, will also be considered as treatment emergent (eg, in the case of premature discontinuation or during the SFU period).

All AEs occurring during the study (i.e., after signature of the informed consent document) will be recorded in the eCRF. For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was classified as a SAE, as an AE of special interest, intensity, relationship to study medication, action taken with study medication, other action taken, outcome, date of outcome, and whether the AE led to study drug discontinuation or to study discontinuation.

The following code lists will be used for AE recording:

- Pattern of event: intermittent or continuous
- Intensity of event: mild, moderate or severe
- Relationship: related or not related
- Action taken with IMP: dose not changed, dose reduced, dose increased, drug temporarily, interrupted, drug permanently withdrawn or not applicable
- Outcome: resolving, not resolved, resolved, resolved with sequelae, worsened, fatal or unknown

For all TEAEs the following variables will be calculated:

- Duration
- Time since first dose

Adverse drug reactions (ADRs) are defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. Any AE that is considered "Related" to study treatment will be classed as an ADR.

…

Has been changed to

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs (including serious AEs) are characterized as either non-treatment or treatment emergent according to the following criteria:

- Non-treatment emergent are the events with onset date and time prior to the very first administration of study medication (bimekizumab or placebo) or after a 140-day period after the final drug administration.
- Treatment-emergent AEs (TEAE) are those with onset date at or after the very first administration of study medication. The events that emerge within 140 days after the final drug administration, will also be considered as treatment emergent (eg, in the case of premature discontinuation or during the SFU period).

All AEs occurring during the study (i.e. after signature of the informed consent document) will be recorded in the eCRF. For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was classified as a SAE, as an AE of special interest, intensity, relationship to study medication, action taken with study medication, other action taken, outcome, date of outcome, and whether the AE led to study drug discontinuation or to study discontinuation.

~~The following code lists will be used for AE recording:~~

- ~~Pattern of event: intermittent or continuous~~
- ~~Intensity of event: mild, moderate or severe~~
- ~~Relationship: related or not related~~
- ~~Action taken with IMP: dose not changed, dose reduced, dose increased, drug temporarily, interrupted, drug permanently withdrawn or not applicable~~
- ~~Outcome: resolving, not resolved, resolved, resolved with sequelae, worsened, fatal or unknown~~

~~For all TEAEs the following variables will be calculated:~~

- ~~Duration~~
- ~~Time since first dose~~

~~Adverse drug reactions (~~ADRs~~)~~ are defined as a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. Any AE that is considered "Related" to study treatment will be classed as an ADR.

If an AE occurs on the same day as the treatment switch (Visit 7, Week 12) then the AE will be allocated to the Double-Blind treatment. An exception from this general rule is made for ADRs, and AE of hypersensitivity reactions and anaphylactic reactions. If those AEs occur on the same days as the treatment switch, the AEs will be allocated to the Dose-Blind treatment.

Section 10.2.3AE of Special Interest and AE of Special Monitoring

AE of special interest is any AE which meets the Hy's Law criteria, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

AEs of special monitoring for this study include: serious infections (including opportunistic infections and TB), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the electronic Columbia-Suicide Severity Rating Scale [eC-SSRS]), depression and anxiety (assessed using the HADS), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin), malignancies, and inflammatory bowel diseases.

The incidence of TEAEs of special monitoring will be summarized by MedDRA system organ class, high level term, and PT. EAIR with associated 95% CI, and the EAER will be included in the summary tables for following TEAEs of special monitoring:

- Fungal infectious disorder
- Opportunistic infection (including TB)
- Malignant or unspecified tumor
- Malignant tumor
- Major cardiovascular event
- Haematopoietic cytopenias
- Neuropsychiatric events
- Inflammatory bowel disease
- Hypersensitivity and anaphylactic reaction
- Hepatic events

Fungal Infectious disorder

Fungal infections will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs which code into the High Level Group Term (HLGT) of "Fungal infectious disorders".

Opportunistic infection

Opportunistic infections (including TB) will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs identified using UCB-defined search criteria as described in Section 12.13.

Malignant or unspecified tumor

These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)".

The output table will include 2 different overall incidence rows:

1. The first overall incidence row will summarize "Any malignancies (including unspecified)" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.

2. The second overall incidence row will summarize "Any malignancy (including unspecified, excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

Malignant tumor

These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria SMQ="Malignant tumours (SMQ)".

Note that the events included in the "Malignant tumours" table will be a subset of the events included in the "Malignant or unspecified tumours" table. The SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each SMQ.

The output table will include 2 different overall incidence rows:

1. The first overall incidence row will summarize "Any malignancies" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High HLT it codes to.

2. The second overall incidence row will summarize "Any malignancy (excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

Major cardiovascular events

The major cardiovascular events are identified using the following UCB-defined search criteria:

- All serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups of the following SMQs:
  - Haemorrhagic central nervous system vascular conditions (SMQ)
  - Ischaemic central nervous system vascular conditions (SMQ)
- All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to PT "Chest Pain" or "Chest discomfort"

• All serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders" as Primary SOC.

Haematopoietic cytopenias

These events will be presented in a stand-alone table that is based on the SMQ = "Haematopoietic cytopenias". The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Neuropsychiatric events

These events will be presented in a stand-alone table including EAIR and EAER. The table will be based on the SMQ = "Depression and suicide/self-injury (SMQ)". The SMQ search will include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLT of "Colitis excl infective".

Hypersensitivity reactions and anaphylactic reactions

Anaphylactic reactions will be summarized together in a stand-alone table.

The first row within the body of the table will be labeled "Any hypersensitivity/anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction or at least one anaphylactic reaction.

The second row within the body of the table will be labeled "Any hypersensitivity reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction.

The third row within the body of the table will be labeled "Any anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one anaphylactic reaction.

Following these three overall incidence rows, all TEAEs that have been identified as either a hypersensitivity reaction or an anaphylactic reaction will be summarized (together – not broken out by type) by SOC, HLT and PT.

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

c) Hypersensitivity reactions: All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, which code to a PT which contains the term "hypersensitivity" will be considered to be a hypersensitivity reaction and included in the summary table as such.

d) Anaphylactic reactions: An algorithmic approach will be used to identify TEAEs that are considered to be anaphylactic reactions. PTs are separated into the 4 distinct categories (A, B, C, D) prior to the algorithmic approach being applied.

All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, and

which fulfill any of the 3 criteria described in Section 12.14 will be included in the summary table.

Hepatic events

Although not officially considered to be AEs of special monitoring but hepatic events are nonetheless considered to be interesting enough to be summarized in stand-alone tables.

Hepatic events will be summarized in a stand-alone table that includes all TEAEs in the SMQ "Drug related hepatic disorders - comprehensive search (SMQ)". Note that the following two sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps)" and "Liver neoplasms, malignant and unspecified (SMQ)".

The SMQ search should include all TEAEs (regardless of whether they have been judged as related to study medication or not) which code to a PT included in the Scope=Narrow group within each SMQ.

Has been changed to

AE of special interest is any AE which meets the Hy's Law criteria, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality.

~~AEs of special monitoring for this study include: serious infections (including opportunistic infections and TB), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the electronic Columbia-Suicide Severity Rating Scale [eC-SSRS]), depression and anxiety (assessed using the HADS), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin), malignancies, and inflammatory bowel diseases.~~

AE of special monitoring for this study include:

- **Infections (serious, opportunistic, fungal and TB)**
- **Malignancies, including lymphoma**
- **Major cardiovascular events**
- **Neutropenia**
- **Neuropsychiatric events (in particular depression and suicide)**
- **Inflammatory bowel disease**
- **Anaphylactic reaction**
- **Hepatic events**

For the definitions of AE of special monitoring the Bimekizumab Safety Topics of Interest (Version date 19Feb2018) will be used.

The incidence of TEAEs of special monitoring will be summarized by MedDRA system organ class, high level term, and PT. EAIR with associated 95% CI~~,~~ and the EAER will be included in the summary tables. **Serious infections are also classified as AE of special monitoring but no separate table will be produced.**

The output table for the search criteria Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)" will include two different overall rows:

- **The first overall incidence row will summarize "Any malignancies (including unspecified)" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.**
- **The second overall incidence row will summarize "Any malignancy (including unspecified, excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".**

The output table for the search criteria SMQ="Malignant tumours (SMQ)" will include two different overall rows:

- **The first overall incidence row will summarize "Any malignancies" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.**
- **The second overall incidence row will summarize "Any malignancy (excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".**

The output table for Anaphylactic reaction will include three different overall rows:

- **The first row within the body of the table will be labeled "Any hypersensitivity/anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction or at least one anaphylactic reaction.**
- **The second row within the body of the table will be labeled "Any hypersensitivity reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction.**
- **The third row within the body of the table will be labeled "Any anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one anaphylactic reaction.**

- ~~Fungal infectious disorder~~
- ~~Opportunistic infection (including TB)~~
- ~~Malignant or unspecified tumor~~
- ~~Malignant tumor~~
- ~~Major cardiovascular event~~
- ~~Haematopoietic cytopenias~~
- ~~Neuropsychiatric events~~
- ~~Inflammatory bowel disease~~
- ~~Hypersensitivity and anaphylactic reaction~~

- Hepatic events

Fungal Infectious disorder

Fungal infections will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs which code into the High Level Group Term (HLGT) of "Fungal infectious disorders".

Opportunistic infection

Opportunistic infections (including TB) will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs identified using UCB-defined search criteria as described in Section 12.13.

Malignant or unspecified tumor

These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)".

The output table will include 2 different overall incidence rows:

1. The first overall incidence row will summarize "Any malignancies (including unspecified)" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.

2. The second overall incidence row will summarize "Any malignancy (including unspecified, excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

Malignant tumor

These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria SMQ="Malignant tumours (SMQ)".

Note that the events included in the "Malignant tumours" table will be a subset of the events included in the "Malignant or unspecified tumours" table. The SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each SMQ.

The output table will include 2 different overall incidence rows:

1. The first overall incidence row will summarize "Any malignancies" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High HLT it codes to.

2. The second overall incidence row will summarize "Any malignancy (excluding non-melanomic skin cancers)" and this row will summarize the incidence of AEs flagged for inclusion in the table, excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

Major cardiovascular events

The major cardiovascular events are identified using the following UCB-defined search criteria:

- All serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups of the following SMQs:
  - Haemorrhagic central nervous system vascular conditions (SMQ)
  - Ischaemic central nervous system vascular conditions (SMQ)
- All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to PT "Chest Pain" or "Chest discomfort"
- All serious TEAEs which code to a PT included in any of the following HLTs: "Heart Failures NEC", "Left Ventricular Failures", or "Right Ventricular Failures" and which also code to the SOC of "Cardiac Disorders" as Primary SOC.

Haematopoietic cytopenias

These events will be presented in a stand-alone table that is based on the SMQ= "Haematopoietic cytopenias". The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Neuropsychiatric events

These events will be presented in a stand-alone table including EAIR and EAER. The table will be based on the SMQ = "Depression and suicide/self injury (SMQ)". The SMQ search will include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLT of "Colitis excl infective".

Hypersensitivity reactions and anaphylactic reactions

Anaphylactic reactions will be summarized together in a stand-alone table.

The first row within the body of the table will be labeled "Any hypersensitivity/anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction or at least one anaphylactic reaction.

The second row within the body of the table will be labeled "Any hypersensitivity reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction.

The third row within the body of the table will be labeled "Any anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one anaphylactic reaction.

Following these three overall incidence rows, all TEAEs that have been identified as either a hypersensitivity reaction or an anaphylactic reaction will be summarized (together – not broken out by type) by SOC, HLT and PT.

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

c) Hypersensitivity reactions: All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication

~~injection was received, which code to a PT which contains the term "hypersensitivity" will be considered to be a hypersensitivity reaction and included in the summary table as such.~~

~~d) Anaphylactic reactions: An algorithmic approach will be used to identify TEAEs that are considered to be anaphylactic reactions. PTs are separated into the 4 distinct categories (A, B, C, D) prior to the algorithmic approach being applied.~~

~~All TEAEs that either emerged on the same day as when a study medication injection reaction was received, or that emerged one day after a study medication injection was received, and which fulfill any of the 3 criteria described in Section 12.14 will be included in the summary table.~~

~~**Hepatic events**~~

~~Although not officially considered to be AEs of special monitoring but hepatic events are nonetheless considered to be interesting enough to be summarized in stand-alone tables.~~

~~Hepatic events will be summarized in a stand-alone table that includes all TEAEs in the SMQ "Drug related hepatic disorders – comprehensive search (SMQ)". Note that the following two sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps)" and "Liver neoplasms, malignant and unspecified (SMQ)".~~

~~The SMQ search should include all TEAEs (regardless of whether they have been judged as related to study medication or not) which code to a PT included in the Scope=Narrow group within each SMQ.~~

Section 10.3 Clinical laboratory evaluations

…

Markedly abnormal values for biochemistry and hematology are defined in Table 10–2 and Table 10–3.The markedly abnormal laboratory results will be listed separately.

Values that are below the lower limit of the reference range will be flagged as "L" (low) and values that are above the upper limit of the reference range will be flagged as "H" (high) and listed as well.

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. In the case where laboratory values are below the lower limit of quantification, then these will be set to the midpoint between 0 and the lower limit of quantification for the purpose of summarizing the data.

Table 13–5: Definitions of Markedly Abnormal Biochemistry Values

Variable (Standard international units)	Markedly abnormal definition	
	Low	High
ALP	N/A	>3 x ULN
ALT	N/A	>3 x ULN
AST	N/A	>3 x ULN
Calcium (mg/dL)	<7.0	>12.5

Table 13–5: Definitions of Markedly Abnormal Biochemistry Values

Variable (Standard international units)	Markedly abnormal definition	
	Low	High
Creatinine (mg/dL)	N/A	>1.8 x ULN
Glucose (mg/dL)	<40	>250
Potassium (mmol/L)	<3.0	>6.4
Sodium (mmol/L)	<125	N/A
Total bilirubin	N/A	≥2 x ULN
Uric acid	N/A	≥3 x ULN

ALP=alkaline phosphatase; AST=aspartate aminotransferase; N/A=Not applicable; ULN=upper limit of normal.

Table 13–6: Definitions of Markedly Abnormal Hematology Values

Variable (Standard international units)	Markedly abnormal definition	
	Low	High
Hemoglobin (g/dL)	<LLN AND >2.0 decrease from Baseline	N/A
Hemoglobin (g/dL)	<8.0	N/A
Leukocytes (total x 1000)	<2.0	N/A
Lymphocytes (x 1000)	<0.5	N/A
Neutrophils (x 1000)	<1.0	N/A
Platelets (x 1000)	<50	N/A

LLN=lower limit of normal; N/A = not applicable.

Has been changed to

…

Markedly abnormal values for biochemistry and hematology will be defined as laboratory values graded 3 or 4 according to the Rheumatology Common Toxicity Criteria (RCTC). Definitions of the markedly abnormal values are given in Table 10–2 and Table 10–3 and are based on the RCTC units. All units in the tables below will be converted to the standard units based on Clinical Data Interchange Standards Consortium (CDISC) standards. The markedly abnormal laboratory results will be listed separately.

Values that are below the lower limit of the reference range will be flagged as “L” (low) and values that are above the upper limit of the reference range will be flagged as “H” (high) and listed as well.

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. In the case where laboratory values are below the lower limit of quantification, then these will be set to the midpoint between 0 and the lower limit of quantification for the purpose of summarizing the data.

Table 13–7: Definitions of Markedly Abnormal Biochemistry Values

Variable (~~Standard international~~ RCTC units)	Markedly abnormal definition	
	Low	High
ALP	N/A	>3 x ULN
ALT	N/A	>3 x ULN
AST	N/A	>3 x ULN
Calcium (mg/dL)	<7.0	>12.5
Creatinine (mg/dL)	N/A	>1.8 x ULN
Glucose (mg/dL)	<40	>250
Potassium (mmol/L)	<3.0	>6.4
Sodium (mmol/L)	<125	N/A
Total bilirubin	N/A	≥2 x ULN
Uric acid	N/A	≥3 x ULN

ALP=alkaline phosphatase; AST=aspartate aminotransferase; N/A=Not applicable; **RCTC= Rheumatology Common Toxicity Criteria**; ULN=upper limit of normal.

Table 13–8: Definitions of Markedly Abnormal Hematology Values

Variable (~~Standard international~~ RCTC units)	Markedly abnormal definition	
	Low	High
Hemoglobin (g/dL)	<LLN AND >2.0 decrease from Baseline	N/A
Hemoglobin (g/dL)	<8.0	N/A
Leukocytes (total x 1000)	<2.0	N/A
Lymphocytes (x 1000)	<0.5	N/A
Neutrophils (x 1000)	<1.0	N/A
Platelets (x 1000)	<50	N/A

LLN=lower limit of normal; N/A = not applicable; **RCTC= Rheumatology Common Toxicity Criteria.**

13.4 Amendment 4

13.4.1 Rationale for the amendment

The main objectives of this SAP amendment are to describe an additional interim analysis Week 48 and correct small errors.

13.4.2 Modifications and changes

Section 2.2.1.3 Other efficacy variables

…

- ASAS5/6 response (Week 1, 2, 4, 8, 12, 16, 24, 36, 48)

…

Has been changed to

…

- ASAS5/6 response (Week ~~1, 2,~~ 4, 8, 12, 16, 24, 36, 48)

…

Section 3.1 General presentation of summaries and analyses

…

All original and derived variables will be listed and described using summary statistics (number of observations [n], mean, standard deviation [SD], median, minimum and maximum, unless otherwise stated) or frequency counts (number of subjects [N] and percentages).

…

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999". Statistical comparisons will be performed by two-sided statistical tests at the 0.0500 level of significance.

…

In the Double-Blind Period the order of treatment groups to be presented in tables from left to right will be placebo, bimekizumab 16mg, bimekizumab 64mg, bimekizumab 160 mg, and bimekizumab 320 mg. The general principle is to go from the lowest to highest dose when moving from left to right. Tables may also include columns for all subjects or all subjects on bimekizumab. An overview of the treatment group assignment is available in Table 12–2.

Selected tables which are specified in the TFL shells will only use data from the Dose-Blind Period. For listings and the selected tables, the label and order of treatment groups will be presented as follows: placebo to bimekizumab 160mg at Week 12, bimekizumab 16mg to bimekizumab 160mg at Week 12, bimekizumab 64mg to bimekizumab 160mg at Week 12, bimekizumab 160mg, placebo to bimekizumab 320mg at Week 12, bimekizumab 16mg to bimekizumab 320mg at Week 12, bimekizumab 64mg to bimekizumab 320mg at Week 12, and bimekizumab 320mg.

The abbreviation for bimekizumab is BKZ and will be used in tables and listings headers. All subjects on bimekizumab will be labeled as "All BKZ" in the TFLs.

…

Has been changed to

…

All original and derived variables will be listed and described using summary statistics (number of observations [n], mean, standard deviation [SD], median, minimum and maximum, unless otherwise stated) or frequency counts (number of subjects [N] and percentages). **For multiple post-Baseline assessments at a specific visit, the first non-missing measurement will be used for summary statistics or frequency counts.**

…

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to **3**~~4~~ decimal places. P-values less than 0.00~~0~~1 will be presented as "<0.00~~0~~1" and p-values greater than 0.999~~9~~ will be presented as ">0.999~~9~~". Statistical comparisons will be performed by two-sided statistical tests at the 0.050~~0~~ level of significance.

…

In the Double-Blind Period the order of treatment groups to be presented in tables from left to right will be ~~placebo, bimekizumab 16mg, bimekizumab 64mg, bimekizumab 160 mg, and bimekizumab 320 mg.~~ **Placebo, BKZ16mg, BKZ64mg, BKZ160mg, and BKZ320mg, where BKZ is the abbreviation for bimekizumab.** The general principle is to go from the lowest to highest dose when moving from left to right. Tables may also include columns for all subjects or all subjects on bimekizumab. An overview of the treatment group assignment is available in Table 12–2.

Selected tables which are specified in the TFL shells will only use data from the Dose-Blind Period. For listings and the selected tables, the label and order of treatment groups will be presented as follows: ~~placebo to bimekizumab 160mg at Week 12, bimekizumab 16mg to bimekizumab 160mg at Week 12, bimekizumab 64mg to bimekizumab 160mg at Week 12, bimekizumab 160mg, placebo to bimekizumab 320mg at Week 12, bimekizumab 16mg to bimekizumab 320mg at Week 12, bimekizumab 64mg to bimekizumab 320mg at Week 12, and bimekizumab 320mg.~~ **Placebo-BKZ160mg, Placebo-BKZ320mg, BKZ16mg-BKZ160mg, BKZ16mg-BKZ320mg, BKZ64mg-BKZ160mg, BKZ64mg-BKZ320mg, BKZ160mg-BKZ160mg, and BKZ320mg-BKZ320mg.**

~~The abbreviation for bimekizumab is BKZ and will be used in tables and listings headers.~~ All subjects on bimekizumab will be labeled as "All BKZ" in the TFLs.

…

Section 3.2.2 Study Periods

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

- Pre-treatment period (Screening period): up to 28 days, ends with the first dose of bimekizumab.

- Double-Blind treatment period: starts with the first dose of study medication (Visit 2), ends at Week 12 prior to the treatment re-randomization.
- Dose-Blind treatment period: starts at the Week 12 visit after the treatment re-randomization, ends at Week 48.
- Post-treatment period: The post-treatment period (Follow-up period) is the period after the last dose of bimekizumab administration.

Has been changed to

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

- Pre-treatment period (Screening period): up to 28 days, ends with the **visit date of the first dose of study medication (Visit 2)** ~~first dose of bimekizumab.~~
- Double-Blind treatment period: starts with the **visit date of the** first dose of study medication (Visit 2), ends at Week 12 **visit date** ~~prior to the treatment re-randomization~~.
- Dose-Blind treatment period: starts at the Week 12 visit ~~after the treatment re-randomization~~, ends at Week 48 **visit**~~.~~
- Post-treatment period: the post-treatment period (Follow-up period) is the period after the **Week 48 visit**~~last dose of bimekizumab administration~~.

Section 3.3 Definition of Baseline values

Unless otherwise specified, the last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value. The same Baseline definition will be used for the follow-up period. However, for some variables, assessments may be scheduled for Screening only and not for Baseline. In this case the Screening value will be utilized as Baseline value. If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead.

If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication.

Has been changed to

~~Unless otherwise specified, t~~**T**he last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value. **If a scheduled Baseline assessment is taken on the same day and after the first administration of study medication, it will be analyzed as the first post-Baseline assessment. If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication.**

The exception of the above rule are the questionnaires collected from the vendor ERT. For those measurement, the last valid measurement at the same day as Visit 2 will be used as the Baseline value.

~~The same Baseline definition will be used for the follow-up period.~~ However, for some variables, assessments may be scheduled for Screening only and not for Baseline. In this case the Screening

value will be utilized as Baseline value. If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead.

~~If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication.~~

Section 3.7 Treatment assignment and treatment groups

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For AE tables and listings, AEs for each subject will be summarized based on the treatment actually received at the onset of each particular AE. It should be noted that this could result in one subject being summarized in two different treatment groups within one output if they were on a treatment regimen that involved treatment switching and experienced AEs under both treatment allocations.

Efficacy analyses will be performed according to randomization and not actual treatment received.

Has been changed to

…

~~For AE tables and listings, AEs for each subject will be summarized based on the treatment actually received at the onset of each particular AE. It should be noted that this could result in one subject being summarized in two different treatment groups within one output if they were on a treatment regimen that involved treatment switching and experienced AEs under both treatment allocations.~~

~~Efficacy analyses will be performed according to randomization and not actual treatment received.~~

Depending on the analysis sets, subjects will be summarized and listed based on the actual received treatment or according to the randomization which will be considered as planned treatment:

- **All subjects screened/ES: planned treatment**
- **RS: planned treatment**
- **SS: actual treatment**
- **FAS: planned treatment**
- **PPS: planned treatment**
- **PK-PPS: actual treatment**
- **PD-PPS: actual treatment**
- **DBS: actual treatment**
- **ESS: planned treatment**
- **DBRS: planned treatment**

Section 4.2.3 Handling of missing data for prior and concomitant medication

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

If the date of first study medication or switch treatment is partial, then the above imputation approach will be applied:

- If only the day of first study medication or switch treatment administration is unknown, then this will be set to either the first of the month, or the day of first treatment allocation visit (excluding placebo run-in), whichever is later.
- If both the day and month of first study medication or switch treatment are unknown, then this date will be imputed to be the date of first treatment allocation visit.

…

Has been changed to

…

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 and the subject did not switch treatment during that month and year, then use the 1st of the month.

- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the month and year are specified and the subject did switch treatment during that month and year, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is not the same as the year of the start date and the subject did not switch treatment during that year, 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 only the year is specified, and the year of first dose is the same as the year the subject did switch treatment, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is the same as the year of the start date and the same as the year the subject did switch treatment, then use the date of first dose.
- **If only the year is specified and the end date is before date of first dose, then set the start date to the 1st of January of the year of the start date.**
- **If only the year and day are specified and month is missing, then only the year will be considered and the month and day will be imputed with the rules above**
- If the start date is completely unknown and the stop date is unknown or not prior to the date of first dose, then use the date of first dose.
- If the start date is completely unknown and the stop date is prior to the date of first dose, then set the start date to the 1st of January of the year of the end date.

If the date of first study medication or switch treatment is partial, then the **below** ~~above~~ imputation approach will be applied:

- If only the day of first study medication or switch treatment administration is unknown, then this will be set to either the first of the month, or the day of first treatment allocation visit (excluding placebo run-in), whichever is later.
- If both the day and month of first study medication or switch treatment are unknown, then this date will be imputed to be the date of first treatment allocation visit.

…

Section 4.3 Interim analyses and data monitoring

…

Exposure of study medication will not be summarized but a listing will be provided including following information: date of first dose, date of last dose, and duration of exposure. The last dose for the Double-Blind Period is planned on Visit 6 (Week 8). For subject who completed the Double-Blind Period the Week 8 date is the date of the last dose. If a subject discontinued within the Double-Blind Period, the discontinuation date will be presented for the date of last dose.

…

Section 4.3.1 Changes from interim analysis to SAP-defined analyses

For TEAE two summary tables were presented as described in previous section with one modification: the first table was displaying all TEAE during the Double-Blind Period instead of limiting it TEAE with a relative TEAE start date less equal 84 days.

The definitions of AE of special monitoring were updated with the third SAP Amendment after the interim analysis. The interim analysis used the previous definition which is displayed in Section 4.3.1.2. The interim analysis only displayed the overall number of AE of special monitoring by treatment group.

The definitions of time since first diagnosis of AS and time since first symptoms were updated with the third SAP Amendment after the interim analysis. In the previous definitions the date of informed consent was subtracted from the date of diagnosis or first symptoms which results in negative values. For the interim analysis following calculations were used:

$$Time\ since\ first\ diagnosis\ (years) = \frac{Date\ of\ Informed\ Consent - \ Date\ of\ diagnosis}{365.25}$$

$$Time\ since\ first\ symptoms\ (years) = \frac{Date\ of\ Informed\ Consent - Date\ of\ first\ symptoms}{365.25}$$

Section 4.3.2 Search and selection criteria for AE of special monitoring for interim analysis

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Has been changed to

Section 4.3 Interim analyses and data monitoring

Two interim analyses are planned for the study after the subjects have completed 12 and 48 weeks.

Section 4.3.1 Interim analysis Week 12

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Exposure of study medication will not be summarized but a listing will be provided including following information: date of first dose, date of last dose, and duration of exposure. The last dose for the Double-Blind Period is planned on Visit 6 (Week 8). ~~For subject who completed the Double-Blind Period the Week 8 date is the date of the last dose. If a subject discontinued within the Double-Blind Period, the discontinuation date will be presented for the date of last dose.~~

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Section 4.3.1.1 Changes from interim analysis Week 12 to SAP-defined analyses

For TEAE two summary tables were presented as described in previous section with one modification: the first table was displaying all TEAE during the Double-Blind Period instead of limiting it TEAE with a relative TEAE start date less equal 84 days.

The definitions of AE of special monitoring were updated with the third SAP Amendment after the interim analysis. The interim analysis used the previous definition which is displayed in

Section 4.3.1.2. The interim analysis only displayed the overall number of AE of special monitoring by treatment group.

~~The definitions of time since first diagnosis of AS and time since first symptoms were updated with the third SAP Amendment after the interim analysis. In the previous definitions the date of informed consent was subtracted from the date of diagnosis or first symptoms which results in negative values. For the interim analysis following calculations were used:~~

$$\textit{Time since first diagnosis (years)} = \frac{\textit{Date of Informed Consent} - \textit{Date of diagnosis}}{365.25}$$

$$\textit{Time since first symptoms (years)} = \frac{\textit{Date of Informed Consent} - \textit{Date of first symptoms}}{365.25}$$

Section 4.3.1.2 Search and selection criteria for AE of special monitoring for interim analysis Week 12

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Section 4.3.2 Interim analysis Week 48

After all enrolled subjects have completed the Week 48 or Early termination visit, a second interim analysis will be performed to analyze the key efficacy and safety data for the whole treatment period.

No separate SAP for that interim analysis will be provided. The interim analysis is a subset of the final analysis and will focus on the primary and secondary efficacy analysis. The TFL shells for the final analysis will be used.

The snapshot for the AS0008 interim analysis Week 48 will occur before all subjects have completed the AS0008 study. Specifically, subjects who do not enter the extension study will need to complete the SFU Visit, which occurs 20 weeks after the last dose of study treatment. The Week 48 interim database lock will be performed based on the last subject completing the Week 48 visit. It is anticipated that there will be some subjects still awaiting the SFU at that time. The number of subjects in that position is expected to be low, and the minimal data to be collected from their SFU visits is not considered mandatory to evaluation of the key efficacy and safety objectives of the study.

Section 6.4 Prior and concomitant medications

Prior medications include any medications that started prior to the start date of study medication. Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first study medication administration. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For bimekizumab, the dosing period is typically from the date of first dose up to (but not including) one dosing interval post last dose. Thus, a concomitant medication is any medication whose start date is on or after the date of first study medication and prior to the date of last study medication administration + 28 days (1 dosing interval), and whose stop date is either missing, or on or after

the date of first study medication administration. Medications may be both prior and concomitant.

In the case of missing data, the classification of medications as prior or concomitant will be performed as described in Section 4.2.3. Imputations of missing data will be performed before calculation of relative study days.

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Has been changed to

Prior medications include any medications that started **and ended** prior to the start date of study medication. ~~Past medications are a subset of prior medications, and include prior medications with a stop date before the date of first study medication administration.~~ Concomitant medications are medications taken at least one day in common with the study medication dosing period. For bimekizumab, the dosing period is typically from the date of first dose up to (but not including) one dosing interval post last dose. Thus, a concomitant medication is any medication whose start date is on or after the date of first study medication and prior to the date of last study medication administration + 28 days (1 dosing interval), and whose stop date is either missing, or on or after the date of first study medication administration. Medications may be both prior and concomitant.

In the case of missing data, the classification of medications as prior or concomitant will be performed as described in Section 4.2.3. ~~Imputations of missing data will be performed before calculation of relative study days.~~

…

Section 7 Measurements of treatment compliance

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where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes treatment 12 doses are expected (Baseline and every 4th week afterwards until Week 48). If a subject discontinues early, then the number of expected doses is based on the time of early discontinuation relative to the dosing visits.

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group.

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Has been changed to

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where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes treatment 12 doses are expected (Baseline and every 4th week afterwards until Week 4**4**~~8~~). If a subject discontinues early, then the number of expected doses is based on the time of early discontinuation relative to the dosing visits. **If a dose is not completely given at a specific visit (eg, subject only received one injection instead of the two planned injections), then the subject will be considered to have no compliance for the visit. In the formula above it will be counted as no dose received at this visit.**

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group **for the overall treatment period as well as for double-blind treatment period**.

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Section 8.3 Statistical analysis of other efficacy variables

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Time to onset of ASAS20 response and ASAS40 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

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Has been changed to

…

Time to onset of ASAS20 response and ASAS40 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates. Subjects who discontinue study ~~treatment~~ prior to achieving a response will be censored at the date of study ~~treatment~~ discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

…

Section 10.1 Extent of exposure

The duration of exposure (in days) will be calculated as:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (12)$$

28 days refer to one half-life of bimekizumab. If a change of treatment occurs prior to completion of the dosing interval, duration of exposure to study medication will be calculated as:

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ injection \quad (13)$$

For subjects who have died the exposure will be as follows:

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ injection + 1 \quad (14)$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose and the duration of exposure will be performed.

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (15)$$

where 140 days refers to 5*half-life of bimekizumab.

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \end{aligned} \quad (16)$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose\ + 1 \end{aligned} \quad (17)$$

Has been changed to

The duration of exposure (in days) will be calculated as:

$$\begin{aligned} &Duration\ of\ exposure \\ &\quad = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \end{aligned} \quad (12)$$

28 days refer to one half-life of bimekizumab. ~~If a change of treatment occurs prior to completion of the dosing interval, duration of exposure to study medication will be calculated as:~~

$$\begin{aligned} &\sout{Duration\ of\ exposure} \\ &\quad \sout{= Date\ of\ treatment\ change - Date\ of\ first\ injection} \end{aligned} \quad \sout{(13)}$$

For subjects who have died the exposure will be as follows:

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ injection + 1 \quad (\mathbf{13}\sout{14})$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose and the duration of exposure will be performed.

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (\underline{14}\sout{15})$$

where 140 days refers to 5*half-life of bimekizumab.

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose + 1 \end{aligned} \quad (\underline{15}\sout{16})$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose + 1 \end{aligned} \quad (\underline{16}\sout{17})$$

Section 10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (18)$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$\begin{aligned} &Time\ since\ first\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset - date\ of\ first\ dose + 1 \end{aligned} \quad (19)$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$\begin{aligned} &Time\ since\ most\ recent\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset \\ &\quad - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \end{aligned} \quad (20)$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (17 and 18) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

Has been changed to

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \qquad (\underline{17}\sout{18})$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2 **and Table 12–1**: Calculation rules for duration of adverse events.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - date\ of\ first\ dose + 1 \qquad (\underline{18}\sout{19})$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \qquad (\underline{19}\sout{20})$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (**18**~~17~~ and **19**~~18~~) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

Section 10.2.2 Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \qquad (21)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [18] in years) at the level of coding evaluated.

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (15) is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \qquad (22)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (23)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (24)$$

where N_{AE} is the total number of AEs.

No confidence interval will be computed for EAER.

Has been changed to

The EAIR is defined as the number of subjects (n_{AE}) with a specific AE adjusted for the exposure and will be scaled to 100 patient-years:

$$EAIR = 100 * \frac{n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (\underline{\mathbf{20}}\sout{21})$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [18] in years) at the level of coding evaluated, **$\underline{n_{noAE}}$ the number of subjects without the specific AE and $\underline{T_{Risk,j}}$ the total time at risk scaled to 100 patient-years (equation [14] in years).**

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (**$\underline{14}$**~~15~~) **in years** is used.

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

$$LCL = \frac{\chi^2_{2n_{AE},\frac{\alpha}{2}}}{2} \quad (\underline{\mathbf{21}}\sout{22})$$

$$UCL = \frac{\chi^2_{2(n_{AE}+1),1-\alpha/2}}{2} \quad (\underline{\mathbf{22}}\sout{23})$$

$$CI_{Lower} = 100 * \frac{LCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (\underline{\mathbf{23}})$$

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (\underline{24})$$

where n_{AE} is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [**18**] in years) at the level of coding evaluated, **n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (equation [14] in years).**

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (\underline{25}\sout{24})$$

where N_{AE} is the total number of AEs, **$T_{Risk,j}$ is a subject's total time at risk in years and n_{All} the number of subjects.**

No confidence interval will be computed for EAER.

Section 10.3 Clinical laboratory evaluations

The routine clinical laboratory evaluations specified in Table 10–1 and will be summarized. If any additional analytes are also recorded then these will be listed only.

Different summary tables for hematology and biochemistry variables will be provided: observed values and change from Baseline, from Baseline to maximum post-Baseline value, from Baseline to minimum post-baseline value, shift from Baseline to end of treatment, shift from Baseline to end of double-blind treatment, and markedly abnormal laboratory data.

…

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	Albumin
Eosinophils	Chloride	Bacteria
Lymphocytes	Magnesium	Crystals
Atypical lymphocytes	Potassium	Glucose
Monocytes	Sodium	pH
Neutrophils	Glucose	RBC
Hematocrit	BUN	WBC
Hemoglobin	Creatinine	Urine dipstick for pregnancy testing[a]

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
MCH	AST	
MCHC	ALT	
MCV	ALP	
Platelet count	GGT	
RBC count	Total bilirubin	
WBC count	LDH	
	Uric acid	
	Total cholesterol	
	Serum pregnancy testing[a]	
	CRP[b]	
	hs-CRP[b]	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=gamma glutamyltransferase; hs-CRP=high sensitivity C-reactive protein; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SFU=Safety Follow-up; WBC=white blood cell

[a] A serum pregnancy test will be performed at Screening for all women of childbearing potential. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles and women during menopause. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause (International Menopause Society, 2015). A urine pregnancy test is also required at the Baseline, Week 48, ET, and at SFU visits. A urine pregnancy test will also be performed at any study visit where there has been a delay in menses. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles. Pregnancy test results must be negative prior to administering IMP.

[b] Both CRP and hs-CRP will be tested at specified visits per Protocol Table 5.1.

…

Has been changed to

The routine clinical laboratory evaluations specified in Table 10–1 and will be summarized. If any additional analytes are also recorded then these will be listed only.

Different summary tables for hematology and biochemistry variables will be provided**, based on data from scheduled visits**: observed values and change from Baseline, from Baseline to maximum post-Baseline value, from Baseline to minimum post-baseline value, shift from Baseline to end of treatment, ~~shift from Baseline to end of double-blind treatment,~~ and markedly abnormal laboratory data.

End of treatment will be defined as the Week 48 visit or the early termination assessment depending if the subject discontinued early or not.

…

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	~~Albumin~~
Eosinophils	Chloride	Bacteria
Lymphocytes	Magnesium	Crystals
~~Atypical lymphocytes~~	Potassium	Glucose
Monocytes	Sodium	pH
Neutrophils	Glucose	RBC
Hematocrit	BUN	WBC
Hemoglobin	Creatinine	Urine dipstick for pregnancy testing[a]
MCH	AST	
MCHC	ALT	
MCV	ALP	
Platelet count	GGT	
RBC count	Total bilirubin	
WBC count	LDH	
	Uric acid	
	Total cholesterol	
	Albumin	
	Serum pregnancy testing[a]	
	CRP[b]	
	~~hs-~~CRP[b]	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=gamma glutamyltransferase; hs-CRP=high sensitivity C-reactive protein; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SFU=Safety Follow-up; WBC=white blood cell

[a] A serum pregnancy test will be performed at Screening for all women of childbearing potential. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles and women during menopause. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause (International Menopause Society, 2015). A urine pregnancy test is also required at the Baseline, Week 48, ET, and at SFU visits. A urine pregnancy test will also be performed at any study visit where there has been a delay in menses. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles. Pregnancy test results must be negative prior to administering IMP.

[b] Both CRP and hs-CRP will be tested at specified visits per Protocol Table 5.1.

…

Section 12.1 Calculation rules for duration of adverse events

The calculation rules for duration of AEs are presented in Table 12–1. AE duration is computed and reported in day.

Table 13–1: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Complete data	D1	D2	Duration = D2 – D1 + 1
Start date missing	-	D2	Duration = < D2 – D0 Where, for a subject in the FAS, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day
End date missing	D1	-	Duration = > Discharge day – D1 For resolved and ongoing AE Duration Where discharge refers to the date of Visit 16 (Week 48) or date of discontinuation
Start and end date missing	-	-	Duration = > Discharge day – D0 For resolved and ongoing AE Duration Where, for a subjects in the FAS, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day, Discharge refers to the date of Visit 16 (Week 48) or date of discontinuation.

Has been changed to

The calculation rules for duration of AEs are presented in Table 12–1. AE duration is computed and reported in day.

Table 13–1: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Complete data	D1	D2	Duration = D2 – D1 + 1
Start date missing	-	D2	Duration = < D2 – D0 **+ 1** Where, for a subject in the **SS**~~FAS~~, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day
End date missing	D1	-	Duration = > **Final contact date**~~Discharge day~~ – D1 **+1** For resolved and ongoing AE Duration ~~Where discharge refers to the date of Visit 16 (Week 48) or date of discontinuation~~

Table 13–1: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Start and end date missing	-	-	Duration = > **Final contact date**~~Discharge day~~ – D0 **+ 1** For resolved and ongoing AE Duration Where, for subjects in the **SS**~~FAS~~, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day~~,~~ ~~Discharge refers to the date of Visit 16 (Week 48) or date of discontinuation.~~

13.5 Amendment 5

13.5.1 Rationale for the amendment

The main objectives are to describe the different presentation of the safety assessments and to define the additional two analysis sets for efficacy analyses.

13.5.2 Modifications and changes

Section 1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required interim and final statistical analysis for study AS0008. It also defines the summary tables, figures, and listings (TFLs) to be generated in the clinical study report according to the final protocol (29 Jul 2016) and Protocol Amendment 1 (15 Mar 2017).

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Has been changed to

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required interim and final statistical analysis for study AS0008. It also defines the summary tables, figures, and listings (TFLs) to be generated in the clinical study report according to the final protocol (29 Jul 2016)**,** ~~and~~ Protocol Amendment 1 (15 Mar 2017)**, and Protocol Amendment 2 (09 Mar 2018)**.

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Section 3.3 Definition of Baseline values

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The exception of the above rule are the questionnaires collected from the vendor ERT. For those measurement, the last valid measurement at the same day as Visit 2 will be used as the Baseline value.

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Has been changed to

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The exception of the above rule are the questionnaires collected from the vendor ERT **and measurements for C-reactive protein (CRP) and high sensitivity C-reactive protein (hs-CRP).** For those measurement, the last valid measurement at the same day as Visit 2 will be used as the Baseline value.

…

Section 3.6 Analysis sets

The primary efficacy variable will be analyzed for all subjects in the FAS. The supportive analysis for the primary efficacy variables will be performed for Randomized Set (RS), PPS, and FAS. All other efficacy variables will be based on the FAS. Demographics tables will be performed for FAS as well as Safety Set (SS). Safety variables will be summarized using the SS. In addition, safety analyses during the Dose-Blind Period will be conducted on all subjects in the Dose-Blind Set (DBS). PK variables will be analyzed for all subjects in the Pharmacokinetics

Per-Protocol Set (PK-PPS). PD variables will be analyzed for all subjects in the Pharmacodynamics Per-Protocol Set (PD-PPS).

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Section 3.6.9 Escape Subject Set (ESS)

The Escape Subject Set (ESS) consists of all subjects starting the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have not achieved at least a 10% reduction from Baseline in PGADA and total and nocturnal spinal pain at either Week 16, Week 24, or Week 36.

Section 3.6.10 Dose-Blind Responder Set (DBRS)

The Dose-Blind Responder Set (DBRS) consists of all subjects starting the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have achieved at least a 10% reduction from Baseline in PGADA and total and nocturnal spinal pain at Week 16, Week 24, and Week 36.

Has been changed to

The primary efficacy variable will be analyzed for all subjects in the FAS. The supportive analysis for the primary efficacy variables will be performed for Randomized Set (RS), PPS, and FAS. All other efficacy variables will be based on the FAS. Demographics tables will be performed for FAS**,** ~~as well as~~ Safety Set (SS)**, and Dose-Blind Set (DBS)**. Safety variables will be summarized using the SS. In addition, safety analyses during the Dose-Blind Period will be conducted on all subjects in ~~the Dose-Blind Set (~~DBS~~)~~. PK variables will be analyzed for all subjects in the Pharmacokinetics Per-Protocol Set (PK-PPS). PD variables will be analyzed for all subjects in the Pharmacodynamics Per-Protocol Set (PD-PPS).

At the time of the Week 48 interim it was discovered that the Dose-Blind Responder Set (DBRS) and Escape Subject Set (ESS) were defined incorrectly from the original intent. The original intent of the ESS analysis set was to have only those subjects that were eligible to receive rescue therapy, that went on to actually receive rescue therapy, with all other subjects remaining in the DBRS. As such, two extra sets, the Corrected Dose-Blind Responder Set (cDBRS) and Corrected Escape Subject Set (cESS) have been added. These analysis sets will correctly select out those subjects that were eligible and received rescue medication. All outputs created on the DBRS and ESS will also be produced on the cDBRS and cESS to give full transparency of the difference. Further all outputs using the DBRS and ESS will be repeated on the DBS and this analysis will be used as the main analysis of the Dose-Blind as this analysis set is the most unbiased set.

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Section 3.6.9 Escape Subject Set (ESS)

The ~~Escape Subject Set (~~ESS~~)~~ consists of all subjects starting the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have not achieved at least a 10% reduction from Baseline in PGADA and total and nocturnal spinal pain at either Week 16, Week 24, or Week 36.

Section 3.6.10 Dose-Blind Responder Set (DBRS)

The ~~Dose-Blind Responder Set (~~DBRS~~)~~ consists of all subjects starting the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have achieved at least a 10% reduction from Baseline in PGADA and total and nocturnal spinal pain at Week 16, Week 24, and Week 36.

3.6.11 Corrected Escape Subject Set (cESS)

The cESS is a corrected version of the ESS, which was incorrectly defined previously. The cESS consists of subjects that have shown less than a 10% improvement in SJC and TJC at either Week 16, Week 24, or Week 36 and received rescue therapy.

3.6.12 Corrected Dose-Blind Responder Set (cDBRS)

The cDBRS is a corrected version of the DBRS, which was incorrectly defined previously. The cDBRS consists of subjects that have shown at least a 10% improvement in SJC or TJC at Week 16, Week 24 and Week 36. Subjects that would be in the cESS, including subjects that discontinue, that did not receive rescue therapy will be in the cDBRS.

Section 3.7

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Depending on the analysis sets, subjects will be summarized and listed based on the actual received treatment or according to the randomization which will be considered as planned treatment:

- All subjects screened/ES: planned treatment
- RS: planned treatment
- SS: actual treatment
- FAS: planned treatment
- PPS: planned treatment
- PK-PPS: actual treatment
- PD-PPS: actual treatment
- DBS: actual treatment
- ESS: planned treatment
- DBRS: planned treatment

Has been changed to

…

Depending on the analysis sets, subjects will be summarized and listed based on the actual received treatment or according to the randomization which will be considered as planned treatment:

- All subjects screened/ES: planned treatment
- RS: planned treatment

- SS: actual treatment
- FAS: planned treatment
- PPS: planned treatment
- PK-PPS: actual treatment
- PD-PPS: actual treatment
- DBS: **planned treatment (demographics, baseline characteristics, and efficacy analyses) or** actual treatment
- ESS: planned treatment
- DBRS: planned treatment

Text added for Section 4.2.1 Handling of missing data for efficacy analysis

The imputation model will be applied for each treatment group separately. However, in the event there are computational challenges with the imputation model (eg, due to a standard deviation of 0 for responses of a given imputation), it is acceptable to modify the imputation model to include treatment as a variable in the model rather than running a separate model for each treatment group. It should be noted that doing so assumes that treatment does not interact with any of the other variables in the imputation model.

Section 4.2.3 Handling of missing data for prior and concomitant medication

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant and for the calculation of relative study days.

…

Has been changed to

Any medications with incomplete start and end dates/times will be handled according to the following rules for classification as prior and concomitant ~~and for the calculation of relative study days~~.

…

Section 4.3.1.1 added

Section 4.3.1.1 Changes from interim analysis Week 12 to SAP-defined analyses

The baseline definition for CRP and hs-CRP measurements were updated with the fifth SAP Amendment after the interim analysis. The interim analysis used the previous definition: The last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value.

Section 4.3.2 Interim analysis Week 48

…

The snapshot for the AS0008 interim analysis Week 48 will occur before all subjects have completed the AS0008 study. Specifically, subjects who do not enter the extension study will

need to complete the SFU Visit, which occurs 20 weeks after the last dose of study treatment. The Week 48 interim database lock will be performed based on the last subject completing the Week 48 visit. It is anticipated that there will be some subjects still awaiting the SFU at that time. The number of subjects in that position is expected to be low, and the minimal data to be collected from their SFU visits is not considered mandatory to evaluation of the key efficacy and safety objectives of the study.

Has been changed to

…

The snapshot for the AS0008 interim analysis Week 48 will occur before all subjects have completed the AS0008 study. Specifically, subjects who do not enter the extension study will need to complete the SFU Visit, which occurs 20 weeks after the last dose of study treatment. The Week 48 interim database lock will be performed based on the last subject completing the Week 48 visit. It is anticipated that there will be some subjects still awaiting the SFU at that time. The number of subjects in ~~that position~~ **the SFU period** is expected to be low, and the minimal data to be collected from their SFU visits is not considered mandatory to evaluation of the key efficacy and safety objectives of the study.

Section 4.3.2.1 and Section 4.3.2.2 added

Section 4.3.2.1 Changes from interim analysis to SAP-defined analyses

The baseline definition for CRP and hs-CRP measurements were updated with the fifth SAP Amendment after the interim analysis. The interim analysis used the previous definition: The last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline vale.

Section 4.3.2.2 Changes during interim analysis to SAP-defined analyses

At the time of the Week 48 interim it was discovered that the DBRS and ESS were defined incorrectly from the original intent. The original intent of the ESS analysis set was to have only those subjects that were eligible to receive rescue therapy, that went on to actually receive rescue therapy, with all other subjects remaining in the DBRS. As such, two extra sets, the cDBRS and cESS have been added. These analysis sets will correctly select out those subjects that were eligible and received rescue medication. For the final analysis, all outputs created on the DBRS and ESS will also be produced on the cDBRS and cESS to give full transparency of the difference. Further all outputs using the DBRS and ESS will be repeated on the DBS and this analysis will be used as the main analysis of the Dose-Blind as this analysis set is the most unbiased set.

Section 6.1 Demographics

…

The summary tables will be performed on the SS and repeated using the FAS. If the SS and FAS analysis sets are identical the summaries will not be repeated. The Listing will be provided for all subjects screened, except the Lifestyle listing will use the RS.

Has been changed to

…

The summary tables will be performed on the SS and repeated using the FAS**, and the DBS**. If the SS and FAS analysis sets are identical the summaries will not be repeated. The Listing will be provided for all subjects screened, except the Lifestyle listing will use the RS.

Section 6.2 Other Baseline characteristics

…

Baseline characteristics (including scores relevant for inclusion and exclusion criteria) will be summarized by treatment group and overall for FAS and SS. Following variables will be summarized:

…

Has been changed to

…

Baseline characteristics (including scores relevant for inclusion and exclusion criteria) will be summarized by treatment group and overall for FAS**,** ~~and~~ SS**, and DBS**. Following variables will be summarized:

…

Section 6.4 Prior and concomitant medications

Prior medications include any medications that started and ended prior to the start date of study medication. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For bimekizumab, the dosing period is typically from the date of first dose up to (but not including) one dosing interval post last dose. Thus, a concomitant medication is any medication whose start date is on or after the date of first study medication and prior to the date of last study medication administration + 28 days (1 dosing interval), and whose stop date is either missing, or on or after the date of first study medication administration. Medications may be both prior and concomitant.

…

Has been changed to

Prior medications include any medications that started and ended prior to the start date of study medication. Concomitant medications are medications taken at least one day in common with the study medication dosing period. For bimekizumab, the dosing period is typically from the date of first dose up to (but not including) one dosing interval post last dose. Thus, a concomitant medication is any medication whose start date is on or after the date of first study medication and prior to the date of last study medication administration + 28 days (1 dosing interval), **or** whose stop date is either missing, or on or after the date of first study medication administration. ~~Medications may be both prior and concomitant.~~

…

Section 7 Measurements of treatment compliance

…

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group for the overall treatment period as well as for Double-Blind treatment period.

A by-subject listing of treatment compliance will be provided.

Has been changed to

…

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group for the overall treatment period as well as for Double-Blind treatment period. **For the Double-Blind treatment period compliance will refer to the first 12 weeks and will be presented by treatment received at baseline. For the overall treatment period, the compliance will be calculated for the following three groups: bimekizumab 160mg, bimekizumab 320mg, and all bimekizumab. Treatment compliance for the bimekizumab 160mg and 320mg group will be calculated for the time the subject receives 160mg or 320mg, eg for a subject who switches from Placebo or bimekizumab 16mg to bimekizumab 160mg at Week 12, the compliance will only be calculated for the time the subject receives bimekizumab 160mg. The all bimekizumab group will consist of all the doses of bimekizumab including bimekizumab 16mg, and will only exclude the time subjects receive Placebo.**

A by-subject listing of treatment compliance will be provided**, presenting percent compliance and numbers of expected and received doses for the Double-Blind Period and for treatment with any dose of bimekizumab.**

Section 8.3 Statistical analysis of other efficacy variables

All other efficacy variables in the Double-Blind Period will be analyzed for all subjects in the FAS. For the Dose-Blind Period, other efficacy variables will be analyzed for all subjects in the DBRS, and ESS.

…

Has been changed to

~~All other efficacy variables in the Double-Blind Period will be analyzed for all subjects in the FAS. For the Dose-Blind Period, other efficacy variables will be analyzed for all subjects in the DBRS, and ESS.~~

Other efficacy variables will be analyzed for all subjects in the FAS, DBRS, ESS, cDBRS, cESS, and DBS.

…

Section 9.1 Pharmacokinetics

Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit using the PK-PPS analysis set.

…

Has been changed to

Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit using the PK-PPS, ~~analysis set~~ **and using a subset of the DBS which includes subjects that belong to both analysis sets, the DBS and the PK-PPS.**

…

Section 9.2 Pharmacodynamics and Immunogenicity

The biomarker data will be separated between LGC assays, mulitplex proinflammatory cytokine and chemokine analysis, flow cytometry - TBNK panel, and flow cytometry - Th1/Th2/Th17/Th22 panel. Biomarker variables will be summarized and listed for each treatment at each scheduled visit using the PD-PPS analysis set.

…

In addition the time point of the first occurrence of AbAb positivity during the treatment period (excluding Baseline and pre-treatment) will be summarized for each treatment group.

…

Has been changed to

The biomarker data will be separated between LGC assays, mulitplex proinflammatory cytokine and chemokine analysis, flow cytometry - TBNK panel, and flow cytometry - Th1/Th2/Th17/Th22 panel. Biomarker variables will be summarized and listed for each treatment at each scheduled visit using the PD-PPS, ~~analysis set~~ **and using a subset of the DBS which includes subjects that belong to both analysis sets, the DBS and the PK-PPS.**

…

In addition**,** the time point of the first occurrence of AbAb positivity during the **Double-Blind Period, and the entire** treatment period (excluding Baseline and pre-treatment) will be summarized for each treatment group.

…

Section 10.1 Extent of exposure

The duration of exposure (in days) will be calculated as:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (12)$$

28 days refer to one half-life of bimekizumab.

For subjects who have died the exposure will be as follows:

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ injection + 1 \quad (13)$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose and the duration of exposure will be performed.

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (14)$$

where 140 days refers to 5*half-life of bimekizumab.

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \end{aligned} \tag{15}$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose\ + 1 \end{aligned} \tag{16}$$

Has been changed to

The duration of exposure and time at risk will be summarized for the Double-Blind Period and the entire treatment period. For the entire treatment period the duration of exposure and time at risk will be calculated for bimekizumab 160mg, bimekizumab 320mg, and all bimekizumab. The calculation of exposure duration and time at risk for the all bimekizumab group is different from that of the other two groups. For all bimekizumab the duration of exposure and time at risk will include the time a subject received any dose of bimekizumab (including 16mg or 64mg) while for the other two treatment groups only the time a subject received 160mg, or 320mg will be included into the calculation.

Duration of exposure Double-Blind Period

The duration of exposure (in days) during the Double-Blind Period will be calculated as:

$$\begin{aligned} &Duration\ of\ exposure \\ &\quad = Date\ of\ last\ injection\ (double-blind\ period) \\ &\quad - Date\ of\ first\ injection\ (double-blind\ period) + 28 \end{aligned} \tag{12}$$

28 days refer to one half-life of bimekizumab.

Note: If the date of last injection (Double-Blind Period) + 28 extends to a date beyond the date of first injection (Dose-Blind Period), then this calculation reverts to

$$\begin{aligned} &Duration\ of\ exposure \\ &\quad = Date\ of\ first\ injection\ (dose-blind\ period) \\ &\quad - Date\ of\ first\ injection\ (double-blind\ period) + 1 \end{aligned} \tag{13}$$

For subjects who die during the Double-Blind Period, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection\ (double - blind\ Period) + 1 \quad (14)$$

Duration of exposure entire treatment period

For subjects who do not switch study treatments, or who receive bimekizumab 16mg or 64mg will be summarized under all bimekizumab group:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (15)$$

Note: If the date of last injection +28 extends to a date beyond the final visit date (not including SFU), then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection + 1 \quad (16)$$

For subjects who die, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection + 1 \quad (17)$$

For subjects who receive Placebo or bimekizumab 16mg or 64mg in the Double-Blind Period and will be summarized under their Dose-Blind treatment in the overall table group bimekizumab 160mg or 320mg, or subjects who received Placebo and will be summarized in the overall table under their Dose-Blind treatment:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 28 \quad (18)$$

Note: If the date of last dose +28 extends to a date beyond the final visit date (not including SFU), then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (19)$$

For subjects who die during the Dose-Blind Period, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (20)$$

The sum over all duration of exposure (in years) will be calculated for the total subject-years of duration of exposure.

The duration of exposure will be summarized by treatment group using descriptive statistics. A by-subject listing of date of first and last dose **in Double-Blind Period, the date of first and last dose in Dose-Blind Period** and the duration of exposure **during Double-Blind Period and under bimekizumab treatment (any dose of bimekizumab)** will be performed.

Time at risk Double-Blind Period

For subjects who complete the final visit of the Double-Blind Period and continue to the Dose-Blind Period:

$$Time\ at\ risk = Date\ of\ first\ injection\ (dose - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (21)$$

For subjects who discontinue on or prior to the final visit of the Double-Blind Period, use the minimum of the following:

$$Date\ of\ last\ injection\ (double - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 140 \quad (22)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (23)$$

$$Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (24)$$

where 140 days refers to 5*half-life of bimekizumab.

For subjects who die during the Double-Blind Period, then this calculation reverts to:

$$Date\ of\ death - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (25)$$

Time at risk entire treatment period

For subjects who do not switch study treatments, or who receive bimekizumab 16mg or 64mg and will be summarized under all bimekizumab group:

For subjects who complete the Dose-Blind Period and enter the extension study:

$$Time\ at\ risk = Date\ of\ Visit\ 16\ (Week\ 48) - Date\ of\ first\ injection + 1 \quad (26)$$

For subjects who die prior to the final visit:

$$Time\ at\ risk = Date\ of\ death - Date\ of\ first\ injection + 1 \quad (27)$$

For all other subjects, use the minimum of the following:

$$Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (28)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection + 1 \quad (29)$$

For subjects who receive Placebo or bimekizumab 16mg or 64mg in the Double-Blind Period and will be summarized under their Dose-Blind treatment in the overall table group bimekizumab 160mg or 320mg, or subjects who received Placebo and will be summarized in the overall table under their Dose-Blind treatment:

For subjects who complete the Dose-Blind Period and enter the extension study:

$$Time\ at\ risk = Date\ of\ Visit\ 16\ (Week\ 48) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (30)$$

For subjects who die during the Dose-Blind Period:

$$Time\ at\ risk = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (31)$$

For all other subjects, use the minimum of the following:

$$Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 140 \quad (32)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (33)$$

The sum over all time at risk (in years) will be calculated for the total subject-years of time at risk.

The days on treatment and days on bimekizumab treatment will be calculated as follows:

$$Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \quad (34)$$

$$Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose\ + 1 \quad (35)$$

Section 10.2 Adverse events (AEs)

…

The incidence of TEAEs will be summarized by MedDRA system organ class, high level term, and PT. Tables with incidences of classified TEAEs by maximum intensity, by relationship, and by subject number will be provided. The incidence of non-serious TEAEs above the reporting threshold of 5% of subjects and relationship will be summarized. Furthermore the incidence of all TEAEs, serious TEAEs, non-serious TEAEs, and TEAEs leading to study discontinuation and/or permanent withdrawal of study medication will be summarized. In addition an overall summary table will be provided.

Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER) will be calculated for following tables in the final analysis: all TEAEs, serious TEAEs, TEAEs leading to study discontinuation and/or permanent withdrawal, ADRs, fungal infectious disorder TEAEs, opportunistic infection (including tuberculosis) TEAEs, malignant or unspecified tumor TEAEs, malignant tumor TEAEs, major cardiovascular event TEAEs, haematopoietic cytopenias TEAEs, neuropsychiatric events TEAEs, inflammatory bowel disease TEAEs, hypersensitivity and anaphylactic Reaction TEAEs, hepatic events TEAEs, and TEAEs by timing of onset relative to AbAb Status.

Has been changed to

…

The incidence of TEAEs will be summarized by MedDRA SOC, high level term, and PT. Tables with incidences of classified TEAEs by maximum intensity, by relationship, and by subject number will be provided. The incidence of non TEAEs, non-serious TEAEs above the reporting threshold of 5% of subjects and relationship will be summarized. Furthermore the incidence of all TEAEs, serious TEAEs, non-serious TEAEs, and TEAEs leading to study discontinuation and/or permanent withdrawal of study medication, adverse drug reactions, fungal infectious disorder TEAEs, opportunistic infection (including tuberculosis) TEAEs, malignant or unspecified tumor TEAEs, malignant tumor TEAEs, major cardiovascular event TEAEs, haematopoietic cytopenias TEAEs, neuropsychiatric events TEAEs, inflammatory bowel disease TEAEs, hypersensitivity and anaphylactic Reaction TEAEs, hepatic events TEAEs, and TEAEs by timing of onset relative to AbAb Status will be summarized. In addition, an overall summary table will be provided.

The tables will be split into the Double-Blind Period and the complete treatment period (exception non TEAE table and TEAEs by timing of onset relative to AbAb Status). Presentations for the Double-Blind Period will summarize AEs that start prior to or at Visit 7 (see details given above) by treatment group as randomized for the Double-Blind Period. Presentations for the complete treatment period will only summarize AEs that occur under treatment with bimekizumab, irrespective of the treatment period. For summaries of the bimekizumab 160mg, and bimekizumab 320mg treatment groups, patients randomized to Placebo, bimekizumab 16mg or 64mg at Baseline will only be included with AEs that start in the Dose-Blind Period. The all bimekizumab treatment group will also present AEs occurring under bimekizumab 16mg or 64mg treatment in the Double-Blind Period. AEs for each subject will be summarized based on the treatment actually received at the onset of each particular AE.

Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER) will only be calculated for the complete treatment period for following tables in the final analysis: all TEAEs, serious TEAEs, TEAEs leading to study discontinuation and/or permanent withdrawal, adverse drug reactions, fungal infectious disorder TEAEs, opportunistic infection (including tuberculosis) TEAEs, malignant or unspecified tumor TEAEs, malignant tumor TEAEs, major cardiovascular event TEAEs, haematopoietic cytopenias TEAEs, neuropsychiatric events TEAEs, inflammatory bowel disease TEAEs, hypersensitivity and anaphylactic Reaction TEAEs, hepatic events TEAEs, and TEAEs by timing of onset relative to AbAb Status.

Section 10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (17)$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2 and Table 12–1.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - date\ of\ first\ dose + 1 \quad (18)$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (19)$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (18 and 19) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

Has been changed to

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (\mathbf{36}\sout{17})$$

For the calculation of duration for AEs with missing start dates, the dates will be imputed as described in Section 4.2.2 and Table 12–1.

The time to first dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - date\ of\ first\ dose + 1 \quad (\underline{37}\sout{18})$$

The time to most recent dose for each AE will be calculated as follows for all TEAEs:

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (\underline{38}\sout{19})$$

Time to first dose and time to most recent dose will not be calculated for pretreatment AEs.

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (**37**~~18~~ and **38**~~19~~) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

Section 10.2.2 E**xposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER)**

The EAIR is defined as the number of subjects (n_{AE}) with a specific AE adjusted for the exposure and will be scaled to 100 patient-years:

$$EAIR = 100 * \frac{n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (20)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [18] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (equation [14] in years).

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (14) in years is used.

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

$$LCL = \frac{\chi^2_{2n_{AE},\frac{\alpha}{2}}}{2} \quad (21)$$

$$UCL = \frac{\chi^2_{2(n_{AE}+1),1-\alpha/2}}{2} \quad (22)$$

$$CI_{Lower} = 100 * \frac{LCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (23)$$

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (24)$$

where n_{AE} is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [18] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (equation [14] in years).

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (25)$$

where N_{AE} is the total number of AEs, $T_{Risk,j}$ is a subject's total time at risk in years and n_{All} the number of subjects.

No confidence interval will be computed for EAER.

Has been changed to

The EAIR is defined as the number of subjects (n_{AE}) with a specific AE adjusted for the exposure and will be scaled to 100 patient-years:

$$EAIR = 100 * \frac{n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (\underline{39}\sout{20})$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [**<u>36</u>**~~18~~] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (Section 10.1 ~~equation [14] in years~~).

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (Section 10.1 ~~14~~) in years is used. **<u>As indicated above, exposure-adjusted incidence rates will only be calculated for the overall treatment period. These presentations do not include AEs that occur under Placebo treatment. Therefore, a subject's exposure time will only</u>**

start at the first dose of bimekizumab in the Dose-Blind Period for subjects randomized to Placebo at Baseline. Also, for subject's randomized to bimekizumab 16mg or 64mg at Baseline, exposure time will only be considered from the start of Dose-Blind Period, when presenting AEs for the bimekizumab 160mg, or bimekizumab 320mg groups. All exposure time on any bimekizumab dose is considered for the all bimekizumab column.

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

$$LCL = \frac{\chi^2_{2n_{AE},\frac{\alpha}{2}}}{2} \quad (40\text{~~21~~})$$

$$UCL = \frac{\chi^2_{2(n_{AE}+1),1-\alpha/2}}{2} \quad (41\text{~~22~~})$$

$$CI_{Lower} = 100 * \frac{LCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (42\text{~~23~~})$$

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (43\text{~~24~~})$$

where n_{AE} is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [**36**~~18~~] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (Section 10.1 ~~equation [14] in years~~).

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (44\text{~~25~~})$$

where N_{AE} is the total number of AEs, $T_{Risk,j}$ is a subject's total time at risk in years and n_{All} the number of subjects.

No confidence interval will be computed for EAER.

Section 10.3 Clinical laboratory evaluations

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Different summary tables for hematology and biochemistry variables will be provided, based on data from scheduled visits: observed values and change from Baseline, from Baseline to

maximum post-Baseline value, from Baseline to minimum post-baseline value, shift from Baseline to end of treatment, and markedly abnormal laboratory data.

End of treatment will be defined as the Week 48 visit or the early termination assessment depending if the subject discontinued early or not.

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Has been changed to

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Different summary tables for hematology and biochemistry variables will be provided, based on data from scheduled visits: observed values and change from Baseline, **shift** from Baseline to maximum post-Baseline value **(in Double-Blind Period), shift from Baseline to maximum post-Baseline value (in Dose-Blind Period), shift** from Baseline to minimum post-Baseline value **(in Double-Blind Period)**, **shift from Baseline to minimum post-Baseline value (in Dose-Blind Period)**, shift from Baseline to end of treatment **(in Double-Blind Period), shift from Baseline to end of treatment (in Dose-Blind Period),** and markedly abnormal laboratory data.

End of treatment (in Double-Blind Period) will be defined as the last visit in the Double-Blind Period or the early termination assessment depending if the subject discontinued in the Double-Blind Period.

End of treatment **(in Dose-Blind Period)** will be defined as the Week 48 visit or the early termination assessment depending if the subject discontinued early or not.

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Table 10-5 updated to align with Table 12-4 from the Protocol Amendment 2.

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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