STATISTICAL ANALYSIS PLAN

Study: PS0015

Product: Bimekizumab

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, SECUKINUMAB-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

SAP/Amendment Number	Date
Final SAP	29-Mar-2019
Amendment 1	21-Feb-2020
Amendment 2	15-Jun-2020
Amendment 3	21-Jan-2021
Amendment 4	14-Mar-2022

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ACP	above cut point
ADAb	anti-drug antibodies
AE	adverse event
AH	abnormal high
AL	abnormal low
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCP	below cut point
BMI	body mass index
BSA	body surface area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CP	confirmed positive
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CV-CAC	Cardiovascular Clinical Event Adjudication Committee
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
EQ-5D-3L	European Quality-of-Life 5-Dimensions 3-Level
EudraCT	European Union Drug Regulating Authorities Clinical Trials
GGT	gamma-glutamyltransferase
FAS	Full Analysis Set
HLT	High Level Term

IGA	Investigator’s Global Assessment
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
LOCF	last observation carried forward
MACE	Major adverse cardiac events
MAR	missing at random
MCID	minimally important clinical difference
MCMC	Markov-Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mNAPSI	Modified Nail Psoriasis Severity Index
MS	Maintenance Set
NCP	not confirmed positive
NRI	nonresponder imputation
OLE	open-label extension
OLE2	open-label extension 2
OLS	open-label set
OLS2	open-label set 2
OC	Observed case
PASE	Psoriatic Arthritis Screening and Evaluation
PASI	Psoriasis Area Severity Index
PD	pharmacodynamic(s)
pDILI	potential drug induced liver injury
PEOT	Premature End of Treatment
PGA	Patients Global Assessment
PGADA	Patient's Global Assessment of Disease Activity
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic(s)
PK-PPS	Pharmacokinetics Per-Protocol Set
pp-IGA	palmoplantar Investigator’s Global Assessment
PPS	Per-Protocol Set
PsA	psoriatic arthritis

PSD	patient symptom diary
PSO	psoriasis
PT	preferred term
Q4W	every 4 weeks
Q8W	every 8 weeks
QOL	quality of life
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
sc	subcutaneous(ly)
scalp IGA	scalp-specific Investigator's Global Assessment
SD	standard deviation
SFU	Safety Follow-Up
SFU2	Safety Follow-Up 2
SIB	suicidal ideation and behavior
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire-specific health problem

1 INTRODUCTION

This statistical analysis plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report. The SAP is based on the following study documents: Protocol Amendments 5.4 (US) 01 Oct 2021, and 5.5 (Canada) 08 Dec 2021.

2 PROTOCOL SUMMARY

2.1 Study objectives

2.1.1 Primary objectives

The primary objective of this study is to compare the efficacy of bimekizumab administered subcutaneously (sc) for 16 weeks versus secukinumab at achieving complete clearance (PASI100) in subjects with moderate to severe chronic plaque psoriasis (PSO).

2.1.2 Secondary objectives

The secondary objectives of the study are to:

- Evaluate the efficacy of bimekizumab compared with secukinumab after 4 weeks, 16 weeks, and 48 weeks of treatment.
- Assess treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal adjusted by duration of subject exposure to investigational medicinal product (IMP).

2.1.3 Other objectives

The other objectives of the study are to demonstrate the effects of bimekizumab on the following aspects of the disease:

- Assess the efficacy of bimekizumab over time
- Assess the change of skin-related quality of life (QOL)
- Assess the change of general health-related QOL
- Assess the change in nail PSO over time in subjects with nail PSO at Baseline
- Assess the change in psoriatic scalp disease over time in subjects with scalp PSO at Baseline
- Assess the change in psoriatic palmoplantar disease over time in subjects with palmoplantar PSO at Baseline
- Assess the change in patient global assessment PSO score
- Assess the change in symptoms of PSO (itch, pain, and scaling) as reported by subjects
- Assess work productivity status
- Assess the safety and tolerability of bimekizumab
- Assess the pharmacokinetics (PK) of bimekizumab
- Assess the immunogenicity of bimekizumab

- Assess the maintenance of efficacy of bimekizumab dosing Q4W versus Q8W
- Assess the safety and efficacy of initiating bimekizumab therapy in subjects who received secukinumab in the double-blind Treatment Period

2.2 Study variable(s)

2.2.1 Efficacy variable(s)

2.2.1.1 Primary efficacy variable

The primary efficacy variable is the PASI100 response, defined as complete clearance from Baseline in the Psoriasis Area Severity Index (PASI) score, at Week 16.

2.2.1.2 Secondary efficacy variables

The secondary efficacy variables are:

- PASI75 response at Week 4
- PASI90 response at Week 16
- PASI100 response at Week 48
- Investigators Global Assessment (IGA) response (Clear or Almost Clear with at least 2-category improvement relative to Baseline) at Week 16

2.2.1.3 Other efficacy variables

The other efficacy variables are:

- PASI75, PASI90, and PASI100 response
- Time to PASI75, PASI90, and PASI100 response
- Absolute and percent change from Baseline in PASI
- Percentage of subjects with PASI ≤1, ≤2, ≤3, and ≤5
- IGA response (Clear with at least 2 category improvement relative to Baseline)
- IGA response (Clear or Almost Clear with at least 2 category improvement relative to Baseline)
- Shift from Baseline in IGA score
- Absolute and percent change from Baseline in the body surface area (BSA) affected by PSO
- Percent of subjects with absolute BSA=0%, ≤1%, ≤3% and ≤5%
- Absolute and percent change from Baseline in the product of IGA and BSA (IGAxBSA)
- Change from Baseline in Dermatology Life Quality Index (DLQI) total score
- Percent of subjects achieving a DLQI total score of 0 or 1
- Percent of subjects achieving a minimal clinically important difference (MCID) (improvement from Baseline of 4 or more) in the DLQI total score

- Change from Baseline in the Patient's Global Assessment of Disease Activity (PGADA) for the arthritis visual analog scale (VAS) in subjects with psoriatic arthritis (PsA) at Baseline
- Shift from Baseline in Patient Global Assessment of PSO score
- Change from Baseline in symptoms of PSO (itch, pain, and scaling)
- Patient Symptom Diary responses for itch, pain, and scaling
- Change from Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) score for subjects with nail PSO at Baseline
- mNAPSI75 response (defined as a subject that achieves at least a 75% reduction from Baseline in the mNAPSI score) for subjects with nail PSO at Baseline
- mNAPSI90 response (defined as a subject that achieves at least a 90% reduction from Baseline in the mNAPSI score) for subjects with nail PSO at Baseline
- mNAPSI100 response (defined as a subject that achieves a 100% reduction from Baseline in the mNAPSI score) for subjects with nail PSO at Baseline
- Scalp IGA response (clear or almost clear with at least a two-category improvement from Baseline) for subjects with scalp PSO at Baseline
- Palmoplantar Investigator's Global Assessment (pp-IGA) response (clear or almost clear with at least a two-category improvement from Baseline) for subjects with palmoplantar PSO at Baseline
- Responses to the European Quality-of-Life 5-Dimensions 3-Level (EQ-5D-3L) dimensions, absolute and changes from Baseline in EQ-5D-3L VAS scores
- Change from Baseline in Work Productivity and Activity Impairment Questionnaire-specific health problem (WPAI-SHP) V2.0 adapted to PSO scores
- Change from Baseline in the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire scores (function score, symptom score, and total score)
- Shift from Baseline in PASE score suggestive of PsA (<47 versus ≥47)

2.2.2 Pharmacokinetic/pharmacodynamic variable

The PK variable is the plasma concentration of bimekizumab. Pharmacokinetic samples from subjects receiving secukinumab will not be analyzed, but stored for potential future PK analysis and anti-drug antibody determination.

No assessment of pharmacodynamics will be done.

2.2.3 Safety variable(s)

2.2.3.1 Secondary safety variables

The secondary safety variables include the following treatment emergent adverse events (TEAEs) and serious adverse events (SAEs).

- TEAEs adjusted by duration of subject exposure to IMP
- SAEs adjusted by duration of subject exposure to IMP

- TEAEs leading to withdrawal adjusted by duration of subject exposure to study treatment

2.2.3.2 Other safety variables

Other safety variables to be assessed are:

- Severity and frequency of adverse events (AEs) (including serious AEs)
- Change from Baseline in vital signs
- Electrocardiogram (ECG) results
- Change from Baseline in clinical laboratory values (chemistry and hematology)
- Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) scores

Physical examination findings considered clinically significant changes since the physical examination at the Screening Visit will be recorded as AEs.

2.2.4 Immunological variable

The immunological variable is the anti-bimekizumab antibody level prior to and following IMP administration.

2.3 Study design and conduct

2.3.1 Study description

PS0015 is a randomized, double-blind, secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab administered sc to subjects with moderate to severe chronic plaque PSO. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe plaque PSO (PASI ≥12 and BSA ≥10% and IGA score ≥3 [on a 5-point scale]) who are candidates for secukinumab, or for systemic PSO therapy and/or phototherapy.

2.3.2 Study periods

This study will include 5 periods, a Screening Period (2 to 5 weeks), a double-blind Treatment Period (48 weeks; final dose at Week 44), an optional open-label extension (OLE) Period (96 weeks, final dose at Week 136 for subjects receiving bimekizumab 320mg Q8W and at Week 140 for subjects receiving bimekizumab 320mg Q4W, followed by a safety follow-up (SFU) Period (20 weeks after the final dose of IMP). Eligible subjects from US and Canada sites who have completed the OLE Period (at Week 144), including subjects in the SFU period and subjects who have completed the SFU Period will have the option to enroll in the 48-week Open-Label Extension 2 (OLE2) Period followed by a SFU Period (SFU2, 20 weeks after the final dose of IMP administered in the OLE2).

The double-blind treatment Period will be separated into an Initial Treatment Period (16 weeks) and a Maintenance Treatment Period (32 weeks). The end of the study is defined as the date of the last visit of the last subject in the study.

Subjects withdrawing early from the study will undergo the premature end of treatment (PEOT) Visit assessments and will enter the SFU Period. Following completion or early withdrawal from the OLE2 Period, subjects will undergo the SFU of the OLE2 Period (SFU2) and will return for the SFU2 Visit 20 weeks after the last dose of IMP administration in the OLE2 treatment period.

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

- Screening Period: Prior to the date of first dose of study drug
- Initial Treatment Period is defined as the time from the first study drug administration up to the start of the Maintenance Treatment Period
- Maintenance Treatment Period starts with the first study drug administration at or after the Week 16 visit
- Open-Label Extension Period starts with the first study drug administration at or after the Week 48 visit
- SFU Period is 20 weeks after the final dose of IMP in the double-blind Treatment Period or Open-Label Extension Period
- Open-Label Extension 2 Period starts with the first study drug administration at or after the Week 144/OLE2 Baseline visit
- SFU2 Period is 20 weeks after the final dose of IMP in the OLE2.

The Double-blind Treatment Period ends either at the Week 48 visit for subjects completing the double-blind Treatment Period, or at PEOT Visit for subjects who discontinued early during the double-blind Treatment Period. If a subject does not have a Week 48/PEOT visit, then the date of the last scheduled or unscheduled visit during the double-blind Treatment Period will define the end date of the double-blind Treatment Period.

The Open-Label Treatment Period ends either at the Week 144 visit for subjects completing the Open-Label Treatment Period, or at PEOT Visit for subjects who discontinued early during the Open-Label Treatment Period. If a subject does not have a Week 144/PEOT visit, then the date of the last scheduled or unscheduled visit during the Open-Label Treatment Period will define the end date of the Open-Label Treatment Period.

The OLE2 Treatment Period ends either at the OLE2 Week 48 visit for subjects completing the OLE2 Period, or at PEOT Visit for subjects who discontinued early during the OLE2 Period. If a subject does not have an OLE2 Week 48/PEOT visit, then the date of the last scheduled or unscheduled visit during the OLE2 Period will define the end date of the OLE2 Period.

2.3.2.1 Screening Period

The Screening Period will last 2 weeks but can be extended up to a total of 5 weeks in cases where a laboratory assessment needs to be repeated or to allow washout of prohibited medications. During this time, eligible subjects will be informed about the study and sign the Informed Consent Form, laboratory data (hematology, urine, and biochemistry tests) will be obtained, and the doses of medications used to treat PsA (if applicable) will be verified as stable. The Screening Period will also enable washout of any medications not permitted for use during the study. Subjects who require prophylaxis for latent tuberculosis infection must be on treatment for at least 8 weeks prior to their first dose of IMP. These subjects may be rescreened once they have completed the first 8 weeks of prophylaxis treatment.

One rescreening may be allowed after consultation with the Medical Monitor.

2.3.2.2 Initial Treatment Period

During the first 16 weeks of the 48-week double-blind Treatment Period, approximately 700 subjects will be randomized 1:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered sc every 4 weeks (Q4W) (350 subjects)
- Secukinumab 300mg administered sc at Baseline and Weeks 1, 2, 3, and 4 followed by dosing Q4W (350 subjects)

Subjects receiving bimekizumab 320mg will receive placebo sc on Weeks 1, 2, and 3 in order to maintain the blind.

Subjects will be classified as completing the initial treatment period if they complete the Week 16 Visit without early withdrawal from the study or if they start treatment in the maintenance treatment period. The start of the maintenance treatment period marks the end of the initial treatment period.

2.3.2.3 Maintenance Treatment Period

At Week 16 subjects in the bimekizumab 320mg treatment arm will be re-randomized 1:2 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W. To maintain the blind after re-randomization, subjects in the bimekizumab 320mg Q8W treatment arm will receive placebo at Weeks 20, 28, 36, and 44. Subjects in the secukinumab arm will continue to receive secukinumab 300mg Q4W.

Subjects will be classified as completing the maintenance treatment period if they complete the Week 48 Visit without early withdrawal from the study or if they start treatment in the Open-Label period. The start of the Open-Label extension period marks the end of the maintenance treatment period for subjects opting to participate in the OLE period. Otherwise the end of the maintenance period is marked by the Week 48 visit.

2.3.2.4 OLE Period

After completion of the Week 48 visit assessments, subjects will be allowed to enroll in the OLE Period. All subjects enrolling in the OLE Period will sign a new ICF, and then receive the following IMP regimens as determined by the subject's treatment regimen and PASI response in the double-blind Treatment Period.

At Week 48, subjects receiving:

- Bimekizumab 320mg Q4W who achieve PASI90 at Week 48 of the double-blind Treatment Period will be randomized 1:1 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W.
- Bimekizumab 320mg Q4W who do not achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q4W.
- Bimekizumab 320mg Q8W who achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q8W.
- Bimekizumab 320mg Q8W who do not achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q4W.

- Secukinumab who achieve PASI90 at Week 48 of the double-blind Treatment Period will be randomized 1:1 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W.
- Secukinumab who do not achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q4W.

From Week 64 the subjects who are receiving bimekizumab 320mg Q4W at the time of implementation of protocol amendment 5.0 will have their dosing interval changed to bimekizumab 320mg Q8W at the next clinical site assessment as described on Table 7–2 for subjects who are receiving bimekizumab 320mg Q4W and have reached Week 96 prior to the implementation of Protocol Amendment 5.0, if PASI90 is achieved, the subject's dosing interval will change from 320mg Q4W to 320mg Q8W (default), unless, based on medical judgment, the Investigator decides differently. Otherwise, if PASI90 is not achieved they will have their dosing interval changed to bimekizumab 320mg Q8W at the next clinical site assessment after implementation of protocol amendment 5.0 as detailed above.

During the OLE Period, subjects will attend study visits at Weeks 52, 56, 64, and 72, and then every 12 weeks. At study visits, IMP will be administered in the clinic by sc injection as applicable. In between study visits, subjects will self-inject IMP at home. Subjects who are unable to or decide not to self-inject IMP or those without a family member/friend/caregiver who can help, will not be discontinued, but may continue to visit the site for unscheduled visits for IMP administration only.

All subjects not enrolling in the Open-Label study will have the Week 48 study assessments and will enter the SFU Period.

2.3.2.5 OLE2 Period

After the implementation of Protocol Amendment #5.4 and 5.5 (with the addition of a 48-week Open-Label treatment period, ie, OLE2 Period), subjects from US and Canada sites will be invited to continue or reinitiate their treatment as per the following OLE2 Groups:

- OLE2 Group A: Subjects in the treatment phase of the OLE Period at the time of Protocol Amendment #5.4 and 5.5 implementation will attend the Week 144 Visit and directly roll over to the OLE2 Period. These subjects will continue receiving bimekizumab 320mg Q8W for 40 additional weeks, starting from the first treatment visit of the OLE2 Period (ie, Week 144/OLE2 Baseline Visit; the Week 144 Visit will coincide with the Week 144/OLE2 Baseline Visit and data collected at this visit will be used as baseline data for the OLE2 Period)
- OLE2 Group B: Eligible subjects who have completed the Week 144 Visit and are in the SFU or have completed the SFU of the OLE Period at the time of Protocol Amendment #5.4 and 5.5 implementation, will be eligible to reinitiate their treatment in the OLE2 Period after having undergone additional screening assessments during a 4-week OLE2 Screening Period
  - The first dose of the IMP will be administered at the OLE2 Baseline Visit and data collected at this visit will be used as baseline data for the OLE2 Period
  - Subjects in OLE2 Group B with an IGA score ≥3 at the OLE2 Baseline Visit will receive bimekizumab Q4W for the first 16 weeks, and then will switch to bimekizumab 320mg Q8W

- Subjects in OLE2 Group B with an IGA score <3 at the OLE2 Baseline Visit will receive bimekizumab Q8W from the OLE2 Baseline Visit.

Following completion or early withdrawal from the OLE2 Period, subjects will enter the SFU2 and will return for the SFU2 Visit 20 weeks after the last dose of IMP administration.

2.3.2.6 Safety Follow-Up

All subjects, including those withdrawn from IMP, will have a SFU Visit 20 weeks after their final dose of IMP.

Two SFU Periods are considered following the implementation of Protocol Amendments #5.4 and #5.5:

- SFU following the OLE Period following the initial, maintenance, and OLE treatment periods
- SFU2 following the OLE2 treatment period.

2.3.2.7 Premature End of Treatment

Subjects withdrawing early from the study will undergo PEOT Visit assessments and will enter the SFU Period or SFU2 Period depending on when subjects withdraw from the study.

2.3.3 Study duration per subject

For each subject not entering the OLE2 treatment period, the study will last a maximum of up to 165 weeks, as follows:

- Screening Period: 2 to 5 weeks
- Double-blind Treatment Period: 48 weeks (final dose at Week 44)
- OLE Period: 96 weeks (final dose at Week 136 for subjects receiving bimekizumab 320mg Q8W and at Week 140 for subjects receiving bimekizumab 320mg Q4W)
- Safety Follow-Up Period: an SFU Visit is planned 20 weeks after the final dose of IMP during the OLE period (this SFU will not apply to subjects directly rolling over from the OLE to the OLE2 Period).

The OLE2 Period will include a 48-week treatment period with a final visit at OLE2 Week 48 and a SFU2 period of 20 weeks after the final dose of IMP administered in the OLE2 Period.

For the subjects in the OLE2 Period, maximum study duration will depend on the time between their participation in the OLE until Week 144 and the start of the OLE2 Period:

- 209 weeks for subjects still being treated in the OLE Period and who will directly roll over to the OLE2 Period at Week 144 visit
- 225 weeks for subjects who have completed Week 144 and the SFU; these subjects will have a 4-week Screening Period before reinitiating treatment in the OLE2 Period. Note: for these subjects, the study duration will not be continuous
- Between 209 and 225 weeks for subjects who have completed Week 144 and are ongoing in the SFU. For these subjects, the maximum study duration will depend upon when they stop the 20-week SFU period to enter the 4-week OLE2 Screening Period.

2.3.4 Planned number of subjects and sites

Approximately 935 subjects will be screened in order to have 700 subjects randomized in the study. There will be approximately 350 subjects in the bimekizumab 320mg treatment arm and 350 subjects in the secukinumab 300mg treatment arm. The planned number of study sites is approximately 86 from approximately 11 countries and 4 geographical regions.

2.3.5 Anticipated regions and countries

The regions and countries planned for study conduct are North America (Canada, USA), Western Europe (Belgium, France, Germany, Netherlands, Spain, United Kingdom), Central/Eastern Europe (Poland), Asia/Australia (Australia, Turkey).

An additional OLE2 will be conducted in US and Canada only.

2.4 Determination of sample size

A total of 700 subjects will be randomly assigned in a 1:1 ratio at Baseline to one of the following treatment groups:

- Bimekizumab 320mg (350 subjects)
- Secukinumab 300mg (350 subjects).

The primary efficacy analysis is based on the comparison of bimekizumab to secukinumab for the primary efficacy variable of PASI100 response at Week 16. The assumed responder rates for PASI100 at Week 16 are 60% and 44% for bimekizumab and secukinumab, respectively. The assumed responder rate for bimekizumab is based on the Phase 2b PS0010 data. The assumptions related to the responder rates for secukinumab are based on those observed in the CLEAR study (Thaçi et al, 2015). The power to show statistical superiority of bimekizumab relative to secukinumab under these assumptions is 98% for the primary endpoint. The power for the non-inferiority comparison (with 10% non-inferiority margin) under these assumptions is >99%.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using Statistical Analysis Software (SAS) Version 9.3 or higher. All tables and listings will use Courier New font size 9.

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

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

- For summaries of demographics and Baseline characteristics: summarize percentages based on all subjects in the analysis set and include a “Missing” category (corresponding to subjects

with missing data for the variable being summarized) as the last row in the list of categories being summarized.

- For summaries of efficacy and safety endpoints, unless otherwise specified: summarize percentages based only on those subjects with observed data for the variable being summarized. As the denominator may be different from the number of subjects in the analysis set being considered, the denominator should be displayed in the table. The general format for displaying this will be "n/Nsub (%)."

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

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

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

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

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

Statistical tests of efficacy variables will be presented as two-sided p-values rounded to three 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 two-sided and will be performed at the 0.05 level of significance.

Per protocol, visit windows of ±3 days from the first dose to Week 24, ±7 days from Week 28 to Week 72 and ±14 days from Week 76 to Week 144 are permissible. For the SFU Visit, visit window is 20 weeks ±7 days from final dose.

Per protocol, visit windows of ±14 days from the first OLE2 dose at all OLE2 visits except SFU2 are permissible, the SFU2 visit window is 20 weeks ±7 days from final dose in OLE2.

All by-visit summaries will contain nominal (i.e. scheduled) visits only. Unscheduled visits will not be mapped to scheduled visits except for assessments that occur within a 3-day time window of a scheduled visit. In that case, the assessment will be mapped to the corresponding scheduled visit and will be used for the analysis. This will only occur for some vendor data.

A complete set of data listings containing all documented data as well as calculated data (e.g. change from Baseline) will be generated. Separate data listings will be generated for the OLE2 period.

3.2 Definition of Baseline values

A Baseline value for a subject is defined as the latest measurement for that subject up to and including the day of administration of first study medication, unless otherwise stated. If a Baseline assessment is taken on the same day as first administration of study medication, it is eligible to be used as the Baseline value, even in the case that the time of the assessment is recorded as taking place after the time of first study medication administration. This is considered acceptable as this measurement is still the best representation of the Baseline value of the given assessment since it is highly unlikely that the study medication could have an impact on any measurement in such a short period of time. However, such cases should be rare as study center personnel are instructed to do all assessments at the Baseline visit prior to administering study medication. One exception to this rule is plasma concentration. If Baseline plasma concentration is measured at a time after the first administration of study medication, then it should not be eligible to be considered as a Baseline plasma concentration. Such cases should be discussed with the quantitative clinical pharmacologist.

If a Baseline measurement is missing or not collected, and a Screening value is available, the Screening value will be utilized as Baseline instead.

Baseline values for component scores should be computed using components from the same visit where the relevant measurements were recorded prior to dosing. For example, if the Screening visit has all of the components, but the Baseline visit is missing one or more components, the Baseline value for the component score should be calculated using the Screening visit values.

When the time of first dose is derived, it should be based on the first injection of study treatment, regardless of whether or not it is an active treatment.

Unless specified otherwise, the process laid out above will always be followed to determine Baseline. An additional Baseline value for the OLE Period will be defined for anti-bimekizumab antibodies for subjects initially randomized to secukinumab and for selected summaries of laboratory evaluations. This baseline for the OLE Period is the latest measurement on/prior to the day of first dose in the OLE Period for subjects switching from secukinumab to bimekizumab.

Note that for any laboratory value that occurs on the day of treatment switch, that lab value will be attributed and summarized for the treatment the subjects were on previously.

For subjects enrolled in OLE2, the OLE2 first dose will be administered at the Week 144/OLE2 Baseline Visit and data collected at this visit will be used as baseline data for safety data in the OLE2 Period. Efficacy data will continue to use the Week 0 Visit as Baseline.

3.3 Mapping of data from early withdrawal visits

If the early withdrawal visit (PEOT visit) occurs at a scheduled visit as outlined in the schedule of assessments, then no mapping is necessary and any early withdrawal assessments should correspond to that scheduled visit. Premature visits that occur between scheduled visits will be assigned to the next scheduled visit. This approach means that there is a chance that data collected will be mapped to a visit where the given assessment would not have been collected as per the protocol schedule of assessments. Such data would not be summarized in by-visit tables (though it would be available in the listings).

The only exception to the above rule is for anti-bimekizumab antibody assessments, in which all early withdrawal visit assessments will be assigned to the next scheduled visit at which anti-bimekizumab antibody are assessed.

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

3.4 Protocol deviations

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

Deviations related to the Coronavirus Disease 2019 (COVID-19) global pandemic are unavoidable deviations from the protocol due to confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 without infection or any other deviation from the protocol due to COVID-19. COVID-19 protocol deviations will also be reviewed separately as part of the ongoing data cleaning process.

3.5 Analysis sets

3.5.1 Enrolled Set

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

3.5.2 Randomized Set

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

3.5.3 Safety Set

The Safety Set (SS) will consist of all subjects that received at least 1 dose of IMP.

3.5.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the RS that receive at least 1 dose of the IMP and have a valid PASI measurement at Baseline.

3.5.5 Maintenance Set

The Maintenance Set (MS) will consist of all subjects that receive at least 1 dose of IMP at Week 16 or later in the double-blind Treatment Period (including the Week 16 dose).

3.5.6 Open-Label Set

The Open-label Set (OLS) will consist of all subjects that received at least 1 dose of bimekizumab at Week 48 or later in the OLE Period (including the Week 48 dose).

3.5.7 Open-Label Set 2

The Open-label Set 2 (OLS2) will consist of all subjects that received at least 1 dose of bimekizumab at Week 144/OLE2 Baseline Visit or later in the OLE2 Period.

3.5.8 Per Protocol Set

The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding of the data.

3.5.9 Pharmacokinetics Per-Protocol Set

The Pharmacokinetics Per-Protocol Set (PK-PPS) consists of all randomized subjects who received at least 1 dose of the IMP and provided at least 1 quantifiable post-dose plasma concentration without important protocol deviations that would affect the concentration.

3.5.10 Bimekizumab Set

The Bimekizumab Set (BKZ Set) consists of all randomized subjects who received at least 1 dose of bimekizumab in the double-blind or Open-Label extension treatment period.

3.6 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 a treatment arm had never received such treatment, then for safety analysis, these subjects will be reallocated to the appropriate received treatment groups, unless otherwise specified.

If subjects randomized to secukinumab received bimekizumab at any time, then for safety analyses these subjects will be reallocated to the appropriate bimekizumab treatment group, unless otherwise specified. Subjects randomized to bimekizumab will only be reallocated to the secukinumab treatment group if they never received bimekizumab.

Efficacy analyses should be performed according to randomized treatment and not actual treatment received.

Randomized treatment groups are Bimekizumab 320mg Q4W and Secukinumab 300mg Q4W. Maintenance treatment groups are Bimekizumab 320mg Q4W, Bimekizumab 320mg Q8W, and Secukinumab 300mg Q4W.

Re-randomized (Open-Label extension) treatment groups are Bimekizumab 320mg Q4W and Bimekizumab 320mg Q8W. Unless otherwise specified, the OLE period will be summarized by treatment sequence comprising randomized treatment at Baseline and OLE period treatment at Week 48.

The following treatment sequences will be used to summarize efficacy data and specific safety data related to laboratory, ECG, PHQ-9, eC-SSRS, and vital signs assessments:

- Subjects receiving bimekizumab in the double-blind treatment period:
  - Initiating OLE on bimekizumab Q8W

  - Initiating OLE on bimekizumab Q4W
- Subjects receiving secukinumab in the double-blind treatment period
  - Initiating OLE on bimekizumab Q8W
  - Initiating OLE on bimekizumab Q4W
- All Subjects

Adverse event data (including for a subgroup of subjects who switched from Q4W to Q8W during OLE period) and study compliance data will be summarized in 2 treatment groups based on the dose most recently received prior to the date of the event or assessment

- Bimekizumab 320mg Q8W
- Bimekizumab 320mg Q4W
- Bimekizumab Total

In addition, the following key efficacy variables:

- PASI90 response
- PASI100 response
- IGA Clear or Almost Clear (with at least a 2-category improvement from Baseline)
- IGA Clear (with at least a 2-category improvement from Baseline)

will be summarized for the Open-Label Extension treatment period by the following randomized treatment sequences:

- Bimekizumab Q4W/Q8W/Q4W for non-responder at Week 48 (<PASI90)
- Bimekizumab Q4W/Q4W/Q4W for non-responder at Week 48 (<PASI90)
- Secukinumab / Bimekizumab Q4W for non-responder at Week 48 (<PASI90)
- Bimekizumab Q4W/Q8W/Q8W for responder at Week 48 (>=PASI90)
- Bimekizumab Q4W/Q4W/Q8W for responder at Week 48 (>=PASI90)
- Bimekizumab Q4W/Q4W/Q4W for responder at Week 48 (>=PASI90)
- Secukinumab / Bimekizumab Q8W for responder at Week 48 (>=PASI90)
- Secukinumab / Bimekizumab Q4W for responder at Week 48 (>=PASI90)

Safety and efficacy assessments for the OLE2 period will only include subjects who entered the OLE2 period and will be summarized based on OLS2, by the assigned treatment as follows:

- Subjects who enroll directly from the OLE treatment period: Group A
  - Bimekizumab Q8W Group A
- Subjects in Group B who reinitiate bimekizumab after having completed treatment in the OLE and have an IGA <3 upon entry to the OLE2: Group B
  - Bimekizumab Q8W Group B

- Subjects in Group B who reinitiate bimekizumab after having completed treatment in the OLE and have an IGA ≥3 upon entry to the OLE2: Group B
  - Bimekizumab Q4W/Q8W Group B
- For safety summaries only
  - BKZ Total.

3.7 Center pooling strategy

Centers will be pooled into regions for analysis purposes. Geographic regions will be categorized as North America, Western Europe, Central/Eastern Europe, and Asia/Australia. Below is a table of geographic regions with corresponding countries.

Region	Countries
North America	Canada, United States
Western Europe	Belgium, France, Germany, Netherlands, Spain, United Kingdom
Central /Eastern Europe	Poland
Asia/Australia	Australia, Turkey

For a sensitivity analysis to test center-by-treatment interaction (see Section 8.1.3.6), the following center pooling algorithm might be used for each geographic region:

- If a center has 10 or more subjects, then no pooling will be done for that center.
- Centers with fewer than 10 subjects will be ordered from largest to smallest with pooling proceeding in the following manner:
  - Two or more centers will be combined until the cumulative subject total is at least 10.
  - Once a pooled center has at least 10 subjects, the process will continue in an iterative fashion for the subsequent centers in the ordered list, where a new pooled center begins each time at least 10 subjects has been reached in the previous pool.
  - If this iterative process reaches the end of the ordered list of centers where the final pooled center has fewer than 10 subjects, then the subjects from the centers in that pool will be combined with the pooled center formed in the previous iteration.

This procedure is only to be performed within a geographic region –there will be no pooling of centers across regions.

In the event that the percentage of randomized subjects is less than 10% in either of the Asia/Australia or Western Europe region, the two regions will be combined as a geographic region stratum for all efficacy modeling, so that there are no modeling convergence issues across efficacy variables.

3.8 Coding dictionaries

All medications other than study drug will be classified by WHO Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1),

Pharmacological Subgroup (ATC level 3), and preferred term, using World Health Organization Drug Dictionary (WHO-DD) version SEP/2015 for Week 48 and Week 96 analysis, and version MAR 2021 for Week 144 and Final analysis, according to UCB standard operating procedures (SOP).

All AEs will be classified by primary system organ class (SOC), high level term (HLT) and preferred term (PT) using version 19.0 of Medical Dictionary for Regulatory Activities (MedDRA®) according to UCB SOPs.

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

3.9 Relative day

Relative day will be calculated the following way

- for days on or after the day of first dose of study drug and prior to or on the day of last study drug dose:
  - the current date minus the date of first dose of study drug plus 1 (e.g., the day of first dose will be Day 1).
- for days prior to the first dose of study drug:
  - date of first dose of study drug minus the current date (e.g., the day prior to first dose will be Day -1).
- For days after the last dose of study drug:
  - the current date minus the date of last dose of study drug including a "+" to denote posttreatment days (e.g., the day after the last dose will be Day +1).

Relative day will only be computed for fully completed dates and will be missing for partial dates. Two relative days will be used as follows:

- Compared to the first dose of study drug in the Initial Treatment Period for all subjects
- Compared to the first dose of study drug in the Open-Label Extension 2 Period for subjects in OLS2 only.

3.10 Changes to protocol-defined analyses

The following endpoints are not listed in the protocol, but have been added to the SAP in order to achieve consistency with other studies from the program:

- Percent of subjects with absolute BSA=0%, ≤1%, ≤3% and ≤5%
- Patient Symptom Diary responses for itch, pain, and scaling

The log-rank statistic for time to PASI response as described in Section 8.3.1.2 will be produced by region and prior biologic exposure although this is not specifically stated in the protocol.

The Treatment Period is further divided into two sub periods -Initial Treatment Period and Maintenance Treatment Period- to aid different analysis summaries and help keep consistency with other studies.

The protocol states that subgroup analyses will be performed on the primary and secondary efficacy variables that are part of the fixed sequence testing procedure. However, subgroup analyses will not only be done for PASI75 and PASI100 but also for PASI90. Additionally, subgroup analyses to assess predictability will also use IGA Response (0/1) (see Section 4.8). Urinalysis will not be analysed in summary tables but will only be included in listings.

Section 14.7 of the protocol describes how multiple imputation should be used to analyse other efficacy endpoints. It is mentioned that the imputation model will use the change from Baseline (instead of actual) values by visit. This statement was omitted from SAP Section 4.2.1.3 as actual values will be used in the imputation algorithm and change from baseline will be calculated based on the imputed values.

3.10.1 Changes related to COVID-19

The following changes have been introduced due to the COVID-19 pandemic:

- COVID-19 protocol deviations have been defined in Section 3.4 and the presentation of COVID-19 protocol deviations is described in Section 5.2
- COVID-19 impact on study visits has been assessed and are described in Section 5.1
- COVID-19 Disposition assessments are described in Section 5.1
- Missing data methods for assessing the impact of COVID-19 are described in Section 4.2.1.7
- Data considerations for assessing the impact of COVID-19 on TEAEs including COVID-19 vaccine AEs are described in Section 10.2.1.1 and the associated analysis is described in Section 10.2.2.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

The primary efficacy analyses and selected secondary analyses will be adjusted for the following covariates:

- Prior biologic exposure
- Region

4.2 Handling of dropouts or missing data

4.2.1 Handling of missing data for efficacy variables

Based on previous studies of biologics in subjects with moderate to severe chronic plaque psoriasis, it is expected that the number of subjects who discontinue prior to Week 16 will be low. For the small percentage of subjects for whom primary endpoint data are unavailable at Week 16, this lack of data is suggestive of an ineffective study treatment, thereby supporting the imputation of nonresponse. Achieving the clinical response and making it through 16 weeks of study treatment are both critical components of the primary outcome. Therefore, non-responder imputation (NRI) is considered an appropriate method for handling missing data.

If a subject discontinues early from the study, all efficacy data that are collected later than 35 days after the last administration of study treatment will be treated as missing and subject to imputation as applicable.

Study variables with multiple components may have rules to account for partial missing data of 1 or more components. Such rules will be defined in section 8 for applicable endpoints. The following rules are outlined for cases where variables are completely missing, including partial missing data where the data handling rules conclude that the variable should be treated as completely missing.

4.2.1.1 Handling missing data for the primary efficacy variable

The analysis of the primary efficacy variable will use NRI for handling of missing data. That is, subjects with missing data or who have discontinued IMP prior to Week 16 will be considered as non-responders for the primary analysis.

In addition, sensitivity analyses using multiple imputation (Markov-Chain Monte Carlo method) (MI-MCMC)/monotone regression, last observation carried forward (LOCF) and observed case (OC) method will be performed which will assess the impact of different methods of handling missing data. These methods are described in Section 8.1.3.1 to Section 8.1.3.4.

4.2.1.2 Handling missing data for the secondary efficacy variables

Missing data for the secondary efficacy variables (which are all binary) will be imputed using NRI. Additionally, MI-MCMC/monotone regression and OC methods will be performed as sensitivity analysis. If the imputation model cannot converge, LOCF will be used. The same analyses are detailed in the analysis for the primary efficacy variable in Section 8.1.3.1 and Section 8.1.3.2.

Additional methods for handling missing data to assess the impact of the COVID-19 global pandemic on planned statistical analyses are detailed in Section 4.2.1.7.

4.2.1.3 Handling missing data for the other efficacy variables

For other binary efficacy variables, missing data will be imputed using NRI as primary method.

For other continuous efficacy variables, multiple imputation (MI) will be used to impute missing data when possible. If the imputation model cannot converge, last observation carried forward (LOCF) will be used. The MI procedure will be similar to sensitivity analysis #1 described in Section 8.1.3.1 with the following differences:

1. No dichotomization will be necessary.
2. Instead of using the stratified Cochran-Mantel-Haenszel (CMH) test, the imputed data sets will be combined, and simple means and standard errors will be calculated using Rubin's rules (via SAS PROC MIANALYZE). For calculation of other descriptive statistics such as the median, minimum and maximum, Rubin's rules do not apply. Multiple imputation estimates will be computed by simply averaging the estimates from the multiple repetitions of the imputation algorithm.

For other ordinal variables (IGA score, EQ-5D-3L and Patient Global Assessment of PSO), OC method will be applied as the primary analysis method. No imputation is applied.

4.2.1.4 Handling missing data for subgroup analyses

For subgroup analyses specified in Section 4.8, NRI will be used for responder variables. Only descriptive statistics will be provided.

4.2.1.5 Missing data overview and summary

In summary, the approaches listed below will be used in this study for handling missing data for efficacy variables as appropriate:

- NRI: Subjects who have missing data at the time point of interest are treated as though they did not respond to the treatment.
- MI –MCMC / Monotone Regression: Using multiple imputation methodology, intermittent missing data are imputed based on the MCMC method, and monotone missing data are imputed using monotone regression. Note: for all analyses and summaries using MI, subjects with missing baseline value will be excluded.
- LOCF: Post-Baseline missing data are imputed by carrying forward the last available observation (including Baseline).
- OC: Missing data are not imputed. Only subjects with available data who have not discontinued study treatment at the given time point are considered.

The following table depicts which missing data handling approaches should be used based on variable priority (primary, secondary, other) and variable type (responder, continuous, ordinal).

Table 4–1: Missing data handling approach by variable priority and type

Variable Priority	Variable Type	NRI	MI (MCMC/ Monotone Regression)	LOCF	OC
Primary	Responder	P	S[a]	S	S
Secondary	Responder	P	S[a]	B	S
Other	Responder	P			S[b,c]
	Continuous[e]		P	B	
	Ordinal				P[d]

P=Primary method, S=Sensitivity method, B=Backup method, NRI=Nonresponder imputation, MI=Multiple imputation, MCMC=Markov Chain Monte Carlo, LOCF=Last observation carried forward, OC=Observed Case
Note: Backup method is only applicable when the primary/secondary method is unable to converge due to challenges with the imputation model.
Note: Additional missing data handling approaches are detailed in Section 4.2.1.7 for assessing the impact of COVID-19 on the secondary efficacy variable PASI100 response at Week 48.
[a] Imputation method is applied on continuous data, and responder variable is derived from the continuous variable based on complete data set.
[b] Only applies to by-visit summaries of variables that are in the multiplicity-controlled testing procedure.
[c] Includes IGA Responses, PASI75, PASI90 and PASI100.
[d] Includes IGA score, Patient Global Assessment of PSO and EQ-5D-3L.
[e] For PASE, OC is the primary analysis method.

4.2.1.6 Missing data algorithm – MI – MCMC / Monotone Regression

Investigators will be given discretion to discontinue study treatment for subjects not responding in order to provide them with alternative therapy to treat the condition. Therefore, in many cases, missing efficacy data due to study treatment discontinuation should be dependent on the observed efficacy scores, but independent of unobserved data. This would be consistent with a

missing at random (MAR) pattern of missingness. To investigate the efficacy results under the assumption of data being MAR, a multiple imputation method will be applied as follows (exemplary for PASI100 at Week 16):

1. Create a data set, one for each treatment group (note that a separate imputation procedure must be invoked in SAS for each treatment group as the seed cannot be set for by groups beyond the first when using a by statement, see notes below about treatment groups to use for different analysis sets), of subjects with observed values and those needing estimation by multiple imputation. The intermittent missing PASI/IGA values in each data set (i.e., missing values for a given subject that has available data before and after the missing time point) will be filled in using the MCMC method, with a total of 100 sets of imputations being performed. The seed used for these imputations will be 852 (note that all other multiple imputation procedures described in this SAP related to MCMC/Monotone Regression analyses will use this same seed as well). For monotone missing data (i.e., where all subject data is missing after a given time point), monotone regression will be used to impute missing data. Again, this will be based on the 100 sets of imputations already created using the MCMC method such that there will be 100 imputations in total. In both cases, biologic exposure, geographic region and PASI/IGA values at Baseline and at each post-Baseline visit (in chronological order, see notes below about visits to include for different analysis sets) will be included in the imputation model. Note that PASI scores at earlier visits will also be used as predictors for the model of PASI at later visits. The resulting data sets for each treatment arm will be combined into one complete data set based on each of the 100 imputations.

   Note: The imputation model will only allow continuous variables. Therefore, prior biologic exposure and region will be re-coded as indicator variables. For prior biologic exposure, this will simply be 0 for biologic-naïve subjects and 1 for biologic-exposed subjects. For region, which has 4 levels, one indicator variable will be defined as 0 for regions other than North America and 1 for North America. Two more indicator variables will be defined similarly replacing North America with Central/Eastern Europe, and Western Europe respectively. An indicator variable for Asia/Australia is not needed as the fourth region will be adequately represented by the other region indicator variables all being 0. In the event that the percentage of randomized subjects is less than 10% in either of the Asia/Australia or Western Europe region, the two regions will be combined as a geographic region stratum for efficacy modeling, so that there are no modeling convergence issues across efficacy variables. In order to achieve model convergence, prior biologic exposure may be dropped from the model. If convergence is still not obtained, then region may also be dropped from the model.

2. For each complete imputed data set, the dichotomous responder variable (PASI100) based on the PASI scores will be computed. Each complete imputed data set will then be analyzed based on the stratified CMH test.

   Note: For derivation of PASI100 response, the PASI value at Week 16 in the imputed data sets will be compared directly to the observed Baseline PASI value to determine whether or not a reduction of 100% was achieved. If values outside of the pre-defined

range of values for PASI (0-72) are imputed, they will be cut off as appropriate after the multiple imputation procedure but before deriving the responder variable. For example, an imputed PASI value of -0.5 would be changed to 0 before deriving the PASI100 responder variable.

Note: Standard rounding rules will be applied to the imputed IGA values in order to derive the binary IGA 0/1 responder variable. In addition, if values outside of the pre-defined range of values for IGA (0-4) are imputed, they will be cut off as appropriate after the multiple imputation procedure but before deriving the responder variable. For example, if a subject has an IGA score imputed as 1.4 (and assuming a Baseline IGA score of 3), this imputed value would be rounded down to 1, and the minimum change from Baseline of 2 would have been met. Therefore, this subject would be considered an IGA 0/1 responder.

Additional ranges of values for other variables are defined in Table 4–2.

Table 4–2: Allowable ranges for imputation by variable

Variable	Minimum value	Maximum value	Integer values only
PASI	0	72	No
IGA	0	4	Yes
PSD items (itch, pain, scaling)	0	10	No
Scalp IGA	0	4	Yes
mNAPSI	0	130	No
BSA	0	100	No
IGAxBSA	0	400	No
DLQI	0	30	Yes
PGADA	0	100	No
EQ-5D-3L VAS	0	100	Yes

Variable	Minimum value	Maximum value	Integer values only
WPAI dimension scores	0	100	No for variables: "Percent work time missed due to problem" and "Percent overall work impairment due to problem". Yes for variables: "Percent impairment while working due to problem" and "Percent activity impairment due to problem". These two variables can only take values that are multiples of 10.
PHQ-9	0	27	Yes

3. The Week 16 results from the specified statistical analysis (e.g. stratified CMH, logistic regression) 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:

If stratified CMH or logistic regression are used, the estimates of the odds ratios from the logistic regression model in step 3 follow a log-normal distribution, and 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). Appropriate transformations to the standard errors and p-values should also be made in order to get the correct confidence intervals, for the CMH test using the p-value for the general association the Wilson-Hilferty transformation should be used (Ratitch, 2013).

For other continuous efficacy variables, MI will be used to impute missing data when possible (see Section 4.2.1.3). If the imputation model cannot converge, LOCF will be used.

Further details about imputation for different analysis sets are below:

Randomized Set: When programming multiple imputations based on the RS, PROC MI will be used with a separate data set for each of the 2 randomized treatment groups (bimekizumab 320mg Q4W and secukinumab) including all scheduled assessment visits from Baseline to Week 48.

Maintenance Set: When programming multiple imputation based on the MS, PROC MI will be used with a separate data set for each of the 3 Maintenance Period treatment groups

(bimekizumab 320mg Q8W, bimekizumab 320mg Q4W, secukinumab) including all scheduled assessment visits from Baseline to Week 48.

Open-Label Set: When programming multiple imputations based on the OLS, PROC MI will be used with a separate data set for each of the 6 treatment sequences based on the combination of randomized treatment at Baseline, Maintenance Period treatment and OLE period treatment at Week 48 including all scheduled assessment visits from Baseline to Week 144. However, the summary values for the 4 treatment sequences based on the combination of randomized treatment at Baseline and OLE period treatment at Week 48 will be computed after the imputation steps

The Open-label Set 2: The analyses will be based on OC. Multiple imputation methods described above will not be applied.

4.2.1.7 Missing data methods for assessing impact of COVID-19

In order to assess the impact of the COVID-19 global pandemic on planned statistical analysis, additional sensitivity analyses will be performed for the secondary efficacy variable PASI100 response at Week 48. The sensitivity analyses in Section 8.2.3 will also still be performed, Assessments for the primary efficacy variable and for other secondary efficacy variables are at timepoints prior to Week 48 and will have been performed prior to the pandemic, therefore additional supplementary analyses of these variables are not necessary.

As described in Section 4.2.1, if a subject discontinues early from the study, all efficacy data that are collected later than 35 days after the last administration of study treatment will be treated as missing and subject to imputation as applicable. Thus if a subject discontinues from the study due to COVID-19 (general circumstances related to the COVID-19 pandemic or due to confirmed or suspected infection with the novel coronavirus) and the PASI assessment at Week 48 is later than 35 days after the last administration of study treatment, this will also be treated as missing.

If the PASI assessment at Week 48 is conducted by video call or telephone, this will be treated as missing since the validity and exchangeability of these assessment modalities has not been established. This will be determined according to collection of COVID-19 protocol deviations (including COVID-19 impact assessment) (see Section 3.4 for further details).

4.2.1.7.1 Hybrid approach for assessing impact of COVID-19

The main sensitivity analysis method to assess the impact of the COVID-19 pandemic on planned statistical analysis uses a hybrid approach and will be applied to the analysis of PASI100 response at Week 48 based on both the RS and the MS. If study subjects have missing PASI score at Week 48, then the imputation method is dependent on the reason for missingness as follows:

- If the data is missing due to COVID-19 then MI-MCMC/monotone regression will be implemented following the method described in Step 1 of Section 4.2.1.6 to impute the missing PASI score at Week 48.
- If the data is missing due to other reasons, then PASI100 response at Week 48 will be imputed as a non-response using NRI.

MI-MCMC/monotone regression will be implemented as described in Step 1 of Section 4.2.1.6 for all subjects in the respective analysis set. However when data is missing or the subject discontinued from the study due to other reasons than COVID-19, they will be considered as PASI100 non-responders at Week 48 for each imputation during Step 2 regardless of their MI-MCMC/monotone regression imputed value. Then Step 3 of Section 4.2.1.6 using stratified CMH can be applied for the PASI100 response at Week 48. If the PROC MIANALYZE leads to non-calculable results (ie, if there are a low amount of data missing or subjects dropped out due to COVID-19), this analysis will not be reported.

4.2.1.7.2 Subgroup approach for assessing the impact of COVID-19

A supplementary sensitivity analysis method to assess the impact of the COVID-19 pandemic on PASI100 response at Week 48 will use a subgroup analysis approach and will be based on the MS. The COVID-19 pandemic subgroups are defined as:

- Week 48 visit date before COVID-19 pandemic start date (ie, prior to COVID-19 pandemic)
- Week 48 visit date on or after COVID-19 pandemic start date (ie, during COVID-19 pandemic)

Where:

  - COVID-19 pandemic start date is 11 March 2020. (The date is chosen as the date the World Health Organization declared COVID-19 as a pandemic.)
  - For subjects with a Week 48 visit, the actual date of the Week 48 PASI assessment will be used to determine subgroup inclusion.
  - For subjects without a Week 48 visit, the scheduled Week 48 visit date will be used to determine subgroup inclusion, where:
    - Scheduled Week 48 visit date = date of first dose of study drug + 336 days.

Note:

- It is not anticipated that there will be any Week 48 visits post-pandemic for this study.
- Although the COVID-19 pandemic subgroups are determined based on an event occurring after randomization, the inclusion of a subject in the applicable subgroup is independent of their PASI assessment at Week 48 and is independent of the subject's Baseline characteristics.

This subgroup analysis for PASI100 at Week 48 will include descriptive statistics with missing data imputed using NRI.

4.2.1.7.3 Approach to assess the impact of out of window assessments due to COVID-19

Another supplementary sensitivity analysis method to assess the impact of the COVID-19 pandemic on the planned statistical analyses will treat PASI assessments that are out of window at Week 48 due to COVID-19 as missing. A window of ±21 days relative to the scheduled Week 48 visit will be evaluated. This will be applied to the analysis of PASI100 response at Week 48 based on both the RS and the MS.

The PASI assessment at Week 48 will therefore be determined as out of window due to COVID-19 if the following criteria are both met:

- There is a corresponding out of window COVID-19 protocol deviation (see Section 3.4 for further details)
- Date of first dose of study drug + 315 days > Week 48 PASI assessment date or Week 48 PASI assessment date > date of first dose of study drug + 357 days

A hybrid approach will then be applied as in Section 4.2.1.7.1 such that if the data is missing due to COVID-19 then MI-MCMC/monotone regression will be implemented and if data is missing due to other reasons, then PASI100 response at Week 48 will be imputed as a non-response using NRI. If the PROC MIANALYZE leads to non-calculable results, this analysis will not be reported.

4.2.2 Handling missing data for safety variables

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

Partial or missing AE and concomitant medication start dates will be imputed as follows:

Imputation of Partial or Missing Start Dates

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

Imputation of Partial Stop Dates

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

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

- If the year of imputed start date is the same as the year of first dose and the stop date is after the date of first dose, then set the start date to the date of first dose
- If the month and year of imputed start date is the same as the year and month of the first dose and the same as the year and month of the stop date, and the stop date is prior to the date of first dose then set the start date to the 1st of the month
- Otherwise, set the start date to the 1st of January of the year of the start date.

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

4.3 Interim analyses and data monitoring

The following data cuts will occur, and corresponding interim analyses will be performed:

- After the final Week 48 visit, an interim analysis will be performed and a corresponding Week 48 interim clinical study report (CSR) will be written. For subjects that participate in the OLE period, data will be cut at the day of their Week 48 study drug administration. Data from the OLE will not be included in this interim analysis.
- An additional Week 96 data cut will occur approximately after the last Week 96 visit. A Week 96 analysis will be performed for the Open-Label treatment period using this Week 96 data cut. Selected tables, figures, and listings based on Week 96 data cut will be produced for these analyses as detailed in Section 12.3 (Appendix C). No corresponding CSR for these analyses was planned.
- In addition, a Week 144 data cut will occur after Week 144 visit and SFU. A Week 144 analysis will be performed using Week 144 and SFU data cut and a corresponding Week 144 interim CSR will be written.
- A final analysis will be conducted when all data for the double-blind, OLE (including SFU), and OLE2 (including SFU2) treatment periods have been collected and final CSR will be written.

An independent Data Monitoring Committee (DMC) will periodically review and monitor the safety data from the Double-blind treatment period of this study and advise UCB.

Cardiovascular, Inflammatory bowel disease (IBD), and Neuropsychiatric Adjudication Committees will also periodically review and monitor safety data from this study including two Open-label Extension (OLE and OLE2) treatment periods and advise UCB. Details will be provided in the DMC Charter and in the Adjudication Committee Charters.

Further details related to the DMC will be outlined in a separate analysis plan.

4.4 Multicenter studies

The center-by-treatment interaction will be tested by replacing region with center in the logistic regression model used for the sensitivity analysis (Section 8.1.3.6 and adding a center-by-treatment interaction term. In the model, center will be based on the original centers prior to pooling (Section 3.7). However, if the model is unable to converge due to a low number of subjects at a given center, a pooling by center will be considered. Detailed strategy from

Section 3.7 will be applied in order to allow the model to converge. If convergence is still not achieved, a pooling by region will be applied. If convergence still cannot be achieved, this analysis will not be performed.

4.5 Multiple comparisons/multiplicity

The statistical analysis of the primary efficacy variable and selected secondary efficacy variables will account for multiplicity and control the familywise Type I error rate at a 2-sided alpha level of 0.05 by using a fixed sequence testing procedure.

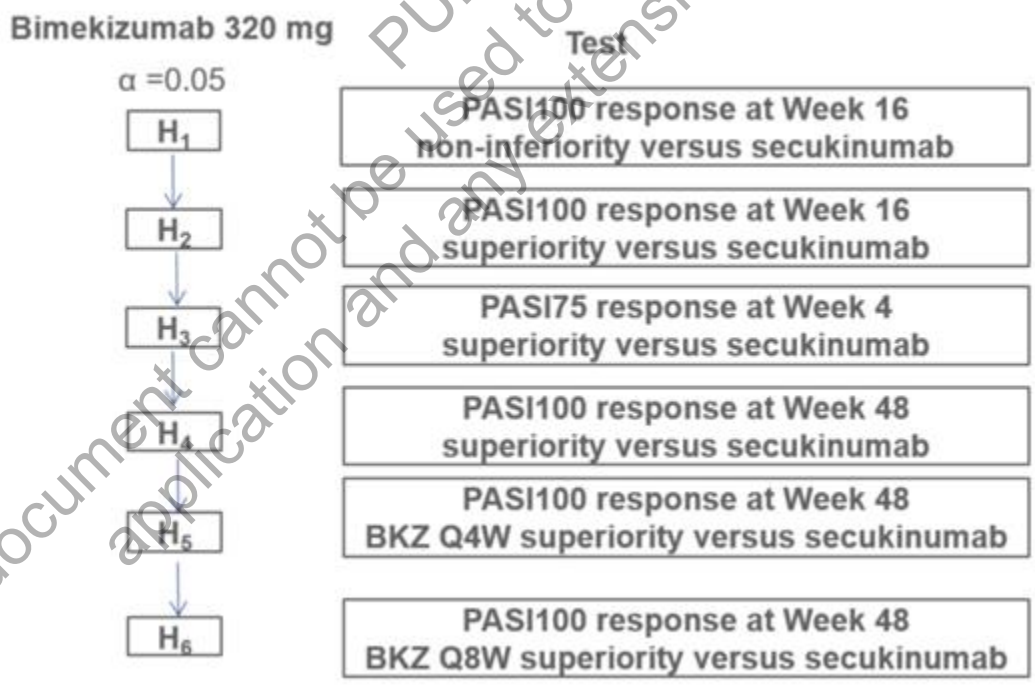
The hypotheses (H_1, H_2, H_3, H_4, H_5, and H_6) comparing bimekizumab vs secukinumab will be tested at a 2-sided alpha level of 0.05.

The first 2 hypotheses (H_1 and H_2) test whether bimekizumab is non-inferior and superior, respectively, to secukinumab for PASI100 response at Week 16. These are the hypothesis tests corresponding to the primary endpoint.

If these hypotheses are rejected at a 2-sided alpha level of 0.05, that alpha will be passed to the next test in the sequence, allowing the testing procedure to proceed. If a hypothesis can not be rejected, p-values for subsequent hypotheses will not be calculated. A combined table will present all hypotheses together with all p-values that were calculated.

The hypotheses associated with the subsequent tests are for secondary efficacy endpoints and are based on testing for superiority relative to secukinumab. Figure 4–1 presents the details on this procedure.

Figure 4–1: Fixed sequence of hypothesis testing procedure



BKZ=bimekizumab; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks

Note: Tests for H_1, H_2, H_3, and H_4 are based on all subjects initially randomized to bimekizumab compared to secukinumab. For H5 and H6, testing is based on the subjects re-randomized at Week 16 to bimekizumab 320mg Q4W, and bimekizumab 320mg Q8W, respectively, compared to secukinumab.

A table will be produced containing the results for all hypotheses. P-values or confidence intervals only will be shown as appropriate.

Other tables will include p-values of primary and secondary endpoints. These p-values should not be considered to evaluate hypotheses as they are not controlled for multiplicity.

4.6 Use of an efficacy subset of subjects

The primary efficacy analysis (described in Section 8.1.2) will be repeated based on FAS and PPS as a sensitivity analysis (see Section 8.1.3.4).

4.7 Active-control studies intended to show equivalence

A non-inferiority margin of 10% has been selected as this is considered to be a clinically relevant difference that could influence the choice of interventions used to treat chronic plaque PSO.

4.8 Examination of subgroups

Subgroup analyses will be based on data up to Week 48 only. These analyses will be performed on the PASI75/90/100 response rates, using by visit summaries only. The following subgroups for analysis will be determined for the RS using baseline data:

- Age (<40 years, 40 to <65 years, ≥65 years)
- Gender (male, female)
- Disease duration (<median, ≥median)
- Region (North America, Western Europe, Central/Eastern Europe, Asia/Australia)
- Weight (≤100 kg, >100 kg)
- Body mass index (BMI) (<25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2)
- Prior systemic phototherapy or chemotherapy (yes, no)
- Prior biologic exposure (yes, no)
- Prior primary failure to biologic (yes/no)
- Prior systemic therapy of any kind (yes, no)
- Baseline disease severity (PASI<20, PASI≥20)
- Antibody positivity (negative, positive)

Antibody positivity is the only subgroup that is not determined by Baseline data (described in Section 9.3.2). It will be presented in a separate table.

The definition of prior systemic therapy of any kind is if a subject received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic chemotherapy or phototherapy. Subjects who never received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic chemotherapy or phototherapy will be classified as not receiving prior systemic treatment for psoriasis.

In addition, in order to assess whether an early response to treatment is predictive of response at later time points, subgroup analyses will be performed for PASI90/100 and IGA over time using the following early response subgroups:

- PASI75 response (OC) at Week 4 (yes, no) to predict PASI90/100 and IGA (clear or almost clear) (NRI) through Week 48 based on RS
- PASI90 response (OC) at Week 16 (yes, no) to predict PASI100 (NRI) through Week 48 based on RS
- PASI90 response (OC) at Week 48 (yes, no) to predict PASI90 (NRI) during the OLE based on OLS
- PASI90 response (OC) at Week 48 (yes, no) to predict PASI100 (NRI) during the OLE based on OLS
- PASI90 response (OC) at Week 48 (yes, no) to predict IGA responder rates (clear) and IGA responder (clear or almost clear) during the OLE based on OLS.

All summaries will be based on imputed data as appropriate and will include descriptive statistics only.

Additional subgroup analyses are described in Section 4.2.1.7.2 to assess the impact of the COVID-19 pandemic on planned statistical analysis of PASI100 response at Week 48.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Summaries of reasons for screen failures (for all subjects screened), disposition of subjects (for all subjects screened), disposition of analysis sets (for RS, MS, OLS, and OLS2), disposition and discontinuation reasons (for RS, MS, OLS, and OLS2), as well as for the subjects who discontinued due to AEs (for RS, MS, OLS, and OLS2) will be produced. The disposition of subjects for all subjects screened will include the number of subjects included in each analysis set (RS, SS, FAS, MS, OLS, OLS2, BKZ Set, PPS, and PK-PPS) overall and by site.

The following listings for subject disposition will be provided: subjects who did not meet study eligibility criteria (all subjects screened), subject disposition (all subjects screened), study discontinuation (for RS), visit dates (for RS), subjects excluded from efficacy analysis (RS).

Summaries of visits at which subjects initiated the switch from bimekizumab 320mg Q4W to bimekizumab 320mg Q8W dosing interval in the Open-Label Extension period will be presented. Similar listings will be provided separately for the OLE and the OLE2 treatment periods.

In addition, the following COVID-19 impact categories will be summarized by country and visit for the MS, OLS, and OLS2 (see Section 2.3.5 for list of countries). Separate listings of COVID-19 impact will be provided for the OLE and the OLE2 treatment periods.

- Visit not done
- Visit performed out of window
- Home Visit

- Visit performed by video call
- Visit performed by telephone
- Investigational product shipped to study participant
- Participant Home administration of investigational product by participant or caregiver
- Home administration of investigational product by a healthcare professional
- Missed study drug administration/dispensation
- Temporary discontinuation of study drug
- Permanent discontinuation of study drug
- Termination of study participation
- Other

Note that home administration was permitted at certain visits (see Table 7–2) and only home administration that was not per the protocol should be captured.

A by-subject listing of COVID-19 impact categories will be provided separately for the OLE and the OLE2 treatment periods.

5.2 Protocol deviations

A summary of number and percentage of subjects with an important protocol deviation (including a summary of subjects excluded from any analysis set due to important protocol deviations) by treatment group will be provided for the RS, MS,OLS, and OLS2.

A by-subject listing of important protocol deviations will be provided separately for Initial and Maintenance treatment periods for RS. Similar listings will be provided separately for the OLE, and the OLE2 treatment periods.

A summary of number and percentage of subjects with COVID-19 protocol deviations by treatment group and visit will be provided for the MS and OLS.

A by-site, subject and visit listing of COVID-19 protocol deviations will be provided.

Separate listings of subjects with COVID-19 protocol deviations will also be provided for the OLE and the OLE2 treatment periods.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

All summaries detailed in this section will be performed on the RS by treatment group. Summaries for demographics and other Baseline characteristics will also be repeated on SS, MS, OLS, and OLS2. All these summaries (including the OLS and the OLS2 summaries) will use the Baseline value from Week 0 of the double-blind treatment period. If the RS and SS analysis sets are identical the summaries will not be repeated.

6.1 Demographics

Demographic variables will be summarized by treatment group and overall.

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

- Age at the time of study entry (years)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

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

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

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

- Age group (18-<65, 65-<85, ≥85 years)
- Age group (≤18, 19-<65, ≥65 years)
- Age group (<40, 40-<65, ≥65 years)
- Body Weight (≤100kg, >100kg)
- BMI (<25 kg/m^2, 25 to <30 kg/m^2, ≥30 kg/m^2)
- Gender
- Race
- Ethnicity

By-subject listings of demographics will be provided.

6.2 Other Baseline characteristics

Baseline characteristics (including Baseline clinical measures) will be summarized by treatment group and overall.

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

- Psoriasis Body Surface Area (BSA; %)
- Psoriasis Area and Severity Index (PASI) score
- Modified Nail Psoriasis Severity Index (mNAPSI) total score
- mNAPSI total score for subjects with nail involvement (i.e. mNAPSI>0)
- Patient Global Assessment of Disease Activity (PGADA) for arthritis visual analogue scale (VAS) score
- Dermatology Life Quality Index (DLQI) total score
- PSD item scores: Pain, Itch, Scaling
- Duration of disease (years)

Duration of disease (years) will be calculated as:

$$Disease\ Duration = \frac{(Date\ of\ randomization - Date\ of\ onset\ of\ Plaque\ Psoriasis^{1})}{365.25}$$

1 If the date of onset of plaque psoriasis 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). Note that if the date of randomization is missing then the duration of disease will be derived using the date of screening.

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

- Region (North America [Canada, USA], Western Europe [Belgium, France, Germany, Netherlands, Spain, United Kingdom], Eastern/Central Europe [Poland], Asia/ Australia [Australia, Turkey]
- Country
- PGADA score (=0, >0)
- DLQI total score (=0, >0)
- Duration of disease (<median, ≥median)
- Investigator's Global Assessment (IGA) score
- Baseline disease severity (PASI<20, PASI≥20)
- Nail involvement (yes, no)
- Scalp involvement (yes, no)
- Palmoplantar involvement (yes, no)
- Prior biologic exposure (yes, no)
- Prior primary failure to biologic (yes, no)
- Prior anti-TNF therapy (yes, no)
- Prior phototherapy or chemotherapy (yes, no)
- Any prior systemic therapy (yes, no)

Baseline nail, scalp, and palmoplantar involvement are based on the number of subjects achieving mNAPSI>0, Scalp IGA>0, and pp-IGA>0, respectively. The categorization of whether or not subjects had prior exposure to biologic therapy will be based on the Psoriasis Treatment History CRF module. Prior anti-TNFs include etanercept, adalimumab, infliximab, certolizumab pegol, and golimumab (or biosimilars of those treatments).

By-subject listings of Baseline characteristics will be provided.

6.3 Medical history and concomitant diseases

Previous and ongoing medical history will be summarized by treatment group(s), SOC and PT using MedDRA® version. Medical procedures are not coded.

The following listings for medical history and concomitant diseases will be provided: medical history, psoriasis history, concomitant medical procedures, previous and ongoing medical history glossary, previous and ongoing medical history conditions, and procedure history.

For subjects enrolling in OLE2 Group B, any additional medical history collected during OLE2 screening will be flagged in the medical history listing.

6.4 Prior and concomitant medications

Medication start and stop dates will be compared to the date of first dose of treatment to allow medications to be classified as either Prior or Concomitant.

Details of imputation methods for missing or partial dates are described in Section 4.2.1.7.

Prior medications include any medications that started prior to the start date of study medication.

Concomitant medications are medications taken at least one day in common with the study medication dosing period (defined as from first dose of study medication [including placebo] up to last dose of study medication + 28 days for the double-blind treatment period, and +28 days or +56 for Q4W and Q8W dosing respectively in the OLE period). Concomitant medications will be summarized separately for the double-blind Treatment Period (SS), the OLE treatment period (OLS).

The number and percentage of subjects taking prior medications (excluding past psoriasis medications) will be summarized by treatment group, overall and by ATC class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term. The number and percentage taking concomitant medications will be summarized similarly.

Past psoriasis medications will be captured separately and will also be summarized by treatment group. These medications are not subject to dictionary coding. In addition, subjects who failed past psoriasis biologic treatment will be summarized by reason of failure as captured on the Psoriasis Treatment History CRF module.

The number and percentage of subjects with concomitant vaccines for COVID-19 will be summarized by treatment group, overall and by World Health Organization Drug Dictionary Standardized Drug Grouping (SDG), presenting SDG subgroup, and preferred term. The SDG subgroup Vaccines for COVID-19 will be used to identify vaccines for COVID-19 using the narrow scope; this subgroup is divided further into separate subgroups which is the level that will be presented. The number of individual occurrences of the vaccine for COVID-19 will also be summarized.

By-subject listings of all Prior and Concomitant medications (including COVID-19 concomitant medications), prior and concomitant medications glossary, and psoriasis treatment history will be provided separately for OLE and OLE2 treatment periods. Ongoing concomitant medications from OLE to OLE2 treatment period will be flagged.

An additional listing of concomitant vaccines for COVID-19 will be provided separately for OLE and OLE2 treatment periods.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Due to the method of administration of the treatments, compliance will be examined in terms of completed injections and by treatment arm.

Treatment compliance will be calculated as:

$$\frac{total\ number\ of\ completed\ injections}{total\ number\ of\ expected\ injections} \times 100$$

where the total number of expected injections is derived relative to when the subject finishes treatment. In this study, bimekizumab, secukinumab, or placebo are administered according to the schedule in Table 7-1 below.

If a subject discontinues early, then the number of expected injections is based on the time of early discontinuation relative to the dosing visits. For example, if a subject discontinues after Week 4 visit and prior to Week 8 visit, the total number of expected injections will be 10.

A summary of percent treatment compliance categorized as <75% and ≥75% will be provided by treatment group and study periods (Initial Treatment Period for the SS, Maintenance Treatment Period for the SS, Initial and Maintenance Treatment Period for the SS, Open-Label Extension Period for the OLS, and Open-Label 2 Extension Period for the OLS2).

A by-subject listing of treatment compliance will be provided. Separate listings of treatment compliance will be provided for the OLE and the OLE2 treatment periods.

Table 7–1: Dosing scheme

Week Dose Assignment	Baseline (first dose)	1	2	3	4	8	12	16[a]	20	24	28	32	36	40	44
Bimekizumab 320mg	●●	○○	○○	○○	●●	●●	●●	Q4W ●●	●●	●●	●●	●●	●●	●●	●●
								Q8W ●●	○○	●●	○○	●●	○○	●●	○○
Secukinumab 300mg	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲	▲▲

Q4W=every 4 weeks; Q8W=every 8 weeks

Notes: A bimekizumab 160mg injection is depicted by a black circle (●). A placebo injection is depicted by a white circle (○). A secukinumab 150mg injection is depicted by a black triangle (▲).

[a] Subjects in the bimekizumab 320mg treatment arm will be re-randomized 1:2 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W.

Table 7–2: Dosing scheme, OLE Period

Week		Year 2												Year 3										
Dose Assignment	48 (1st OLE dose)	52	56	60	64[ab]	68	72[ab]	76	80	84[ac]	88	92	96[ab]	100	104	108[ac]	112	116	120[ab]	124	128	132[ac]	136	140
Bimekizumab 320mg Q4W	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●
Bimekizumab 320mg Q8W	●●		●●		●●		●●		●●		●●		●●		●●		●●		●●		●●		●●	

OLE=Open-Label Extension; Q4W=every 4 weeks; Q8W=every 8 weeks

Notes: A bimekizumab 160mg injection is depicted by a black circle (●).

[a] The subject's dosing interval will change from Q4W to Q8W at Week 64 or at the next scheduled clinic visit after implementation of Protocol Amendment 5.0 if the subject has already completed the Week 64 visit.

[b] Subjects whose dosing interval is changed to Q8W should be dosed at this visit and will receive kits for home administration 8 weeks later.

[c] Subjects whose dosing interval is changed to Q8W should NOT be dosed at this visit and will receive kits for home administration 4 weeks later.

Table 7–3: Dosing scheme, OLE2 Period

Visit/Week / Dose Assignment	OLE2 Period									
	Week 144/OLE2 Baseline	OLE2 Week 4	OLE2 Week 8	OLE2 Week 12 [a]	OLE2 Week 16	OLE2 Week 24 [b]	OLE2 Week 32	OLE2 Week 36 [c]	OLE2 Week 40	OLE2 Week 48
	C	H	H	C	H	C	H	C	H	C
Bimekizumab 320mg Q4W/Q8W[d]	●●	●●	●●	●●	●●	●●	●●		●●	
Bimekizumab 320mg Q8W	●●		●●		●●	●●	●●		●●	

C=Clinic, H=home, IGA=Investigator's Global Assessment, IMP=investigational medication product, OLE=Open Label Extension, Q4W/Q8W=every 4 weeks for 16 weeks, followed by every 8 weeks, Q8W=every 8 week, W=week.
Notes: A bimekizumab 160mg injection is depicted by black circle (●).

[a] Subjects will receive kits for home administration 4 weeks later.

[b] Subjects will receive kits for home administration 8 weeks later.

[c] Subjects should NOT be dosed at this visit and will receive kits for home administration 4 weeks later.

[d] Q4W/Q8W IMP administration only applies to those subjects who have entered the OLE2 Period as part of Group B and had an IGA ≥3 upon entry of OLE2 Period. These subjects will receive Q4W dosing for 16 weeks until OLE2 Week 16, then will change from Q4W to Q8W and will receive their next dose at the scheduled clinic visit OLE2 Week 24.

8 EFFICACY ANALYSES

8.1 Statistical analysis of the primary efficacy variable

8.1.1 Derivations of primary efficacy variable

Unless otherwise specified, the Baseline value to be used in the analysis of efficacy endpoints will be the assessments from Week 0 of the double-blind treatment period of the study. A table of efficacy variables analyzed at each treatment period is provided in Section 12.4 (Appendix D).

8.1.1.1 Psoriasis Area and Severity Index (PASI)

PASI100 is defined to be equal to 1 if the percentage improvement from Baseline in the PASI scores is 100% and 0 if the percentage improvement from Baseline is less than 100%. This definition is introduced for the purpose of identifying subjects who respond to the treatment (1 = responder, 0 = non-responder).

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

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

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

where

R_h, R_u, R_t, R_l = redness score of plaques on the head, upper extremities, trunk, and lower extremities, scored 0-4 respectively;

T_h, T_u, T_t, T_l = thickness score of plaques on the head, upper extremities, trunk, and lower extremities, scored 0-4 respectively;

S_h, S_u, S_t, S_l = scaliness score of plaques on the head, upper extremities, trunk, and lower extremities, scored 0-4 respectively;

A_h, A_u, A_t, A_l = numerical value translation of % area of psoriatic involvement score for the head, upper extremities, trunk, and lower extremities, respectively (where 0 = 0% [clear], 1 = >0% to <10%, 2 = 10% to <30%, 3 = 30% to <50%, 4 = 50% to <70%, 5 = 70% to <90%, and 6 = 90% to 100%).

The highest potential PASI score is 72 for severe disease; the lowest is 0 for no psoriasis lesions. PASI scores are treated as continuous. The percent improvement in PASI scores from Baseline will be computed as:

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

If a subject has experienced an improvement, this measure will be positive. If a subject has experienced a worsening in their condition, this measure will be negative.

If a subject is missing 1 or 2 severity measurements for a certain region, the average of the remaining severity measurement(s) within that region will be utilized to substitute for the missing severity measurement(s) in that region. If the area of affected skin and/or all severity measurements for up to 2 regions are missing, then the missing (R+T+S) x A for a region will be substituted by the average of the available (R+T+S) x A. Otherwise, the PASI will be set to missing.

8.1.1.2 PASI100 Response at Week 16

The primary efficacy variable, PASI100 at Week 16, is a categorical response variable and is defined to be equal to 1 if the percentage improvement from Baseline to Week 16 in the PASI scores is 100% and 0 if the percentage improvement from Baseline to Week 16 is less than 100%. This definition is introduced for the purpose of identifying subjects who respond to the treatment (1 = responder, 0 = non-responder). The definition of percentage improvement from Baseline is given in Section 8.1.1.1.

8.1.2 Primary analysis of the primary efficacy variable

The analysis of the primary efficacy variable (PASI100 at Week 16) will be based on the RS. A stratified Cochran-Mantel-Haenszel (CMH) test will be performed, where region and prior biologic exposure (yes/no) will be used as stratification variables.

Treatment comparisons between bimekizumab and secukinumab will be made based on the CMH test using the p-value for the general association. For the assessment of non-inferiority, a non-inferiority margin of 10% will be used and evaluated based on the CI for the stratified Mantel-Haenszel risk difference between bimekizumab and secukinumab. The evaluation of superiority will use pairwise treatment comparisons based on the CMH test using the p-value for the general association. The odds ratio and associated confidence interval (CI) based on the Wald test will be presented.

To calculate the stratified Mantel-Haenszel risk difference, the method of Greenland and Robins (1985) is used. For each combination of strata, a 2x2 table of treatment group and response is created. A theoretical 2x2 table for a given stratum is shown below, where n = a+b+c+d.

	Response	
Treatment Group	**Yes**	**No**
Bimekizumab	a	c
Secukinumab	b	d

Given that structure, the stratified Mantel-Haenszel risk difference, standard error, and two-sided (1-α)*100% confidence interval may be written as follows:

$$RD_{MH=}\frac{\sum_i((a_i * (b_i + d_i)/n_i) \ - (b_i * (a_i + c_i)/n_i)}{\sum_i((a_i + c_i) * (b_i + d_i))/n_i}$$

$$SE_{MH} = \sqrt{\frac{\sum_i \left\{ \frac{[a_i * c_i * (b_i + d_i)^3] + [b_i * d_i * (a_i + c_i)^3]}{(a_i + c_i) * (b_i + d_i) * n_i^2} \right\}}{\left\{ \sum_i \left[\frac{(a_i + c_i) * (b_i + d_i)}{n_i} \right] \right\}^2}}$$

$$CI_{MH} = RD_{MH} \pm \text{probit}\big(1 - (\alpha/2)\big) * SE_{MH}$$

For the assessment of non-inferiority of bimekizumab to secukinumab, the lower 97.5% confidence limit for the stratified Mantel-Haenszel risk difference will be considered. If that value is greater than -10%, then non-inferiority will have been established.

NRI will be used to account for missing data in the primary analysis. Specifically, any subject who withdraws from IMP prior to Week 16 or who has missing data for the primary efficacy variables at the Week 16 time point will be considered a nonresponder.

The number and percentage of subjects who are PASI100 responders at Week 16 will be summarized.

A line plot of the percentage improvement from Baseline in PASI score over time by treatment group will be produced by randomized treatment group for the RS and repeated for the MS. An additional plot will be produced for the OLS by OLE treatment groups.

By-subject listings of PASI and PASI responder variables will be provided for the Initial and the Maintenance periods combined based on RS. This listing will also be provided separately for the OLE and the OLE2 treatment periods.

8.1.3 Supportive and sensitivity analyses of the primary efficacy variable

The following sensitivity analyses for the primary efficacy variable will be performed to evaluate the assumptions related to the handling of missing data

8.1.3.1 Sensitivity Analysis #1

Missing data will be addressed by using MI (MCMC) method for intermittent missing data, followed by monotone regression for monotone missing data (see Section 4.2.1.6) to evaluate the effect of the method for handling missing data on the analysis. The actual PASI scores will be imputed and then dichotomized to obtain the response status. The treatment differences for each imputed data set will subsequently be evaluated using the stratified CMH test as used in the primary analysis. The results from each of the 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. This procedure assumes a MAR pattern of missingness and corresponds to an estimand of the difference in outcome improvement if all subjects tolerated or adhered to treatment (Mallinckrodt et al, 2012). This is an estimand of efficacy to evaluate the de jure hypothesis.

8.1.3.2 Sensitivity Analysis #2

This sensitivity analysis will be based on observed data at Week 16. Subjects with missing data or who have prematurely discontinued IMP will be treated as missing (see Section 4.2.1.5). The same stratified CMH test as in the primary efficacy analysis will be used.

8.1.3.3 Sensitivity Analysis #3

The primary efficacy analyses from Section 8.1.2 will be repeated using LOCF as the imputation method (see Section 4.2.1.5).

8.1.3.4 Sensitivity Analysis #4

The primary efficacy analyses from Section 8.1.2 will be repeated based on the FAS and the PPS.

8.1.3.5 Sensitivity Analysis #5

As a sensitivity analysis to the primary analysis method, logistic regression based on the RS will be used. The odds ratio of the responder rates at Week 16 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and prior biologic exposure (yes/no). The odds ratio, associated confidence interval (CI), and p-value based on the Wald test will be presented. If the logistic regression model is unable to converge, then prior biologic exposure may be dropped from the model to facilitate convergence. If the model is still unable to converge, then region may be removed from the model as well. In addition, if the logistic regression model cannot converge, then Fisher's exact test will be used for inferential comparisons. As with the primary analysis, missing data will be handled using NRI.

8.1.3.6 Sensitivity Analysis #6

The center-by-treatment interaction will be tested by replacing region with center in the logistic regression model described in Section 8.1.3.5 and adding a center-by-treatment interaction term. In the model, center will be based on the original centers prior to pooling. However, if the model is unable to converge due to a low number of subjects at a given center, a pooling (see Section 3.7) will be described in order to allow the model to converge. In order to obtain reasonable estimates of variability for a treatment arm at a given center, a minimum of 10 subjects will be considered acceptable for a center to be included in the model without pooling. Given the 1:1 randomization allocation scheme at the start of the study, this should provide a minimum of about 5 subjects in each treatment group. Centers with fewer than 10 subjects will be eligible for pooling. The pooling algorithm used is described in Section 3.7. In order to achieve model convergence, region may be used instead of center or prior biologic exposure may be dropped from the model. If convergence still cannot be achieved, this analysis will not be performed.

If the center-by-treatment interaction is not found to be significant (α=0.10), then no further analyses will be performed. On the other hand, if the interaction is significant, further analyses will be conducted to determine which center or centers may be the source of interaction. This will be done by running the logistic regression model (including the interaction term) where each center will be systematically removed from the model. This impact of a given center will be based on the change in the interaction p-value when that center is removed. The center or centers that appear to be driving the significant interaction effect will then be removed from the model to verify that conclusions remain the same with or without the influential center(s). This sensitivity analysis will be based on RS with NRI for missing data.

8.2 Statistical analysis of the secondary efficacy variables

8.2.1 Derivations of secondary efficacy variables

8.2.1.1 PASI75 Responder at Week 4

A categorical response variable, PASI75 at Week 4 is defined to be equal to 1 if the percentage improvement from Baseline to Week 4 in the PASI scores is 75% or greater and 0 if the percentage improvement from Baseline to Week 4 is less than 75%. The definition of percentage improvement from Baseline is given in Section 8.1.1.1.

8.2.1.2 PASI90 Responder at Week 16

A categorical response variable, PASI90 at Week 16 is defined to be equal to 1 if the percentage improvement from Baseline to Week 16 in the PASI scores is 90% or greater and 0 if the percentage improvement from Baseline to Week 16 is less than 90%.

The definition of percentage improvement from Baseline is given in Section 8.1.1.1.

8.2.1.3 PASI100 Responder at Week 48

PASI100 response definition and derivation are outlined in Section 8.1.1.1 and Section 8.1.1.2.

8.2.1.4 IGA Response (0/1) at Week 16

A static IGA for psoriasis will be used to assess disease severity in all subjects during the study.

The Investigator will assess the overall severity of psoriasis using the following five-point scale:

Table 8–1: Investigator's Global Assessment

Score	Short Descriptor	Definition
0	Clear	No signs of psoriasis; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

IGA response at Week 16 is defined as clear [0] or almost clear [1] with at least a two-category improvement from Baseline at Week 16.

8.2.2 Primary analysis of the secondary efficacy variables

All secondary efficacy variables are binary (responder) variables and will be summarized using frequency tables by randomized treatment group for each visit. Primary analysis for secondary efficacy variables will be summarized based on imputed data (NRI for binary variables) and for the RS, unless otherwise specified. A stratified CMH test will be performed, where region and prior biologic exposure (yes/no) will be used as stratification variables.

Treatment comparisons between bimekizumab and secukinumab will be made based on the CMH test using the p-value for the general association. PASI90 and IGA (clear or almost clear) at Week 16 are not in the closed testing procedure therefore the related p-values should only be considered descriptive statistics.

PASI100 at Week 48 is the only secondary variable that is affected by the re-randomization at Week 16. The way the analysis for this variable is conducted will depend on which comparison is being made. The following comparisons will be performed:

- Compare all subjects initially randomized to bimekizumab (regardless of re-randomization assignment at Week 16) to all subjects initially randomized to secukinumab based on the RS (H_4)
- Compare subjects who were assigned to bimekizumab 320mg Q4W at Week 16 to subjects on secukinumab based on the MS (H_5)
- Compare subjects who were assigned to bimekizumab 320mg Q8W at Week 16 to subjects on secukinumab based on the MS (H_6)

8.2.3 Sensitivity analyses of the secondary efficacy variables

For all secondary efficacy variables, sensitivity analyses #1 and #2 (Section 8.1.3.1 and Section 8.1.3.2) will be performed. In addition, for PASI100 response at Week 48, the sensitivity analyses described in Section 4.2.1.7 will be performed.

8.3 Analysis of other efficacy variables

The other efficacy variables are listed below and will be evaluated according to the planned assessments in the protocol. This excludes the time points for the primary and secondary variables specified above in Section 8.1.1.2 and Section 8.2.1.

Three different types of tables will be produced by visit through Week 48:

1. Subjects in the MS summarized by the 3 maintenance treatment groups (bimekizumab 320mg Q4W, bimekizumab 320mg Q8W, and secukinumab).
2. A subset of Group 1 above. Specifically, this will include only those subjects who are responders at Week 16 for the variable being summarized.
3. Subjects in the RS summarized by the 2 randomized treatment groups (bimekizumab and secukinumab).

All efficacy variables will be summarized in the manner described for Group 1 and Group 3 above. Summaries for Group 2 will be done only for a subset of efficacy variables, namely, PASI90/100 responder rate, IGA Clear or Almost Clear. Examination of subgroups will only be done for Group 3.

Binary (responder) variables will be summarized using frequency tables by treatment group for each visit. Continuous variables will be summarized using descriptive statistics by treatment group for each visit. All variables will be summarized based on imputed data (NRI and MCMC/Monotone Regression for binary and continuous variables, respectively), unless otherwise specified.

For variables that are part of the sequence testing procedure, summaries based on observed case data will also be provided. There may be cases where the multiple imputation model fails to converge. In such situations, the LOCF approach will instead be used to impute the missing data. Selected efficacy variables will also be summarized by visit through Week 144 for the OLE Period for the OLS. Subjects will be summarized by treatment sequence comprising randomized treatment at Baseline and OLE period treatment at Week 48.

The OC approach will be used to summarize the following efficacy variables for subjects in the OLE2 treatment period: PASI90, PASI100, IGA (0/1), IGA (0), DLQI (0/1), and PSD response.

8.3.1 PASI

8.3.1.1 PASI75, PASI90 and PASI100 response rates

Categorical response variables, PASI75, PASI90 and PASI100 over time are defined to be equal to 1 if the percentage improvement from Baseline to visit time point in the PASI scores is 75%, 90% and 100% respectively or greater and 0 if the percentage improvement from Baseline to visit time point is less than 75%, 90% and 100% respectively (1 = responder, 0 = non-responder).

The definition of PASI score percentage improvement from Baseline is given in Section 8.1.1.1.

A line plot of the PASI responder (PASI75, PASI90, and PASI100) rate over time, by treatment group will be produced for the RS and by randomized treatment groups. Additional plots will be produced separately for the MS by maintenance treatment groups, for the OLS and for the OLS2 (excluding PASI75) by OLE and OLE2 treatment sequence respectively.

8.3.1.2 Time to PASI75, PASI90 and PASI100 response

Time to PASI75, PASI90, and PASI100 response (in days) will each be calculated as:

$$Min\ (Date\ of\ first\ PASIxx\ response) - Date\ of\ Baseline\ visit\ +\ 1,$$

where xx represents 75, 90, 100 respectively. All visits including unscheduled visits are considered.

Subjects who discontinue study treatment without achieving a given PASI response prior to discontinuation will be censored at the date of the last observed PASI assessment on or prior to the date of treatment discontinuation. Subjects who reach the Week 48 Visit without achieving the given response will be censored at the date of the last observed PASI assessment on or prior to the Week 48 Visit. Subjects will be censored at Baseline if there is no Baseline PASI assessment or no Post Baseline PASI assessment

Time to PASI75, PASI90, and PASI100 response during the initial and maintenance treatment period will each be estimated and presented using the Kaplan-Meier product-limit method based on the RS by initially randomized treatment groups (bimekizumab vs secukinumab).

Time to a given response will be defined as the length in days from the first dose of IMP until the first date when the response is achieved. The median time to response, including the two-sided 95% CI, will be calculated for each treatment. Between group differences (bimekizumab vs secukinumab) will be analyzed with the log-rank statistic by region and prior biologic exposure. Kaplan-Meier plots of time to PASI responses will also be presented by initially randomized treatment group. In these Kaplan-Meier plots, the line will start at 0 (since there are no responders at Week 0) and will increase over time, representing time to achieving the response.

Time to PASI75. PASI90, and PASI100 response analyses will not be conducted for the OLE and the OLE2 treatment periods.

8.3.1.3 PASI score

Absolute and percent change from Baseline in PASI score is defined in Section 8.1.1.1.

The percentage of subjects with absolute PASI score ≤1, ≤2, ≤3 and ≤5 will be presented over time using NRI for the RS, the MS, and the OLS.

Absolute PASI score categories will not be summarized for the OLE2 treatment period.

8.3.2 IGA response

- IGA response (Clear) is defined when IGA score is clear [0] (Table 8–1) with at least a two-category improvement from Baseline at visit time point.
- IGA response (Clear or Almost Clear with at least 2 category improvements relative to Baseline) is defined as IGA score of clear [0] or almost clear [1] with at least a two-category improvement from Baseline at visit time point.
- Shift from Baseline in IGA score is defined at each Post-Baseline visit time point relative to Baseline.
- Scalp-specific IGA response

A static IGA for scalp PSO will be used to assess disease severity on the scalp.

All subjects will complete the scalp IGA at Baseline. Only subjects with scalp involvement at Baseline will complete the scalp IGA at the other visits specified in the protocol. Subjects with scalp involvement at Baseline are defined as those with a scalp IGA score >0 at Baseline.

Scalp lesions will be assessed in terms of clinical signs of redness, thickness, and scaliness using a 5-point scale as outlined in Table 8–2 below.

Table 8–2: Scalp IGA

Score	Short Descriptor	Detailed Descriptor
0	Clear	Scalp has no signs of PSO; post-inflammatory hyperpigmentation may be present
1	Almost clear	Scalp has no thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Scalp has just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Scalp has clearly distinguishable to moderate thickening; dull to bright red, moderate scaling
4	Severe	Scalp has severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

Scalp IGA response is defined as clear [0] or almost clear [1] with at least a two-category improvement from Baseline. For analysis purposes, the evaluation of scalp IGA will be limited

to subjects with a Baseline scalp IGA of at least 2. Therefore, if a subject has a score of 2 at Baseline, they can only be considered a responder if their IGA is 0 (thereby meeting the criterion for a two-category improvement from Baseline). Subjects with a Baseline scalp IGA of 1 will be assessed per the protocol but will not be part of the scalp IGA analysis.

- pp-IGA response

A static IGA for palmoplantar PSO will be used to assess palmoplantar disease severity.

Only subjects with palmoplantar involvement at Baseline will complete the pp-IGA at the other visits specified in the protocol. Subjects with palmoplantar involvement at Baseline are defined as those with a pp-IGA score >0 at Baseline.

Palmoplantar disease will be assessed in terms of clinical signs of redness, thickness, and scaliness using a 5-point scale as outlined in Table 8–3 below.

Table 8–3: Palmoplantar IGA

Score	Short Descriptor	Detailed Descriptor
0	Clear	Palmoplantar has no signs of PSO; post-inflammatory hyperpigmentation may be present
1	Almost clear	Palmoplantar has no thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Palmoplantar has just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Palmoplantar has clearly distinguishable to moderate thickening; dull to bright red and clearly distinguishable coloration; moderate scaling
4	Severe	Palmoplantar has severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions; numerous fissures

PSO=psoriasis.

Palmoplantar IGA response is defined as clear [0] or almost clear [1] with at least a two-category improvement from Baseline. For analysis purposes, the evaluation of pp-IGA will be limited to subjects with a Baseline pp-IGA of at least 2. Therefore, if a subject has a score of 2 at Baseline, they can only be considered a responder if their IGA is 0 (thereby meeting the criterion for a two-category improvement from Baseline). Subjects with a Baseline pp-IGA of 1 will be assessed per the protocol but will not be part of the palmoplantar IGA analysis.

IGA response rate, Scalp IGA response rate, and Palmoplantar IGA response rate will be summarized for RS by treatment group and for OLS by treatment sequence and visit.

A line plot of the IGA responder rates (both clear or almost clear and clear) over time, by treatment group will be produced for the RS and by randomized treatment groups. This plot will include assessments from the Initial and Maintenance Treatment Period. An additional plot will be produced by re-randomized maintenance treatment groups only for the Maintenance Treatment Period for the MS. Additional plots will be produced based on the OLS and the OLS2 for IGA clear [0] and for IGA (clear [0] or almost clear [1] only by treatment sequence.

8.3.3 Body Surface Area (BSA)

- Absolute change from Baseline in the BSA affected by PSO is defined as Post Baseline BSA minus Baseline BSA affected by PSO.
- Percent change from Baseline in BSA affected by PSO is defined as

$$\text{Percent change from Baseline } = 100 \times \frac{\text{Post Baseline BSA} - \text{Baseline BSA}}{\text{Baseline BSA}}$$

The percent of subjects with absolute BSA=0%, ≤1%, ≤3% and ≤5% will be presented over time using NRI.

BSA results will be listed but will not be summarized for the OLE2 treatment period.

8.3.4 Product of IGA and BSA (IGAxBSA)

- Absolute change from Baseline in the product IGAxBSA is defined as Post Baseline IGAxBSA minus product of Baseline IGAxBSA.
- Percent change from Baseline in the product of IGAxBSA is defined as

$$\text{Percent change from Baseline } = 100 \times \frac{\text{Post Baseline IGAxBSA} - \text{Baseline IGAxBSA}}{\text{Baseline IGAxBSA}}$$

The absolute and percentage change from baseline will be summarized for each study period (Initial randomized, Maintenance) by treatment group and visit.

The product of IGA and BSA will not be summarized for the OLE2 treatment period.

8.3.5 Dermatology Life Quality Index (DLQI)

The DLQI questionnaire is used for subjects with psoriasis and consists of 10-questions. This is a validated quality-of-life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment, as assessed over the past week.

The scoring of each answer for the DLQI is as follows:

Table 8–4: Dermatology Life Quality Index

DLQI Scoring	
Response	Score
Very much	3
A lot	2
A little	1
Not at all	0
Not relevant	0
Question unanswered	0
Q7: 'prevented work or studying' = yes	3

The DLQI total score is calculated by adding the score of each question. The maximum score is 30, and the minimum score is 0. The higher the score, the more quality of life is impaired.

Meaning of DLQI Scores

0-1 = no effect at all on patient's life

2-5 = small effect on patient's life

6-10 = moderate effect on patient's life

11-20 = very large effect on patient's life

21-30 = extremely large effect on patient's life

This categorization will not be utilized in the analysis.

Because Q7 has a sub-question (referred to as Q7a here) after the leading yes/no question, some clarifying rules for scoring are provided:

- If Q7 is marked as "yes", a score of 3 is given regardless of the responses to Q7a.
- If Q7 is marked as "no", "not relevant", or is missing and Q7a is "A lot", a score of 2 is given.
- If Q7 is marked as "no", "not relevant", or is missing and Q7a is "A little", a score of 1 is given.
- If Q7 is marked as "no", "not relevant", or is missing and Q7a is "Not at all", a score of 0 is given.
- If Q7 is marked as "no" or "not relevant" and Q7a is missing, a score of 0 is given.
- If Q7 is missing and Q7a is missing, Q7 is considered unanswered (see below for details on how this impacts the overall DLQI score).

If 1 question is left unanswered, this is scored 0 and the scores are summed and expressed as usual out of a maximum of 30. If 2 or more questions are left unanswered, the questionnaire is not scored.

A subject is considered to have achieved the minimally clinical important difference (MCID) if their individual improvement from Baseline score is > 4. A 4-point improvement in the DLQI total score (DLQI response) has been reported to be meaningful for the subject (within-subject MCID).

The DLQI related efficacy variables are defined as follows:

- Change from Baseline in DLQI total score is defined as Post-Baseline DLQI total score minus Baseline DLQI total score.
- Percent of subjects achieving a DLQI total score of 0 or 1 is defined as the number of subjects with DLQI absolute score of 0 or 1 divided by the number of subjects in RS.
- Percent of subjects achieving a MCID in DLQI is defined as the number of subjects with improvement from Baseline total score of 4 or more divided by the number of subjects in RS. Only subjects with a Baseline DLQI total score of 4 or greater will be considered for this analysis.

The DLQI related efficacy variables will be summarized for the double-blind treatment visits separately for the RS and MS, and separately for OLS and OLS2 [DLQI(0/1) only] by treatment sequence respectively and visit.

8.3.6 Patient's Global Assessment of Disease Activity (PGADA) for arthritis visual analog scale (VAS)

The PGADA for arthritis VAS will be used to provide an overall evaluation of arthritis disease symptoms. Subjects will respond to the question, "Considering all the ways your arthritis affects you, please mark a vertical line on the scale below to show how you are feeling today," using a VAS where 0 is "very good, no symptoms" and 100 is "very poor, severe symptoms.

All subjects will complete the PGADA at Baseline. Subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47) will complete the PGADA at the visits specified in the protocol. Change from Baseline in PGADA is defined as Post-Baseline PGADA minus Baseline PGADA.

The absolute and change from baseline in PGADA will be summarized for the double-blind treatment visits separately for the RS and MS and OLS by treatment sequence and visit.

8.3.7 Patient Global Assessment of PSO

The Patient Global Assessment of PSO is a PSO-specific item in which the subject responds to the multiple-choice question, "How severe are your psoriasis-related symptoms right now?" Possible responses to the question are "no symptoms," "mild symptoms," "moderate symptoms," "severe symptoms," or "very severe symptoms."

The Patient Global Assessment of psoriasis will be summarized based on OC as the primary analysis. No imputation is applied.

Shift from Baseline in Patient Global Assessment (PGA) of PSO score is defined to each Post-Baseline visit time point relative to Baseline.

The absolute value and shift from baseline in Patient Global Assessment (PGA) of PSO score will be summarized for each study period (Initial randomized, Maintenance) by treatment group.

8.3.8 Symptoms of PSO (Itch, pain, and scaling)

UCB has developed a new Patient Reported Outcome measure, in the form of a patient symptom diary (PSD), which is used to assess key signs, symptoms, and impacts relevant to subjects with moderate to severe chronic plaque PSO. In this study itch, pain, and scaling items from the diary will be used to assess the patient-reported level of these symptoms over time. The items will be administered on an electronic site tablet, during visits, as specified in the protocol.

Each of the 3 items is measuring the severity of the symptom. Each item will be scored separately on a 0-10 scale with 0 meaning no symptom and 10 for very severe or worst symptom.

- Change from Baseline in PSD item score for each item is defined as post Baseline PSD item score minus Baseline PSD item score.
- Percent change from Baseline in PSD item score for each item is defined as

$$\text{Percent change from Baseline} = 100 \times \frac{\text{Post Baseline PSD score - Baseline PSD score}}{\text{Baseline PSD score}}$$

Absolute and percent changes from Baseline PSD item scores for each item will be summarized for each study period (Initial randomized, Maintenance) by treatment group.

PSD response and the proportion of subjects with score of 0 (or 0/1) will be summarized for OLE Treatment Period by treatment sequence and visit.

In addition, each of the 3 PSD scores will be characterized in terms of the percent of subjects demonstrating a 4-point improvement at each visit. Subjects with a missing score will be imputed using NRI. The analysis will be limited to subjects with a Baseline PSD score at or above the applicable threshold score.

The PS0009 and PS0013 analyses determined a 4-point reduction as a marked within-subject clinically meaningful improvement in the weekly score each of these 3 PSD items that can be used to define different marked response to treatment over 16 weeks in patients with moderate-to-severe plaque psoriasis. Such a threshold has also been used to support US label claims of other compounds approved in the same indication based on different PSO symptom diaries using an 11-point numeric response scale and was suggested in previous interactions with the FDA. Analyses conducted on blinded PS0015 data support the 4-point threshold as indicative of marked within-subject clinically meaningful improvement that can be used for responder definition.

Cumulative distribution plots will also be provided for absolute change from Baseline PSD at Week 16 and Week 48 for each item.

Listings of responses to individual questions of the patient diary will be provided separately for the Initial, Maintenance, OLE, and the OLE2 treatment periods.

Summaries of PSD response (Itch, Pain, and Scaling symptoms) will be produced for the OLE2 by treatment sequence as described in Section 3.6.

8.3.9 Modified Nail Psoriasis Severity Index (mNAPSI) score

Psoriatic nail disease will be evaluated at the Baseline visit using the mNAPSI. All affected nails will be scored (0 to 3) for onycholysis/oil drop dyschromia, nail plate crumbling, and pitting and will be scored (0 for “no” or 1 for “yes”) for leukonychia, nail bed hyperkeratosis, splinter

haemorrhages and red spots in the lunula. The score for an individual nail ranges from 0 to 13 with higher scores indicative of more severe nail disease. The total mNAPSI score is the sum of the scores for each individual nail. If a nail is unaffected, it will be recorded as such and will not contribute to the total mNAPSI score.

If any of the 7 response items that contribute to mNAPSI is present, while other items are missing (ie, partial mNAPSI data), then the missing items are assumed to be 0 for the mNAPSI calculation. In some cases, the data may be captured in such a way that only non-zero component scores are present in the database. Again, those components that are not present are simply assumed to be 0 for the mNAPSI calculation.

Change from Baseline in mNAPSI score for subjects with nail PSO at Baseline is defined as Post-Baseline mNAPSI score minus Baseline mNAPSI.

An mNAPSI75 responder is defined as a subject who achieved at least a 75% improvement from Baseline in the mNAPSI score. mNAPSI90 and mNAPSI100 are defined accordingly. The proportion of mNAPSI75/90/100 responders for subjects with nail PSO at Baseline over time will be summarized for each study period (Initial randomized, Maintenance) by treatment group and OLE by treatment sequence.

8.3.10 Psoriatic Arthritis Screening and Evaluation (PASE)

The PASE questionnaire is a self-administered tool to screen for active PsA in subjects with PSO (Husni et al, 2014). The questionnaire consists of 15 items that are divided into a 7-item symptoms subscale and an 8-item functions subscale. Standardized responses are based on 5 categories relating to agreement (strongly agree [5], agree [4], no idea [3], disagree [2], and strongly disagree [1]). The total maximum score is 75 points (symptom score: 35 points and function score: 40 points). Psoriatic Arthritis Screening and Evaluation questionnaire scores ≥47 points are indicative of active PsA.

PASE will be collected at Baseline, Week 48/PEOT, Week 96 and Week 144/PEOT visits. PASE will be summarized based on OC only. No imputation is applied.

- Change from Baseline in the PASE questionnaire scores (function score, symptom score, and total score) is defined as Post-Baseline PASE questionnaire score (function, symptom, and total) minus Baseline PASE questionnaire score (function, symptom, and total).
- Shift from Baseline in PASE score suggestive of PsA (<47 versus ≥47) is defined to Week 48/PEOT visit time point relative to Baseline.

Change from Baseline in the PASE and Shift from Baseline in PASE will be summarized for each study period (Initial randomized, Maintenance) by treatment group and for OLE by treatment sequence and visit.

8.3.11 Euro-Quality of Life 5-Dimensions, 3 levels (EQ-5D-3L)

The EQ-5D-3L health questionnaire provides a descriptive profile and a single index value for health status. The instrument is comprised of a 5-item health status measure and a VAS measurement.

Responses to EQ-5D-3L are scored as 1 for “no problem”, 2 for “some or moderate problems”, and 3 for “extreme problems”.

Absolute EQ-5D-3L VAS score records the respondent's self-rated health status on a vertical 20cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status).

Change from Baseline in EQ-5D-3L VAS scores is defined as Post-Baseline EQ-5D-3L VAS score minus Baseline EQ-5D-3L VAS score.

Responses to EQ-5D-3L will be summarized for each study period (Initial randomized, Maintenance) by treatment group and for OLE by treatment sequence and visit. The analysis will be based on OC only as primary analysis. No imputation is applied to responses to EQ-5D-3L but is applied to EQ-5D-3L VAS scores.

8.3.12 Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP)

The WPAI-SHP is a subject-reported questionnaire that assesses subject's employment status, work absenteeism, work impairment while working, overall work, and daily activity impairment attributable to a specific health problem. Five out of 6 items of the WPAI-SHP are regrouped into the 4 dimensions, with scores expressed as percentage, where higher numbers indicate greater impairment and less productivity, i.e., worse outcomes, as described in the WPAI-SHP scoring rules.

The scoring rules for the WPAI-SHP are as follows:

Questions:

1 = currently employed

2 = hours missed due to specified problem

3 = hours missed other reasons

4 = hours actually worked

5 = degree problem affected productivity while working

6 = degree problem affected regular activities

Scores:

- Percent work time missed due to problem: [Q2 hours/(Q2 hours +Q4 hours)]*100
- Percent impairment while working due to problem: [Q5 score/10]*100
- Percent overall work impairment due to problem:

  [Q2 hours/(Q2 hours +Q4 hours)+[(1-(Q2 hours/(Q2 hours +Q4 hours))x(Q5 score/10)]] *100
- Percent activity impairment due to problem: [Q6 score/10]*100

Change from Baseline score is derived as post Baseline score minus Baseline score. A negative change score indicates a reduction in the score/improvement for the subject.

The Change from Baseline in WPAI-SHP will be summarized for each study period (Initial randomized, Maintenance) by treatment group and for OLE by treatment sequence at each visit.

8.4 Additional Statistical Analysis of other Efficacy Variables

For selected other efficacy variables, it is of interest to perform statistical tests and to calculate inferential statistics. As these tests are not part of the multiplicity-controlled procedure, the associated p-values are considered nominal and are not controlled for multiplicity. For responder variables, the analysis will follow what was specified for the primary analysis. Specifically, a stratified Cochran-Mantel-Haenszel (CMH) test will be used, where region and prior biologic exposure (yes/no) will be stratification variables. The p-value will be based on the CMH test for a general association. Missing values will be imputed using NRI. For continuous variables, the MI – MCMC / Monotone Regression approach used for other continuous variables will be applied for the imputation model. The analysis model will be based on analysis of covariance (ANCOVA) with fixed effects of treatment, region, and prior biologic exposure and Baseline value as a covariate. Below is a list of variables for which these nominal p-values will be calculated (with the time points in parentheses). The results of these inferential tests will all be presented in a single table summarizing the testing performed outside of the multiplicity-controlled testing procedure.

- PASI90
  - Bimekizumab vs Secukinumab (Weeks 1, 2, 4, 8, 12, 16 and 48)
- IGA Clear or Almost Clear
  - Bimekizumab vs Secukinumab (Weeks 1, 2, 4, 8, 12, 16 and 48)
- PASI100
  - Bimekizumab vs Secukinumab (Weeks 4, 8, and 12)
- IGA Clear
  - Bimekizumab vs Secukinumab (Weeks 4, 8, 12, 16, and 48)
- PASI75
  - Bimekizumab vs Secukinumab (Weeks 1, 2, and 16)
- Scalp IGA Clear or Almost Clear (subjects with Baseline Scalp IGA ≥2)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- pp-IGA Clear or Almost Clear (subjects with Baseline pp-IGA ≥2)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- mNAPSI75 response (subjects with Baseline mNAPSI>0)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- mNAPSI90 response (subjects with Baseline mNAPSI>0)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- mNAPSI100 response (subjects with Baseline mNAPSI>0)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)

- DLQI 0/1 response
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- PASI percentage change from Baseline
  - Bimekizumab vs Secukinumab (Weeks 1, 2, 4, 8, 12, 16, and 48)
- PASI ≤1 response
  - Bimekizumab vs Placebo (Weeks 1, 2, 4, 8, 12, 16, and 48)
- PASI ≤2 response
  - Bimekizumab vs Placebo (Weeks 1, 2, 4, 8, 12, 16, and 48)
- PASI ≤3 response
  - Bimekizumab vs Placebo (Weeks 1, 2, 4, 8, 12, 16, and 48)
- PASI ≤5 response
  - Bimekizumab vs Placebo (Weeks 1, 2, 4, 8, 12, 16, and 48)
- Patient Symptom Diary responses for itch, pain, and scaling
  - Bimekizumab vs Secukinumab (Weeks 16, 32, 48)

9 PHARMACOKINETICS AND PHARMACODYNAMICS

For the Week 48 interim the following treatment groups were summarized for the Initial and Maintenance Treatment Period.

- Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 16
- Bimekizumab 320mg Q4W.

PK and ADAb will also be summarized through to Week 144 by the following treatment sequence and by visit for Initial, Maintenance, and Open-Label Extension treatment period combined. No PK or ADAb samples will be collected in the OLE2 treatment period.

- Subjects receiving bimekizumab in the double-blind treatment period until Week 144 or until treatment discontinuation:
  - Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 16
  - Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 48
  - Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 72 or 84
  - Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 96 or later
  - Bimekizumab Total (only for immunogenicity analyses).

Subjects with any other treatment sequence groups (eg, Bimekizumab 320mg Q4W/Q8W/Q4W or Q4W/Q8W/Q4W/Q8W) will be allocated the "Bimekizumab Total" treatment sequence group for immunogenicity analysis only. All data will be included in the listings.

- Subjects receiving secukinumab in the double-blind treatment period:
  - Bimekizumab 320mg Q8W from Week 48
  - Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 72 or 84
  - Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 96 or later
  - Bimekizumab Total (only for immunogenicity analyses)

Note that subjects who received Bimekizumab 320mg Q4W only, ie, those who discontinued before switching to Q8W, will be allocated to the corresponding Q4W/Q8W treatment sequence group depending on when the subject discontinued. For example, if a subject discontinued at week 68, they will be allocated to group Bimekizumab 320mg Q4W/Q8W, switch occurring at Week 72 for PK summary table and figure purposes.

9.1 Pharmacokinetics

Pharmacokinetic variables will be analyzed for all subjects in the PK-PPS. Bimekizumab plasma concentrations will be summarized for each treatment sequence as described in Section 9, at each scheduled visit. A separate summary table will be created for the Open-Label Extension Period for subjects that are both in the PK-PPS and the OLS.

PK summaries will be based on observed values. No imputation will be used however, if plasma concentration measurements are below the level of quantification (BLQ), then for calculation of the derived statistics the result will be set to 0.125 µg/ml, which is ½ of the lower level of quantification (LLOQ). Descriptive statistics including geometric mean, geometric coefficient of variation, and geometric mean 95% CI if applicable will be calculated if at least 2/3 of the values of interest are above the LLOQ. If this is not the case, only median, minimum, and maximum will be presented. In cases where n<3 only the minimum and maximum will be presented.

In addition, geometric mean plasma concentration (with the 95% CI) will be plotted versus time on linear and semi-logarithmic scales by treatment sequence group. The summary table and figures will be repeated by cumulative antibody status for subjects randomized to bimekizumab.

If a dose is +/- 21 days out of window, then the plasma concentration from that visit and all subsequent visits will be excluded from the PK summary tables and graphs.

If the PK sampling date is >1 day after the dosing date, the plasma concentration at this visit will be excluded from the PK summary tables and figures, but not from the listing.

If a subject misses an administration of bimekizumab, receives less or more than the intended dose, then the plasma concentration from the next scheduled visit will be excluded from PK summary tables and graphs.

All PK concentration data will be listed.

9.2 Pharmacodynamics

Not applicable.

9.3 Immunogenicity

The analysis of immunogenicity for the Week 48 Interim will be based on the SS All other analyses will be based on the BKZ Set.

9.3.1 Anti-nuclear antibodies

Not applicable.

9.3.2 Anti-bimekizumab antibodies

Anti-bimekizumab antibodies will be measured using a three tiered assay approach: screening assay, confirmatory assay and titration assay. Samples confirmed as positive within the confirmatory assay, will be further evaluated in a neutralizing assay to evaluate the potential of the ADAb to neutralize the activity of Bimekizumab (IL17A or IL17F, or both) in-vitro. Samples were taken at baseline, week 1, week 2, week 4, week 8, week 12, week 16, week 20, week 24, week 36, week 48, Week 72, Week 96, Week 120, Week144 (or PEOT) and at SFU which is 20 weeks after the last dose. Due to the planned entry of some subjects to the OLE2 period, not all subjects will have an SFU period immediately following Week 144 with PK and immunogenicity samples.

Anti-bimekizumab antibody samples are not analyzed when subjects are on a treatment other than bimekizumab. For subjects who switch from secukinumab to bimekizumab, samples are analyzed starting at the visit when the switch to bimekizumab occurs. The sample at the visit when the switch occurs will act as the Baseline for that treatment group.

Screening, confirmatory and titer cut points of the respective assays will be determined by the bioanalytical laboratory based either on using commercially available drug-naïve samples or on the pre-dose samples of the study itself. The samples (or a subset) will also be subject to a neutralizing assay to evaluate whether the anti-bimekizumab antibody neutralizes the activity of bimekizumab (IL17 A or IL17F or both) in- vitro.

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

- An ADAb status will be confirmed as positive for any sample with an ADAb level that is positive screen and positive immunodepletion.
- An ADAb status of negative will be concluded for any sample with an ADAb level that is either negative screen or (positive screen and negative immunodepletion).

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

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

For each subject an overall ADAb status in the treatment and OLE periods (Baseline to Week 144) will be derived:

- Overall Positive is defined as having at least one value that is confirmed positive during the treatment period.

- Overall Negative is defined as having no values that are confirmed positive at any time up to Week 144 and at least 2/3 of the protocol scheduled post-baseline assessments up to Week 144 are evaluable (i.e. neither missing as per schedule nor inconclusive)
- Overall Missing is defined as having no values that are confirmed positive at any visit in the treatment period, but the subject has 1/3 or more protocol scheduled post-baseline assessments missing (or inconclusive) up to Week 144.

This differs from the Week 48 interim analysis where all subjects were defined as either overall positive or overall negative only (a missing category was not considered). As the time on treatment is protracted in this open label extension study (up to 144 Weeks), missing data or subject discontinuation may be more prevalent and is therefore considered for the final analysis

- The double-blind and OLE treatment periods do not include Baseline/pre-treatment samples or SFU.

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

1. **Pre anti-bimekizumab antibody negative – treatment emergent anti-bimekizumab antibody negative**: Includes subjects who are negative at Baseline and antibody negative at all sampling points post treatment (excluding SFU)
2. **Pre anti-bimekizumab antibody negative – treatment emergent anti-bimekizumab antibody positive**: Includes subjects who are negative at Baseline and antibody positive at any sampling point post treatment (excluding SFU). This group also includes subjects who have a missing pre-treatment sample (either missing or insufficient volume) at Baseline with one or more anti-bimekizumab antibody positive post-treatment samples.
3. **Pre anti-bimekizumab antibody positive – treatment emergent reduced anti-bimekizumab antibody**: Includes subjects who are positive at Baseline, and antibody negative at all sampling points post treatment (excluding SFU).
4. **Pre anti-bimekizumab antibody positive – treatment emergent unaffected anti-bimekizumab antibody positive**: Includes subjects who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with titer values of the same magnitude as Baseline (ie, less than a 2.07 fold difference from the Baseline value).
5. **Pre anti-bimekizumab antibody positive – treatment emergent anti-bimekizumab antibody boosted positive**: Includes subjects who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with increased titer values compared to baseline (greater than a 2.07 fold difference increase from Baseline value which will be defined within the validation of the assay).
6. **Inconclusive**: Includes subjects who have a positive pre-treatment sample and some post-treatment samples are missing, while other post-treatment samples are anti-bimekizumab antibody negative.
7. **Total treatment-emergent ADAb positivity** (**Category 7** [Categories 2 and 5 combined]): Includes study participants who are pre ADAb negative – treatment-

emergent ADAb positive (Category 2) and pre ADAb positive – treatment boosted ADAb positive (Category 5).

8. **Total prevalence of pre- ADAb positivity (Category 8** [Categories 3, 4 and 5 combined]): Study participants that are tested ADAb positive at Baseline.
9. **Missing:** Includes subjects who are antibody negative at baseline, are not positive at any post-baseline visit, and have at least one missing post-treatment scheduled assessment. Note this is also applicable to subjects who have missing baseline.

For the Week 144 analysis, when all OLE and SFU data will be available, data from the OLE and SFU visits will be considered. That is, each instance of "excluding SFU" in the categories above, should be changed to "including SFU."

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

Analysis

- Immunogenicity will be assessed through summary tables, figures, and listing of individual results by subject. The analysis of immunogenicity will be summarized by treatment sequence as described in Section 9 and visit. All analyses will be run on the safety population, unless specified otherwise. Summary of anti-bimekizumab antibody status overall and by each visit separated by treatment sequence
- Summary of the time-point of the first occurrence of anti-bimekizumab antibody positivity during the treatment period by treatment sequence. A plot of the titer by time to first anti-bimekizumab antibody positivity will be prepared
- All individual subject-level anti-bimekizumab antibody results will be listed.
- The number and percentage of subjects in each of the 8 anti-bimekizumab antibody categories during the treatment period by treatment sequence, with an additional category combining subjects in categories 2 and 5, summarized as total treatment emergent. In addition, the count and percentage of subjects who are pre anti-bimekizumab positive will be calculated (this is the sum of categories 3, 4, and 5)
- The prevalence of immunogenicity, separated by treatment sequence, and defined subcategory, will be reported by visit, defined as (cumulative) proportion of subjects having confirmed positive anti-bimekizumab antibody samples at any visit up to and including that visit. Missing samples will not be included in the denominator
- The time to achieving treatment-emergent anti-bimekizumab antibody positivity, separated by treatment sequence and defined sub-category, will be analyzed based on Kaplan-Meier methods. Subjects will be considered to have an event at the time point at which treatment emergent anti-bimekizumab antibody positive is first achieved. Subjects classified as treatment-emergent anti-bimekizumab antibody negative will be censored at the time of the last available anti-bimekizumab antibody result

- A summary of PASI 100 responders, separated by treatment sequence and defined sub-category, at weeks 16, 48 and 144 as a function of ADAb titer will be presented graphically. This will be repeated for PASI 75 and 90 responders
- Individual plots of Bimekizumab Concentrations/ anti-bimekizumab antibody titer and PASI score all plotted on the Y-axes by visit (x-axis) for the full treatment period (excluding SFU and OLE period for interim analyses and including SFU and OLE period for final analyses), where a patient has not progressed into the OLE. Plots should be labeled and grouped into the 7 sub-categories
- Spaghetti plots of ADAb titer (y-axis) by visit (x-axis), separated by treatment sequence (as specified above) for all anti-bimekizumab antibody positive subjects, including Baseline positive subjects
- Box plots Plot of ADAb titer (logscale) by time to first ADAb positivity by treatment sequence.

For purposes of efficacy subgroup analyses based on anti-bimekizumab antibody status, two categories will be used:

- Anti-bimekizumab antibody positive – This is defined as subjects who have anti-bimekizumab antibody levels above the specified cut point on at least 2 time points while on treatment (ie, excluding Baseline, excluding SFU)
- Anti-bimekizumab antibody negative – Subjects who are not defined as anti-bimekizumab positive (as described above) will be defined as anti-bimekizumab antibody negative.

The groups for defining anti-bimekizumab antibody status for safety subgroup analyses are as follows:

- AEs starting before first anti-bimekizumab antibody positive result
- AEs starting on or after first anti-bimekizumab antibody positive result
- AEs for subjects who were always anti-bimekizumab antibody negative.

In addition to the anti-bimekizumab antibody classifications, subjects will be assigned an overall neutralizing anti-BKZ antibodies (NAb) classification for each NAb assay separately (IL-17AA and IL-17FF), inclusive of Baseline and post-Baseline results, on the NAb assay results. The classifications are as follows:

- NAb negative: No NAb positive samples at Baseline or post-Baseline and did not discontinue prior to Week 144. Subject can have up to 1 missing sample.
- NAb positive: One or more positive samples (IL-17AA positive, IL-17FF positive, or both) at Baseline or post-Baseline (regardless of missing samples). Subjects who are NAb positive will be further classified as follows:
  - Positive for IL-17AA only: one or more positive samples for IL-17AA at Baseline or post Baseline. No positive samples for IL-17FF
  - Positive for IL-17FF only: one or more positive samples for IL-17 FF at Baseline or post Baseline. No positive samples for IL-17AA

- Positive for both IL-17AA and IL-17FF: one or more positive samples for both IL-17AA and IL-17FF at Baseline or post Baseline

– NAb Missing: >1 relevant NAb samples are missing, eg, if subject had samples selected for NAb testing based on their anti-bimekizumab antibody levels, but there was insufficient sample left for NAb testing.

A summary table covering the initial, maintenance and OLE periods combined by treatment sequence will be produced, in addition, to summarize the NAb status overall.

A listing will be produced to summarize the NAb status by visit. The listing should be sorted by treatment sequence, subject identifier, and visit and would provide the following information for each subject:

– Visit
  - Study week since first BKZ dose
  - Sample date and time
  - Time since previous dose (weeks)

– NAb status and the corresponding bimekizumab plasma concentration (ug/mL) and the anti-bimekizumab antibody level titer at this visit

– IL-17AA NAb status and corresponding IL-17AA signal/negative control result
IL-17FF NAb status and corresponding IL-17FF signal/negative control result

The tables will provide the following overall summary statistics by treatment group:

– Total number and percentage of anti-bimekizumab antibody positive, anti-bimekizumab antibody negative and missing subjects at each visit

– Number and percentage of subjects who are NAb positive, NAb negative and missing at each visit

– The number and percentage of subjects who are IL-17AA NAb positive, IL-17FF NAb positive, or both.

10 SAFETY ANALYSES

If not specified otherwise, all safety summaries and listings will be created using all subjects in the SS.

10.1 Extent of exposure

Summaries for exposure will be provided for the SS, MS, OLS, OLS2, and BKZ set. These consist of a descriptive summary of study medication duration in days. In addition, total study medication duration and time at risk will be summarized in years by treatment group

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

- >0 weeks
- >=16 weeks

- >=24 weeks
- >=48 weeks

For the Week 144 analysis and for the final analysis, the table will also be created for the BKZ set and will include the above categories plus the below categories. A bimekizumab total column will also be displayed.

- >=72 weeks
- >=96 weeks
- >=120 weeks
- >=144 weeks

In addition, the OLE2 exposure will be displayed separately as follow:

- >0 weeks
- >=16 weeks
- >=24 weeks
- >=48 weeks.

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

Throughout this section, date of last clinical contact for each subject is defined as the maximum of (last visit date including SFU or SFU2 visit, last imputed AE start date, date of study termination or completion, last date of study drug administration).

10.1.1 Exposure during the Initial Treatment Period for SS

Definitions for study medication duration (days) and time at risk (days) during the Initial Treatment Period are provided as follows:

Study medication duration (days)

- Date of last active dose of IMP in the Initial Treatment Period – date of first dose + 28 days

  Note: If date of last active dose of IMP in the Initial Treatment Period + 28 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:

- Final visit date (including PEOT, but not including SFU) – date of first dose + 1.

  Note: If date of last active dose of IMP in the Initial Period + 28 days extends to a date beyond the date of first dose in the Maintenance Treatment Period, then this calculation reverts to:

  – Date of first dose in the Maintenance Period – date of first dose in the Initial Treatment Period + 1.

  Note: For subjects who die, if date of last active dose of IMP in the Initial Treatment Period + 28 days extends to a date beyond the date of death, then this calculation reverts to:

- Date of death – date of first dose + 1.

Time at risk (days)

- For subjects who die:
  - Date of death – date of first dose +1.
- For subjects who complete the final visit of the Initial Period and continue to the Maintenance Period:
  - Date of first dose in the Maintenance Treatment Period – date of first dose in the Initial Treatment Period + 1.
- For subjects who discontinue on or prior to the final visit of the Initial Period, use the minimum of the following:
  - Date of last active dose of IMP in the Initial Treatment Period– date of first dose + 140 days.
  - The total number of days in the Initial Treatment Period (112 days). For AEs that emerged after 112 days but still within the 140 days window, those AEs would be classified as TEAE, but will be excluded from the output based on the Initial Treatment Period. However, these AEs will be included in the AE summaries for Initial Treatment Period and Maintenance Treatment Period combined.
  - Date of last clinical contact – date of first dose + 1.

10.1.2 Exposure during the Maintenance Treatment Period for MS

Definitions for study medication duration (days) and time at risk (days) during the Maintenance Treatment Period are provided as follows:

Study medication duration (days)

- Date of last bimekizumab or secukinumab dose in the Maintenance Treatment Period – date of first dose in the Maintenance Treatment Period + 28 days (for subjects on Q4W dosing or secukinumab)
- Date of last bimekizumab in the Maintenance Treatment Period – date of first dose in the Maintenance Treatment Period + 56 days (for subjects on Q8W dosing)

  Note: If date of last bimekizumab or secukinumab dose in the Maintenance Treatment Period + 28 days (or 56 days for subjects on Q8W dosing) extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:
  - Final visit date (including PEOT, but not including SFU) – date of first dose in the Maintenance Treatment Period+ 1.

  Note: If date of last bimekizumab or secukinumab dose in the Maintenance Period + 28 (or 56 days for subjects on Q8W dosing) days extends to a date beyond the date of first dose in the Open-Label Extension Period, then this calculation reverts to:
  - Date of first dose in the Open-Label Extension Period – date of first dose in the Maintenance Treatment Period + 1.

Note: For subjects who die, if date of last bimekizumab or secukinumab dose in the Maintenance Treatment Period + 28 days (or 56 days for subjects on Q8W dosing) extends to a date beyond the date of death, then this calculation reverts to:

- Date of death – date of first dose in the Maintenance Treatment Period+ 1.

Time at risk (days)

- For subjects who die:
  - Date of death – date of first dose in the Maintenance Treatment Period+1.
- For subjects who complete the final visit of the Maintenance Period and continue to the OLE Period:
  - Date of first dose in the OLE Period - date of first dose in the Maintenance Treatment Period + 1 day.
- For subjects who discontinue on or prior to the final visit of the Maintenance Period, use the minimum of the following:
  - Date of last dose in the Maintenance Treatment Period – date of first dose in the Maintenance Treatment Period + 140 days.
  - Date of last clinical contact – date of first dose in the Maintenance Treatment Period + 1.

10.1.3 Exposure during the Initial and Maintenance Treatment Period for SS

Definitions for study medication duration (days) and time at risk (days) during the Initial and Maintenance Treatment Period are provided as follows:

10.1.3.1 For subjects who do not switch study treatments

Study medication duration (days)

- Date of last active dose of IMP in the Initial and Maintenance Treatment Period – date of first dose + 28 days

  Note: If date of last active dose of IMP in the Initial and Maintenance Treatment Period + 28 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:

  - Final visit date (including PEOT, but not including SFU) – date of first dose + 1.

  Note: If date of last bimekizumab or secukinumab dose in the Maintenance Period + 28 days extends to a date beyond the date of first dose in the Open-Label Extension Period, then this calculation reverts to:

  - Date of first dose in the Open-Label Extension Period – date of first dose + 1.

  Note: For subjects who die, if date of last dose in the Initial Treatment and Maintenance Period + 28 days extends to a date beyond the date of death, then this calculation reverts to:

  - Date of death – date of first dose + 1.

Time at risk (days)

- For subjects who continue into the OLE period:

- Date of first dose in the OLE Period – date of first dose + 1.

- For subjects who die: Date of death – date of first dose +1.
- For all other subjects, use the minimum of the following:
  - Date of last active dose of IMP in the Initial and Maintenance Treatment Period– date of first dose + 140 days.
  - Date of last clinical contact – date of first dose + 1.

10.1.3.2 For subjects who switch from BKZ 320mg Q4W to Q8W at Week 16:

Study medication duration (days)

- Initial Treatment Period (attributed to BKZ 320mg Q4W)
  - Date of last dose in the Initial Treatment Period – date of first dose + 28 days

  Note: If date of last dose in the Initial Treatment Period + 28 days extends to a date beyond the first dose in the Maintenance Treatment Period, then this calculation reverts to:
  - Date of first dose in the Maintenance Treatment Period – date of first dose + 1.
- Maintenance Treatment Period (attributed to BKZ 320mg Q8W)
  - Use the study medication duration algorithm specified for the Maintenance Treatment Period in Section 10.1.2
- Initial and Maintenance Treatment Period (attributed to Total BKZ)
  - Study medication duration in Initial Treatment Period + Study medication duration in Maintenance Treatment Period.

Time at risk (days)

- Initial Treatment Period (attributed to BKZ 320mg Q4W)
  - Date of first dose in the Maintenance Treatment Period - date of first dose + 1 day.
- Maintenance Treatment Period (attributed to BKZ 320mg Q8W)
  - Use the time at risk algorithm specified for the Maintenance Treatment Period in Section 10.1.2
- Initial and Maintenance Treatment Period (attributed to Total BKZ)
  - Use the time at risk algorithm specified for subjects who do not switch study treatments in Section 10.1.3.1

10.1.4 Exposure during the Open-Label Extension Period based on OLS

Definitions for study medication duration (days) and time at risk (days) during the Open-Label Extension Period are provided as follows:

10.1.4.1 For subjects who do not switch study treatments

Study medication duration (days)

- For subjects who receive Q4W in the Open-Label Extension Period (subjects who discontinue prior to switching to Q8W):
  - Date of last bimekizumab dose in the Open-Label Extension Period – date of first dose in the Open-Label Extension Period + 28 days (for subjects on Q4W dosing)
- For subjects who receive Q8W in the Open-Label Extension Period use the minimum of:
  - Date of last bimekizumab dose in the Open-Label Extension Period – date of first dose in the Open-Label Extension Period + 56 days
  - First dose date in Open-Label Extension 2 Period – date of first dose in the Open-Label Extension Period + 1

  Note: If date of last bimekizumab dose in the Open-Label Extension Period + 28 days (or 56 days for subjects on Q8W dosing) extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:
  - Final visit date (including PEOT, but not including SFU) – date of first dose in the Open-Label Extension Period+ 1.

  Note: For subjects who die, if date of last bimekizumab dose in the Open-Label Extension Period + 28 days (or 56 days for subjects on Q8W dosing) extends to a date beyond the date of death, then this calculation reverts to:
  - Date of death – date of first dose in the Open-Label Extension Period+ 1.

Time at risk (days)

- For all subjects, use the minimum of the following:
  - Date of last dose in the Open-Label Extension Period – date of first dose in the Open-Label Extension Period + 140 days,
  - Date of first dose in OLE2 - date of first dose in the Open-Label Extension Period + 1 day
  - Date of last clinical contact in OLE and SFU – date of first dose in the Open-Label Extension Period + 1.
  - Date of death – date of OLE first dose

10.1.4.2 For subjects who switch from BKZ 320mg Q4W to Q8W during Open-Label Extension Period

Following Protocol Amendment 5.0, subjects receiving Q4W should switch to Q8W during the Open-Label extension period. (see Section 2.3.2.4 for further details).

Study medication duration (days)

- Attributed to BKZ 320mg Q4W:
  - Date of last BKZ 320mg Q4W dose in the OLE Period – date of first BKZ 320mg Q4W dose in the OLE Period + 28 days

Note: If date of last BKZ 320mg Q4W dose in the OLE Period + 28 days extends to a date beyond the date of first BKZ 320mg Q8W dose in the OLE Period, then this calculation reverts to:

- Date of first BKZ 320mg Q8W dose in the OLE Period – date of first BKZ 320mg Q4W dose in the OLE Period + 1.

- Attributed to BKZ 320mg Q8W use the minimum of:
  - Date of last BKZ 320mg Q8W dose in the OLE Period – date of first BKZ 320mg Q8W dose in the OLE Period + 56 days.
  - First dose date in Open-Label Extension Period 2 – date of first BKZ 320mg Q8W dose in the Open-Label Extension Period+ 1.

  Note: If date of last bimekizumab dose in the Open-Label Extension Period + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:
  - Final visit date (including PEOT, but not including SFU) – date of first BKZ 320mg Q8W dose in the OLE Period + 1.

  Note: For subjects who die, if date of last bimekizumab dose in the Open-Label Extension Period + 56 days extends to a date beyond the date of death, then this calculation reverts to:
  - Date of death – date of first BKZ 320mg Q8W dose in the OLE Period + 1.
- Attributed to Total BKZ
  - Sum of study medication duration in OLE period attributed to BKZ 320mg Q4W and study medication duration in OLE period attributed to BKZ 320mg Q8W-1.

Time at risk (days)

- Attributed to BKZ 320mg Q4W:
  - Date of first BKZ 320mg Q8W dose in the OLE Period – date of last BKZ 320mg Q4W dose in the OLE Period + 1 day
- Attributed to BKZ 320mg Q8W:
  - For all subjects, use the minimum of the following:
    - Date of last BKZ 320mg Q8W dose in the OLE Period – date of first BKZ 320mg Q8W dose in the OLE Period + 140 days.
    - Date of first BKZ 320mg Q8W dose in OLE2 - date of first BKZ 320mg Q8W dose in the Open-Label Extension Period + 1 day
    - Date of last clinical contact – date of first BKZ 320mg Q8W dose in the OLE Period + 1.
    - Date of death – date of first BKZ 320mg Q8W dose in the OLE Period + 1.
- Attributed to Total BKZ:

– Use the time at risk algorithm specified for subjects who do not switch study treatments in Section 10.1.4.1

10.1.5 Exposure during the Double-blind and Open-Label Extension Period based on BKZ set

Definitions for study medication duration (days) and time at risk (days) during the double-blind and Open-Label Extension Period are provided as follows:

10.1.5.1 For subjects who do not switch dose

For subjects randomized to bimekizumab 320mg Q4W at Baseline who continue on the Q4W dose schedule without switching:

Study medication duration (days)

- Date of last bimekizumab dose – date of first bimekizumab dose + 28 days
- Note: If date of last bimekizumab dose + 28 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:
  - Final visit date (including PEOT, but not including SFU) – date of first dose + 1.

  Note: For subjects who die, if date of last bimekizumab dose + 28 days extends to a date beyond the date of death, then this calculation reverts to:
  - Date of death – date of first dose + 1.

Time at risk (days)

- For all subjects, use the minimum of the following:
  - Date of last dose – date of first + 140 days.
  - Date of last clinical contact – date of first dose + 1.
  - Date of death – date of first dose + 1.

For subjects randomized to secukinumab at Baseline who initiate bimekizumab at Week 48 and continue on the same dose schedule in the OLE without switching, use the study medication duration and time at risk algorithms specified for subjects who do not switch study treatments in Section 10.1.4.1

10.1.5.2 For subjects who switch dose

Subjects can switch bimekizumab 320mg dose schedule up to three times during the Double-blind and Open-Label Extension Period. Switches can occur at Week 16, Week 48, and Week 96 or at specific visits during the OLE following amendment 5.0. See Section 2.3.2 for further details regarding switching.

Study medication duration (days)

Total study medication duration attributed to each dose will be obtained by summing the study medication duration(s) at each specific dose in each individual study period. Total study medication duration attributed to BKZ Total will be obtained by summing the study medication durations in each individual study period and deducting n-1, where n is the number of periods covered that are being summed.

Study medication duration at each specific dose in each individual study period is calculated separately as follows:

- Attributed to BKZ 320mg Q4W:
  - Date of last consecutive BKZ 320mg Q4W dose in current study period– date of first consecutive BKZ 320mg Q4W dose in current study period + 28 days

  Note: If date of last consecutive BKZ 320mg Q4W dose in current study period+ 28 days extends to a date beyond the date of first BKZ 320mg Q8W dose in the next study period, then this calculation reverts to:

  - Date of first BKZ 320mg Q8W dose in the next study period – date of first BKZ 320mg Q4W dose in the current study period.

  Note: If BKZ 320mg Q4W is the last dosing schedule received in the last study period the subject receives bimekizumab in and date of last consecutive BKZ 320mg Q4W dose in current study period+ 28 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:

  - Final visit date (including PEOT, but not including SFU) – date of first BKZ 320mg Q4W dose in the current study period + 1.

  Note: For subjects who die, where BKZ 320mg Q4W is the last dosing schedule received in the last study period the subject receives bimekizumab in and date of last consecutive BKZ 320mg Q4W dose in current study period+ 28 days extends to a date beyond the date of death, then this calculation reverts to:

  - Date of death – date of first BKZ 320mg Q4W dose in the current study period + 1.

- Attributed to BKZ 320mg Q8W
  - Date of last consecutive BKZ 320mg Q8W dose in current study period– date of first consecutive BKZ 320mg Q8W dose in current study period + 56 days

  Note: If date of last consecutive BKZ 320mg Q8W dose in current study period+ 56 days extends to a date beyond the date of first BKZ 320mg Q4W dose in the next study period, then this calculation reverts to:

  - Date of first BKZ 320mg Q4W dose in the next study period – date of first BKZ 320mg Q4W dose in the current study period.

  Note: If BKZ 320mg Q8W is the last dosing schedule received in the last study period the subject receives bimekizumab in and date of last consecutive BKZ 320mg Q8W dose in current study period+ 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:

  - Final visit date (including PEOT, but not including SFU) – date of first BKZ 320mg Q8W dose in the current study period + 1.

  Note: For subjects who progress into the OLE2, if date of last bimekizumab dose in the Open-Label Extension Period + 56 days extends to a date beyond the date of first dose in the Open-Label Extension 2 Period then this calculation reverts to:

- First dose date in Open-Label Extension 2 Period– date of first BKZ 320mg Q8W dose in the current study period + 1.

Note: For subjects who die, where BKZ 320mg Q8W is the last dosing schedule received in the last study period the subject receives bimekizumab in and date of last consecutive BKZ 320mg Q8W dose in current study period+ 56 days extends to a date beyond the date of death, then this calculation reverts to:

- Date of death – date of first BKZ 320mg Q8W dose in the current study period + 1.

Time at risk (days)

Total time at risk attributed to each dose will be obtained by summing the time(s) at risk at each specific dose in each individual study period and deducting n-1, where n is the number of non-consecutive periods covered that are being summed. Total time at risk attributed to BKZ Total will be obtained by using the time at risk algorithms specified for subjects who do not switch study treatments in Section 10.1.5.1.

- Time at risk at each specific dose in each individual study period is calculated separately as follows:
  - Attributed to BKZ 320mg Q4W:
    - Date of first BKZ 320mg Q8W dose in the next study period – date of first BKZ 320mg Q4W dose in the current study period.

    Note: If BKZ 320mg Q4W is the last dosing schedule received in the last study period, then this calculation reverts to:

    - For all subjects, use the minimum of the following:
    - Date of last BKZ 320mg Q4W dose in the current study period – date of first BKZ 320mg Q4W dose in the current study period + 140 days.
    - Date of first BKZ 320mg Q8W dose in OLE2 - date of first BKZ 320mg Q4W dose in the Open-Label Extension Period + 1 day. The OLE and The OLE2 treatment periods should not overlap by more than 1 day
    - Date of last clinical contact – date of first BKZ 320mg Q4W dose in the OLE Period + 1.
    - Date of death – date of first BKZ 320mg Q4W dose in the current study period + 1
  - Attributed to BKZ 320mg Q8W:
    - Date of first BKZ 320mg Q4W dose in the next study period – date of first BKZ 320mg Q8W dose in the current study period.

    Note: If BKZ 320mg Q8W is the last dosing schedule received in the last study period, then this calculation reverts to:

    - For subjects who die

      Date of death – date of first BKZ 320mg Q8W dose in the current study period + 1.

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

- Date of last BKZ 320mg Q8W dose in the current study period – date of first BKZ 320mg Q8W dose in the current study period + 140 days.
- Date of first dose in OLE2 - date of first BKZ 320mg Q8W dose in the Open-Label Extension Period + 1 day.
- Date of last clinical contact – date of first BKZ 320mg Q8W dose in the OLE Period + 1.

10.1.6 Exposure during the OLE2 Period based on OLE2 set

Eligible subjects from sites in the US or Canada who have completed the Week 144 Visit or are in the SFU or have completed the SFU of the OLE Period can roll over to an additional OLE2 period.

Definitions for study medication duration (days) and time at risk (days) during the OLE2 Period will be provided for the following subjects:

- Group A: Subjects who roll over directly from OLE to OLE2
- Group B: Subjects who reinitiate bimekizumab and who were in the SFU or had completed the SFU of the OLE Period.

10.1.6.1 Group A: Subjects who roll over directly from OLE to OLE2

Study medication duration (days)

- Date of last bimekizumab dose in the OLE2 Period – date of first dose in the OLE2 Period + 56 days

  Note: If date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

  – Final visit date (including PEOT, but not including SFU2) – date of first dose in the OLE2 Period+ 1.

  Note: For subjects who die, if date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the date of death, then this calculation reverts to:

  – Date of death – date of first dose in the OLE2 Period+ 1.

Time at risk (days)

- Use the minimum of the following:
  – Date of last dose in the OLE2 Period – date of first dose in the OLE2 Period + 140 days.
  – Date of last clinical contact – date of first dose in the Open-Label Extension Period + 1.
  – Date of death – date of first dose in the OLE2 Period+1.

10.1.6.2 Group B: Subjects who reinitiate bimekizumab

10.1.6.2.1 Subjects reinitiated to receive BKZ Q8W at OLE2 start

- Study medication duration (days)

– Date of last bimekizumab dose in the OLE2 period– date of first bimekizumab dose in the OLE2 + 56 days

Note: If date of last bimekizumab dose in the OLE2 + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

– Final visit date (including PEOT, but not including SFU2) – date of first dose in the OLE2 Period + 1.

Note: For subjects who die, if date of last bimekizumab 320mg Q8W dose + 56 days extends to a date beyond the date of death, then this calculation reverts to:

– Date of death – date of first dose in the OLE2 Period + 1.

- Time at risk (days)
  - Use the minimum of the following:
    - Date of last dose – date of first dose in OLE2 + 140 days.
    - Date of last clinical contact – date of first dose in OLE2 + 1.Date of death – date of first dose + 1.

10.1.6.2.2 Subjects reinitiated to receive BKZ Q4W/Q8W at OLE2 start

- Attributed to BKZ Q4W/Q8W
  - Date of last BKZ 320mg Q8W dose in the OLE2 Period – date of first BKZ 320mg Q4W dose in the OLE2 Period + 56 days.

Note: If date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

– Final visit date (including PEOT, but not including SFU2) – date of first BKZ 320mg Q4W dose in the OLE2 Period + 1.

Note: For subjects who die, if date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the date of death, then this calculation reverts to:

– Date of death – date of first dose in the OLE2 Period + 1

- If the subject discontinued prior to the switch to Q8W then:
  - Date of last BKZ 320mg Q4W dose in the OLE2 Period – date of first BKZ 320mg Q4W dose in the OLE2 Period + 28 days.

If date of last bimekizumab dose in the OLE2 Period + 28 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

– Final visit date (including PEOT, but not including SFU2) – date of first BKZ 320mg Q4W dose in the OLE2 Period + 1.

Note: For subjects who die prior to switch to Q8W, if date of last bimekizumab dose in the OLE2 Period + 28 days extends to a date beyond the date of death, then this calculation reverts to:

– Date of death – date of first dose in the OLE2 Period + 1.

Time at risk (days)

- Attributed to BKZ Q4W/Q8W:
  - Use the time at risk algorithm specified for subjects who do not switch study treatments in Section 10.1.6.1.

10.2 Adverse events

An AE is any untoward medical occurrence in a subject 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.

Adverse events will be coded according to the MedDRA. AEs will be allocated to the respective randomized treatment arm. For subjects who switch treatment at Week 16, Week 48 or (on or after Week 64), any adverse events that occur after initiation of the new treatment are attributable to the new treatment. If an adverse event occurs on the date of a treatment switch, the event is attributed to the original treatment. The only exception to this is if the AE fulfills any of the criteria specified below:

- Events that fulfill the anaphylaxis criteria for acute events
- Events that fulfill the hypersensitivity criteria
- Events with an HLT of "Administration site reactions NEC"
- Events with an HLT of "Injection site reactions"

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent adverse events and treatment-emergent serious adverse events will be published.

10.2.1 Data considerations

TEAEs are defined as those AEs that have a start date on or following the first dose of study treatment through the final dose of study treatment + 140 days (covering the 20-week 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.

The rules for imputing partial start or stop dates are outlined in Section 4.2.1.7.

If the intensity of an adverse event is unknown, it is considered as severe. If the relationship to study drug is missing, it is considered as related.

AEs will be presented as "number of subjects (percentage of subjects) [number of events]". In this style of output, "[number of events]" will include all cases of an AE including repeat occurrences in individual subjects, while "number of subjects" will count each subject only once.

Subject time at risk represents the time a subject is at risk for having an AE. The definitions for subject time at risk (in days) are outlined in Section 10.1. These definitions will be used for exposure-adjusted AE summaries.

Selected AE summaries will include the exposure adjusted incidence rate (EAIR) with associated 95% CI and the 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:

$$\text{EAIR} = 100 \times \text{n} / \sum_{\text{i}=1}^{\text{N}} \left(\text{T}_{\text{Exp(i)}}\right)$$

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

If a subject has multiple events, the time of exposure is calculated to the first occurrence of the AE being considered. 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):

$$LCL = \chi^2_{2n,\alpha/2}/2$$

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

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 $\chi 2$.

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:

$$\text{EAER} = 100 \times \text{N}_{\text{AE}} / \sum_{\text{i}=1}^{\text{N}} \left(\text{T}_{\text{Risk(i)}}\right)$$

where N_{AE} is the total number of AEs, $T_{Risk(i)}$ is the time at risk for then ith subject, and N is the total number of subjects at risk.

No confidence interval will be computed for EAER.

Selected summaries, as specified in Section 10.2.2, will include the risk difference between bimekizumab and secukinumab. The risk difference is calculated as:

$$RD = IP_{BKZ} - IP_{SEC}$$

where IP_{BKZ} is the incidence proportion for the bimekizumab-treated group and IP_{SEC} is the incidence proportion for the secukinumab group. Note that incidence proportion simply refers to the percentage of subjects within the specified treatment group that experienced a given adverse event.

The standard error for the risk difference is calculated as follows:

$$SE_{RD} = \sqrt{\left(IP_{BKZ} \times \left(\frac{1 - IP_{BKZ}}{n_{BKZ}}\right)\right) + \left(IP_{SEC} \times \left(\frac{1 - IP_{SEC}}{n_{SEC}}\right)\right)}$$

where n_{BKZ} is the number of subjects in the bimekizumab-treated group and n_{SEC} is the number of subjects in the secukinumab group.

The corresponding confidence interval for the risk difference is as follows:

$$CI_{RD} = RD \pm Z_{1-\alpha/2} \times (SE_{RD})$$

where $Z_{1-\alpha/2}$ is the Z statistic for the corresponding level of alpha. For the risk difference confidence intervals calculated in this SAP, 1.96 will be used (corresponding to a two-sided alpha of 0.05 and 95% confidence interval).

Separate by-subject listings of all TEAEs for the OLE and the OLE2 treatment periods will be provided.

10.2.1.1 COVID-19 related data considerations

In order to assess the impact of the COVID-19 global pandemic on TEAEs, an additional AE summary based on the BKZ set will be presented for the combined Initial, Maintenance, and OLE periods. The following data considerations are introduced to support this presentation by the following periods:

- Prior to COVID-19 pandemic
- During COVID-19 pandemic

The COVID-19 pandemic start date is defined as 11 March 2020 as it is the date the World Health Organization declared COVID-19 as a pandemic, see also Section 4.2.1.7.2. Note that the Week 48 and Week 96 interim analyses will be conducted during the pandemic therefore a post COVID-19 pandemic period is not defined for these analyses. If WHO declares the COVID-19 pandemic has ended prior to Week 144, then that date may be used to support presentation of a post COVID-19 pandemic period.

Where a subject's time at risk includes 11 March 2020, the subject is included in the denominator for both periods and their time at risk is split as follows:

- Prior to COVID-19 pandemic:
  - Start of time at risk to 10 March 2020
- During COVID-19 pandemic:
  - 11 March to end of time at risk

Where a subject's time at risk does not include 11 March 2020, the subject is only included in the denominator for the Prior to COVID-19 pandemic period and their time at risk would be included entirely in the Prior to COVID-19 pandemic period.

Detailed definitions for subject time at risk are outlined in Section 10.1.

AEs are assigned to the appropriate period according to start date:

- Prior to COVID-19 pandemic:

  - AE start date ≤ 10 March 2020

- During COVID-19 pandemic:
  - AE start date ≥ 11 March 2020

Incidence of COVID-19 TEAEs will be summarized for the OLE treatment periods based on the OLS by treatment group.

The following PTs will be used to identify COVID-19 related TEAEs. These will include confirmed and suspected COVID-19 infection:

- Corona virus infection
- Coronavirus test positive

By-subject listings of COVID-19 TEAEs will be produced separately for OLE and OLE2 treatment periods.

To assess the impact of COVID-19 mass vaccination on TEAEs, a sensitivity analysis will present all TEAEs excluding TEAEs assessed as exclusively related to COVID-19 vaccine by the investigator. TEAEs recorded as related to both study medication and COVID-19 vaccination should not be excluded. A complementary table of TEAEs related to COVID-19 vaccine will be presented.

Another sensitivity analysis will present vaccine interval censored TEAEs, that is all TEAEs excluding TEAEs with start date on or up to 5 days after date of COVID-19 vaccine. Note that subjects may receive more than one administration of COVID-19 vaccine. A complementary table and listing of vaccine interval TEAEs, that is TEAEs with start date on or up to 5 days after date of COVID-19 vaccine will also be presented.

Complementary listings of TEAEs related to COVID-19 vaccine will be presented for the OLE and the OLE2 treatment periods separately.

10.2.2 AE summaries

AE summaries will be provided by actual treatment at the time of the adverse event. Separate AE summaries for OLE2 treatment period will be provided by treatment sequence as specified in Section 3.6 and will be based on OLS2.

For subjects who discontinue on or prior to the final scheduled visit of the Initial Treatment Period, any AEs that emerged more than after 112 days relative to the first dose but still within the 140 days SFU window will be classified as TEAE. However, these AEs will be excluded from AE summaries based on the Initial Period but included in the AE summaries for Initial and Maintenance Treatment Period. See the description of time at risk in Section 10.1.1 for further details.

The following selected outputs will be produced for the SS for the Initial Treatment Period, for the MS for the Maintenance Treatment Period, for the SS for the Initial and Maintenance Treatment Period, for the OLS for the Open-Label Extension Period:

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT

- Incidence of Serious TEAEs per 100 subject years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Discontinuation per 100 subject-years by SOC, HLT and PT
- Incidence of TEAEs by decreasing frequency of PT

The following summaries will be provided for the SS for the Initial Treatment Period, for the SS for the Initial and Maintenance Treatment Period:

- Incidence of TEAEs Leading to Death by SOC, HLT, and PT
- Incidence of TEAEs by Maximum Relationship by SOC, HLT, and PT
- Incidence of Serious TEAEs by Relationship, SOC, HLT, and PT – Note: For European Union Drug Regulating Authorities Clinical Trials (EudraCT) reporting purposes
- Incidence of Related Serious TEAEs by SOC, HLT, and PT
- Incidence of TEAEs Leading to Death by Relationship by SOC, HLT, and PT – Note: For EudraCT reporting purposes
- Incidence of TEAEs by Maximum Severity, SOC, HLT, and PT
- Incidence of TEAEs Above Reporting Threshold of 5% by SOC and PT
- Incidence of Non-Serious TEAEs by SOC, HLT, and PT
- Incidence of Non-Serious TEAEs by Maximum Relationship SOC, HLT, and PT
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by SOC and PT
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by Relationship SOC and PT
- Incidence of Related TEAEs by SOC, HLT, and PT
- Incidence of Related TEAEs Above Reporting Threshold of 5% with Risk Differences by SOC and PT

The following summary will be provided by treatment for the Initial and Maintenance Treatment Period (combined) for the SS (only subjects treated with BKZ, only Total BKZ will be summarized):

- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT and by Time of Onset Relative to Anti-bimekizumab Antibody Status

Incidence of TEAEs per 100 subject years by SOC, HLT, and PT and by Time of Onset Relative to COVID-19 pandemic (prior to COVID-19 pandemic, during COVID-19 pandemic).

The following summaries will be provided by treatment for the Initial Treatment Period (SS) as well as for Initial and Maintenance Treatment Period combined (SS):

- Incidence of TEAEs Above Reporting Threshold of 5% with Risk Differences by SOC and PT
- Incidence of Serious TEAEs and Risk Differences by SOC and PT

The tables with risk differences will also be accompanied by figures (dot plots) which show the incidence of the adverse events and corresponding 95% risk difference confidence intervals. These will be ordered by descending order of risk difference (bimekizumab vs secukinumab).

The following selected AEs summaries will be provided separately for the Open-Label Extension Period. Separate AEs summaries will be provided for the OLE2 treatment period by treatment sequence as described in Section 3.6 and will be based on the OLS2:

- Incidence of COVID-19 TEAEs
- Incidence of TEAEs Overview
- Incidence of TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs by Relationship
- Incidence of TEAEs Leading to Discontinuation per 100 subject-years
- Incidence of TEAEs Leading to Death
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by SOC and PT
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by Relationship SOC and PT

In addition, the following AEs summaries will be provided for the Open-Label Extension Periods only, by treatment at the time of AE onset, and will be based separately on the OLS and OLS2.

- Incidence of TEAEs Excluding TEAEs Exclusively Related to COVID-19 Vaccine by SOC, HLT, and PT
- Incidence of TEAEs Exclusively Related to COVID-19 Vaccine by SOC, HLT, and PT
- Incidence of COVID-19 Vaccine Interval Censored TEAEs by SOC, HLT, and PT
- Incidence of COVID-19 Vaccine Interval TEAEs by SOC, HLT, and PT

The following listings will be provided separately for the OLS and OLS2:

- Listing of TEAEs Related to COVID-19 Vaccine
- Listing of COVID-19 Vaccine Interval TEAEs

The following summaries will be provided for the BKZ Set by treatment at the time of AE onset. These tables will include AEs from both the double-blind and Open-Label treatment period (excluding OLE2 treatment period). AEs that occurred while subjects received secukinumab will not be included.

- Incidence of TEAEs Overview
- Incidence of TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs per 100 Subject-Years
- Incidence of TEAEs by decreasing frequency of PT

- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT and by Time of Onset Relative to COVID-19 pandemic (prior to COVID-19 pandemic, during COVID-19 pandemic).

In addition, all summaries of TEAEs based on "100 subject years" will include EAIR (with 95% CI) and EAER.

The following summaries will be presented for subjects who switched from secukinumab to bimekizumab at Week 48. The analyses will assign AEs according to the AE onset date relative to last secukinumab dose and accounting for approximately 5 times half-life (Onset ≤ 140 days from last secukinumab dose or Onset > 140 days from last secukinumab dose):

- Incidence of TEAEs Overview
- Incidence of TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs per 100 Subject-Years

10.2.3 Other Safety topics of interest

The following summaries for AEs of other safety topics of interest will be provided by actual Treatment at the time of the adverse event. The following outputs will be produced separately for the SS for the initial treatment period, for the SS for the Initial and Maintenance Treatment Period, and for the OLS for the Open-Label Extension Period by treatment group (see Section 3.6). No safety topics of interest AE summaries will be produced for the Open-Label Extension 2 treatment period (OLS2).

Similar outputs for hypersensitivity events and hepatic events will also be produced for the Maintenance Treatment Period for the MS.

Additional analyses will be presented for subjects who switched from secukinumab to bimekizumab at Week 48 and the AEs will be assigned according to the onset date relative to last secukinumab dose and accounting for approximately 5 times half-life (Onset ≤ 140 days from last secukinumab dose or Onset > 140 days from last secukinumab dose).

Along with the tables described, there will be tables which displays the risk difference and 95% confidence intervals for each of the topics of interest during the Initial Treatment Period (SS) as well as for Initial and Maintenance Treatment Period combined (SS). Corresponding figures (with dot plots) will be prepared.

Listings of all treatment emergent adverse events of other safety topics of interest will be provided separately for the OLE and the OLE2 treatment periods.

10.2.3.1 Infections (serious, opportunistic, fungal and Tuberculosis [TB])

- **Incidence of Serious Infection TEAEs per 100 subject years by SOC, HLT and PT**

Serious infections will be identified based on MedDRA classification (SOC "Infections and infestations") using the "Any SAE" table. A separate table does not need to be produced to summarize these events.

- **Incidence of Fungal Infection TEAEs per 100 subject years by SOC, HLT and PT**

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

- **Incidence of Opportunistic Infection TEAEs per 100 subject years by SOC, HLT and PT**

Opportunistic infections (including tuberculosis) will be summarized in a stand-alone table. The table will include all opportunistic infection TEAEs identified using UCB-defined search criteria which were adjudicated as opportunistic infections.

The following steps are followed for identifying and reviewing opportunistic infections:

Identification Process

The two steps below outline two ways in which opportunistic infections (or potential opportunistic infections) can be identified:

Step 1: Refer to column B of the spreadsheet which identifies the Preferred Terms (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 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.

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 to determine whether or not it is an opportunistic infection. If Column C has a single 'x', then the corresponding preferred term should be flagged for case-by-case review by the study physician.

Review Process

Opportunistic infections for a given study will be reviewed on the following occasions:

- At quarterly Infectious Disease Committee (IDC) Meetings, listings will be produced for each study (see details below) and reviewed by the corresponding study physician ahead of the IDC Meeting. These listings will be posted as part of the broader SSD deliverable to a folder named for the given quarter (eg, 2018Q4) on the SharePoint. They should be based on the same data cut as the one used for SSD and should be delivered at the same time as the SSD outputs. The IDC will then agree on the final adjudication for each potential opportunistic infection.
- For each study, a final listing for opportunistic infections (in the format described below) will be produced and agreed upon between the study physician and the IDC prior to finalizing the database.

In each of the circumstances described above, the study programming team will produce an Excel listing that will be provided to the project lead statistician, project lead programmer, and to the study physician (who will subsequently provide it to the IDC). The Excel listing will contain the following columns (using the descriptions below as the column headings in the Excel listing):

- Study ID

- Unique Subject ID
- AE Term (Verbatim)
- AE Preferred Term
- AE System Organ Class
- AE High Level Term
- AE Low Level Term
- Date of Onset
- Outcome of Adverse Event
- Date of Outcome
- TEAE Flag
- Serious Adverse Event?
- Relationship to Study Medication
- Intensity
- Action Taken with IMP
- Opportunistic Infection – Automatic
- Opportunistic Infection – Manual Review
- Flag
- Data Cut Date
- Opportunistic Infection – Final Adjudication

Note the following about the final 5 variables in this listing:

- *Opportunistic Infection – Automatic*: This is flagged as "Y" if the criteria for automatic selection as described in "Step 1" of the identification process are met.
- *Opportunistic Infection – Manual Review*: This is flagged as "Y" if the criteria for case-by-case selection as described in "Step 2" of the identification process are met.
- *Flag* – This has a value of either "NEW" or "OLD". It is marked as "NEW" if the event is appearing for the first time in that run of the listing. Otherwise, if it has appeared previously, it is marked as "OLD". Unique records are determined by USUBJID AESPID for purposes of identifying whether an event has been modified from a previous run.
- *Date* – Only for cases where Flag is "NEW", this field will be populated with the data cut date for that particular run of the listing.
- *Opportunistic Infection – Final Adjudication* – For new events, this is always left blank by the programmers. It should be completed by the study physician/IDC for every event that appears in the listing. For events adjudicated as opportunistic, the field should be populated with a "Y".

Following each review by the study physician and IDC, the Opportunistic Infection –Final Adjudication column will be completed (as described above), and the spreadsheets for each study will be returned to the study programming team via e-mail (coordinated by the IDC secretary). Then, for subsequent runs of the listing, the study programming teams will incorporate adjudications from previous runs.

10.2.3.2 Malignancies

- **Incidence of Malignant or Unspecified Tumours TEAEs per 100 subject years by SOC, HLT and PT**

These events will be presented in the following tables:

- One table will be based on the criteria (SMQ) = "Malignant or unspecified tumours (SMQ)"
- One table will be based on the criteria SMQ = "Malignant tumours (SMQ)".

SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each 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. While the "Malignant tumours (SMQ)" is most relevant, "Malignant or unspecified tumours (SMQ)" must be reviewed for potential malignancies.

The output table will include 2 different overall incidence 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 (using the appropriate SMQ depending on the table), regardless of the High Level Term (HLT) it codes to
- The second overall incidence row will summarize "Any malignancy excluding non-melanomic skin cancers HLT" and this row will summarize the incidence of AEs flagged for inclusion in the table (using the appropriate SMQ depending on the table), excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".

10.2.3.3 Cardiac events

- **Incidence of Major Adverse Cardiac Event (MACE) TEAEs per 100 subject years by SOC, HLT and PT**

Potential cardiovascular events are adjudicated by the independent Cardiovascular Event Adjudication Committee (CV-CAC) according to the CV-CAC Charter (version 6.0). Adjudicated events are classified by the CV-CAC to one of the event types as defined in the cardiovascular event classifications Table below. The classification of an event as a Major Adverse Cardiac Event (MACE) is also determined by the CV-CAC. Events which are classified by the CV-CAC as any of the event types identified in the third column of the table will be considered an extended MACE. Note that extended MACE is determined programmatically and includes a broader scope definition of MACE.

MACE as determined by the CV-CAC will be presented in a table and listing. Extended MACE will be presented separately in a table and listing. Additional listings of all MACE as determined by the CV-CAC will be presented separately for the OLE and the OLE2 treatment periods.

Another table and listing will present the adjudicated cardiovascular events by type. For each cardiovascular event type, the individual PTs which fall within each event type will be summarized. This listing will indicate whether each event was determined to be a MACE and/or an extended MACE. Similar listings of the adjudicated cardiovascular events by type will be presented separately for the OLE and the OLE2 treatment periods.

Additionally, a listing of all events identified for potential review by the CV-CAC will be produced. This listing will indicate whether each event was identified by the CV-CAC Chair for full committee review. Similar listings of all events identified for potential review by the CV-CAC will be produced separately for the OLE and the OLE2 treatment periods.

Cardiovascular event classifications

Event Type Code	Event Type	Extended MACE
1	Non-Fatal Myocardial Infarction (MI)	Yes
2	Non-Fatal Stroke: hemorrhagic	Yes
3	Non-Fatal Stroke: ischemic	Yes
4	Non-Fatal Stroke: embolic	Yes
5	Non-Fatal Stroke: undeterminable	Yes
6	Hospitalization or ER for Unstable Angina with urgent revascularization	Yes
7	Hospitalization or ER for Unstable Angina without urgent revascularization	No
8	Hospitalization for Heart Failure	Yes
9	Transient Ischemic Attack (TIA)	No
10	Coronary Revascularization Procedures (e.g. percutaneous coronary intervention, coronary artery bypass grafting)	Yes
11	Urgent Revascularization Procedures (i.e. due to symptoms of brain ischemia or pending infarction)	Yes
12	Arrhythmia (not associated with ischemia)	No
13	Peripheral Arterial Event	No
14	Venous Thromboembolic Event: pulmonary embolism (PE)	No
15	Venous Thromboembolic Event: deep vein thrombosis (DVT)	No
16	Venous Thromboembolic Event: PE and DVT	No

Cardiovascular event classifications

Event Type Code	Event Type	Extended MACE
17	Other CV Event	No
18	Death due to Myocardial Infarction (MI)	Yes
19	Death due to Stroke	Yes
20	Sudden Cardiac Death	Yes
21	Other CV Death (e.g. heart failure, pulmonary embolism, cardiovascular procedure-related)	Yes
22	Cardiovascular: Undetermined Cause of Death (i.e. cause of death unknown)	Yes
23	Non-Cardiovascular Death	No
24	Non-Cardiovascular Event	No
99	Inadequate information to adjudicate	No

CV=Cardiovascular; DVT=Deep Vein Thrombosis; ER=Emergency Room; MACE=Major Adverse Cardiac Event; MI=Myocardial Infarction; PE=Pulmonary Embolism; TIA=Transient Ischemic Attack.
MACE is determined by the adjudication committee and is not identified programmatically based on event type.

10.2.3.4 Neutropenia

- **Incidence of Neutropenia TEAEs per 100 subject years by SOC, HLT and PT**

A table based on the following PTs (regardless of seriousness) will be produced:

- Autoimmune neutropenia
- Band neutrophil count decreased
- Cyclic neutropenia
- Febrile neutropenia
- Idiopathic neutropenia
- Neutropenia
- Neutropenic infection
- Neutropenic sepsis
- Neutrophil count decreased

10.2.3.5 Suicidal Ideation and Behavior (SIB)

- **Incidence of SIB-Adjudicated Neuropsychiatric TEAEs per 100 subject years by SOC, HLT and PT**

Potential neuropsychiatric events are adjudicated by the independent Neuropsychiatric Adjudication Committee according to the Neuropsychiatric Adjudication Committee (version 8.0). Adjudicated events are classified by the Committee as Suicidal or Non-suicidal. Adjudicated events are also further classified by the Committee to one of the event types as defined in neuropsychiatric event classifications Table below. Suicidal Ideation and Behavior (SIB) is defined as events classified by the Committee as Suicidal.

A table and listing will present SIB events. This listing will also be provided separately for OLE and OLE2 treatment periods.

Another table and listing will present the adjudicated neuropsychiatric events by type. For each neuropsychiatric event type, the individual PTs which fall within each event type will be summarized. This listing will indicate whether each event was determined to be Suicidal or Non-Suicidal. For event type suicidal ideation, the listing will also indicate if intent was present and if the suicidal ideation was clinically significant. A similar listing of the adjudicated neuropsychiatric events by type will be presented.

Additionally, a listing of all events identified for potential review by the Committee will be produced. This listing will indicate whether each event was identified by the Neuropsychiatric Event Adjudication Committee Chair for full committee review. Similar listings will be provided separately for the OLE and the OLE2 treatment periods.

Neuropsychiatric event classifications

Event Type Code	Event Classification	Event Type
1	Suicidal	Suicidal events/completed suicide
2	Suicidal	Suicide attempt
3	Suicidal	Preparatory acts toward imminent suicidal behavior
4	Suicidal/Non-suicidal[a]	Suicidal ideation
7	Non-suicidal	Nonsuicidal Self-injurious behavior
8	Non-suicidal	Nonsuicidal Other
99	Not applicable	Inadequate information to adjudicate

Suicidal ideation event types can be classified by the Neuropsychiatric Adjudication Committee as Suicidal or Non-suicidal depending on whether intent to die was present

10.2.3.6 Inflammatory bowel disease

- **Incidence of Inflammatory Bowel Disease TEAEs per 100 subject years by SOC, HLT and PT**

Selected gastrointestinal events are adjudicated by the independent Inflammatory Bowel Disease (IBD) Adjudication Committee (IBD-CAC) according to the IBD-CAC Charter (version 3.0). Adjudicated events are classified by the IBD-CAC into one of the diagnostic types as defined in

the IBD event classifications Table below. The events will further be classified as definite, probable or possible IBD.

An overview of adjudicated IBD events will be stratified by subjects with or without a previous medical history of IBD. Previous medical history of IBD will be determined using the information recorded on the Extra-Articular Assessment at Screening CRF page ("Does subject have a history of IBD?"). This overview table will present events adjudicated by the IBD-CAC as either possible, probable or definite IBD. Definite and probable IBD will also be aggregated and summarized in this table. In addition, this table will summarize each IBD event classification (possible, probable or definite) separately.

Another table and listing will present the adjudicated IBD events by type. For each IBD event type, the individual PTs which fall within each event type will be summarized. Similar listings of the adjudicated IBD events by type will be presented separately for OLE and OLE2 treatment periods.

Additionally, a listing of all events identified for potential review by the IBD-CAC will be produced. This listing will indicate whether each event was identified by the IBD-CAC Chair for full committee review. Similar listings of all events identified for potential review by the IBD-CAC Chair for full committee review will be produced separately for the OLE and the OLE2 treatment periods.

A further supportive listing will present the individual diagnostic criteria met for each adjudicated IBD event. This listing will also be presented separately for the OLE and the OLE2 treatment periods combined.

IBD event classifications

Event Type Code	Event Type (Classification and diagnosis)	Classification
1	Possible Inflammatory Bowel Disease – Crohn's Disease	Possible
2	Probable Inflammatory Bowel Disease – Crohn's Disease	Probable
3	Definite Inflammatory Bowel Disease – Crohn's Disease	Definite
4	Possible Inflammatory Bowel Disease – Ulcerative Colitis	Possible
5	Probable Inflammatory Bowel Disease – Ulcerative Colitis	Probable
6	Definite Inflammatory Bowel Disease – Ulcerative Colitis	Definite
7	Possible Inflammatory Bowel Disease – type unclassified	Possible
8	Probable Inflammatory Bowel Disease – type unclassified	Probable
9	Definite Inflammatory Bowel Disease – type unclassified	Definite
10	Symptoms not consistent with Inflammatory Bowel Disease	Not applicable
11	Possible Inflammatory Bowel Disease – Microscopic Colitis	Possible
12	Probable Inflammatory Bowel Disease – Microscopic Colitis	Probable

IBD event classifications

Event Type Code	Event Type (Classification and diagnosis)	Classification
13	Definite Inflammatory Bowel Disease – Microscopic Colitis	Definite
14	Possible Inflammatory Bowel Disease – no further differentiation possible	Possible
15	Probable Inflammatory Bowel Disease – no further differentiation possible	Probable
16	Definite Inflammatory Bowel Disease – no further differentiation possible	Definite
99	Not enough information to adjudicate	Not applicable

IBD=inflammatory bowel disease.

Note: IBD diagnoses of "microscopic colitis" and "no further differentiation possible" were added in an adjudication charter amendment, accounting for the event type numbering.

10.2.3.7 Hypersensitivity (including anaphylaxis)

- **Incidence of Anaphylactic Reaction TEAEs per 100 subject years by SOC, HLT and PT**

A separate table will be prepared based on the MedDRA anaphylaxis Algorithm (see Appendix A) for acute anaphylactic events (reported on the same day as when an injection was administered or one day after). An AE glossary table will also be produced to summarize the MedDRA coding for these events. The glossary table will include the following fields: reported term, PT, LLT, HLT, and SOC.

A separate table will be prepared to summarize hypersensitivity events, identified using the SMQ "Hypersensitivity (SMQ)". All TEAEs which code to a PT included in the Scope=Narrow search will be included in this table. In addition, a separate table will be prepared to summarize serious hypersensitivity events, identified using the SMQ "Hypersensitivity (SMQ)". All serious TEAEs which code to a PT included in the Scope=Narrow search will be included in this table. An AE glossary table will also be produced to summarize the MedDRA coding for these events. The glossary table will include the following fields: reported term, PT, LLT, HLT, and SOC.

Furthermore, a separate table will be prepared to summarize injection site reactions, identified using the HLTs: "Administration site reactions NEC" and "Injection site reactions".

10.2.3.8 Hepatic events

- **Incidence of hepatic events TEAEs per 100 subject years by SOC, HLT and PT**

A table for hepatic events will be created based on the SMQ of "Drug related hepatic disorders - comprehensive search (SMQ)". However, these 2 sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)". For each of the above SMQs, include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow.

Note that all AEs meeting the above criteria are to be included. It should not be limited to events that the investigator determined to be related to study drug.

Cases of Hy's Law will be reported separately in a liver function test table.

A by-subject listing of all AEs of safety topics of interest by type of safety topics of interest will be provided.

10.3 Clinical laboratory evaluations

If not specified otherwise, laboratory values, including markedly abnormal laboratory values will be presented descriptively by treatment group for the SS. Tables presenting markedly abnormal values and those based on CTCAE grade only include selected laboratory variables.

For tables where data are summarized by visit, unscheduled and repeat visits will not be summarized, but these data will be included in listings. For tables where multiple measurements over a period of time are considered (as in shift tables), unscheduled and repeat visits will be considered as long as they were collected in the period being summarized. All summaries will be presented in SI units and will be based on observed case values. 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. The following summaries are required:

- A summary of observed results and change from Baseline values in each laboratory variable by treatment group and visit
- A summary of the number and percentage of subjects experiencing markedly abnormal values at any time while on treatment (assessment on or following the first dose of study treatment through the final dose of study treatment + 140 days) by laboratory variable and treatment group. Two separate tables will show results for the initial treatment period (for the SS) and the Initial and Maintenance Treatment Period (for the MS). An additional table for the OLE period will be provided for the OLS by treatment the subjects were receiving at the time of the assessment of the abnormal value.
- A summary of the number and percentage of subjects with a given CTCAE grade (0, 1, 2, 3, or 4) based on minimum/maximum post-baseline value by laboratory variable and treatment group. Two separate tables will show results for the initial treatment period (for the SS) and the Initial and Maintenance Treatment Period (for the MS). An additional table for the OLE period will be provided for the OLS by treatment the subjects were receiving at the time of the assessment of the value with the given CTCAE grade.
- A shift table of the number and percentage of subjects experiencing CTCAE grade 0, 1, 2, 3, or 4 values (as applicable) at Baseline to minimum/maximum post-Baseline CTCAE grade, by laboratory variable and treatment group. Two separate tables will show results for the initial treatment period (for the SS) and the Initial and Maintenance Treatment Period (for the MS). An additional table for the OLE period will be provided for the OLS by treatment the subjects were receiving at the time of the assessment of the value with the given CTCAE grade. A lipid profile table of treatment emergent markedly abnormal laboratory data will be provided for the Initial and Maintenance Treatment Period (SS) and the Open-label Extension treatment period (OLS) separately.

In addition, a shift table of number and percentage of subjects experiencing post-Baseline HDL Low risk (≥ 1.55 mmol/L), Intermediate risk (≥ 1.04 - < 1.55 mmol/L) and High risk (< 1.04 mmol/L) compared to baseline will be provided for the Initial and Maintenance Treatment Period (SS) and the Open-Label Extension Treatment Period (OLS).

Shift laboratory summaries will use the Baseline for Open-Label Extension Period for subjects switching from secukinumab to Bimekizumab as described in Section 3.2.

A figure of neutrophil values over time for subjects with at least one markedly abnormal neutrophil value (CTCAE Grade 3 or 4) will also be presented.

A by-subject listing of all laboratory data (including urinalysis) will be provided. Separate by-subject listings for the OLE and the OLE2 treatment periods will be provided. These listings will be presented by treatment group and will include: center, subject identifier, age, sex, race, weight, visit, laboratory variable, result (with abnormal values flagged as "L" or "H" accordingly) and unit.

Markedly abnormal values are defined as those with a severity of Grade 3 and above based on the common terminology criteria for adverse events (CTCAE) criteria (U.S. Department of Health and Human Services 2010). Definitions of markedly abnormal values using the Grade 3 cut points are given in the tables below for age ranges of ≥17 years (Table 10–1 for markedly abnormal liver function test values, Table 10–2 for markedly abnormal biochemistry values and Table 10–3 for markedly abnormal hematology values). Tables summarizing markedly abnormal values should include a summary (counts and percentages) of markedly abnormal labs observed at any time while on treatment (ie, treatment-emergent markedly abnormal [TEMA]). For this summary, Baseline values and values observed more than 140 days after the last administration of study medication are not considered. The laboratory results classified as Grade 3 or Grade 4 will be summarized and listed separately.

Table 10–1: Definitions of Markedly Abnormal Liver Function Values

Parameter Name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Alkaline Phosphatase	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH
ALT	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH
AST	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH
Total Bilirubin	mg/dL	>3.0 x ULN	umol/L	>3.0 x ULN	AH
GGT	U/L	>5.0 x ULN	U/L	>5.0 x ULN	AH

Table 10–2: Definitions of Markedly Abnormal Biochemistry Values

Parameter Name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Creatinine	mg/dL	>3.0 x ULN	mmol/L	>3.0 x ULN	AH

Parameter Name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Glucose	mg/dL	<40 >250	mmol/L	<1.7 >13.9	AL AH
Calcium	mg/dL	>12.5 <7.0	mmol/L	>3.1 <1.75	AH AL
Magnesium	mg/dL	>3.0 <0.9	mmol/L	>1.23 <0.4	AH AL
Potassium	mmol/L	>6.0 <3.0	mmol/L	>6.0 <3.0	AH AL
Sodium	mmol/L	>155 <130	mmol/L	>155 <130	AH AL
Total Cholesterol	mg/dL	>400	mmol/L	>10.34	AH
HDL Cholesterol	mg/dL	<40	mmol/L	<1.04	AL
LDL Cholesterol	mg/dL	≥190	mmol/L	≥ 4.90	AH
Triglycerides	mg/dL	>500	mmol/L	> 5.7	AH

Table 10–3: Definitions of Markedly Abnormal Hematology Values

Parameter Name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Hemoglobin	g/dL	<8.0 >4.0 above ULN	g/L	<80 >40 above ULN	AL AH
Lymphocytes Absolute	$10^{9/L}$	<0.5 >20.0	$10^{9/L}$	<0.5 >20.0	AL AH
Neutrophils Absolute	$10^{9/L}$	<1.0	$10^{9/L}$	<1.0	AL
Platelets	$10^{9/L}$	<50	$10^{9/L}$	<50	AL
WBC/Leukocytes	$10^{9/L}$	<2.0 >100	$10^{9/L}$	<2.0 >100	AL AH

Abbreviations: AH=abnormal high; AL=abnormal low; ALT= alanine aminotransferase; AST = aspartate aminotransferase; dL = deciliter; GGT: gamma-glutamyl transferase; L = liter; mg = milligram; mmol = millimoles; µg = microgram; ULN = upper limit of normal.

The table for markedly abnormal liver function tests (LFTs) will contain data beyond the CTCAE Grade 3 thresholds outlined above in Table 10–1 in order to allow for a more thorough

review of elevated LFTs. There will be one table which will list the count and percentage of subjects meeting the below criteria at any time during the study:

- AST: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- AST or ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN
- Bilirubin: >1.5xULN, >2xULN

In addition, a table will be produced to summarize potential Hy's Law cases. The following two definitions will be used in that table:

- [AST ≥3xULN or ALT ≥3xULN] and
- Total Bilirubin ≥2xULN in the absence of ALP ≥2xULN

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST (and the absence of ALP elevation, if applicable) at the same visit. For example, a subject who experiences a ≥2 x ULN elevation of bilirubin at one visit and a ≥3xULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria.

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

A table for potential drug induced liver injuries (pDILI) will be presented by treatment group for subjects with at least one post-Baseline liver laboratory assessment. Number and percentage of subjects meeting laboratory criteria for pDILI for at least 1 visit and reporting at least 1 symptom potentially associated with hepatitis or hypersensitivity according to the Investigator on the pDILI CRF will be presented. Subjects who potentially meet Hy's law criteria at least 1 time during exposure must meet all criteria at the same visit to be counted as potential Hy's Law.

Spaghetti plots of AST values over time for the subset of subjects with at least one markedly abnormal AST value (CTCAE Grade 3 or 4) will also be presented. A similar set of plots will be produced for ALT values over time for the subset of subjects with at least one markedly abnormal ALT value (CTCAE Grade 3 or 4).

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

10.4.1 Vital signs

The following vital signs variables should be summarized: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C) and heart rate (beats/min). The following summary will be provided for the Initial Treatment Period (SS) for Initial and Maintenance Treatment Period, and for the Open-Label Extension Period (OLS). Vital signs will not be summarized for the OLE2.

- A summary of the absolute and change from Baseline value for each vital sign variable by treatment group and visit.

- A shift from Baseline to Post-Baseline systolic and diastolic blood pressure values based on the following categorization will be provided for the Initial and Maintenance Treatment Period (SS), and the Open-label Extension Period (OLS):
  - Hypotension: systolic blood pressure <90 mmHg *or* diastolic blood pressure <60
  - Normal: systolic blood pressure ≥90 and <120 mmHg *and* diastolic blood pressure ≥60 and <80 mmHg
  - Elevated: systolic blood pressure between 120-129 mmHg *and* diastolic blood pressure <80
  - Stage 1: systolic blood pressure between 130-139 mmHg *or* diastolic blood pressure between 80-89
  - Stage 2: systolic blood pressure ≥140 and ≤180 mmHg *or* diastolic blood pressure ≥90 and ≤120 mmHg
  - Hypertensive crisis: systolic blood pressure >180 mmHg *and/or* diastolic blood pressure >120 mmHg.

The following summary will be provided for the Initial Treatment Period (SS), the Initial and Maintenance Treatment Period (SS), and the open-Label Extension Period (OLS):

- A summary of the number and percentage of subjects experiencing at least one markedly abnormal value for a vital sign variable as defined in Table 10–4, by treatment group.

Table 10–4: Definitions of Markedly Abnormal Blood Pressure Values

Parameter (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

A by-subject listing of all vital signs data will be provided. This listing will be presented by treatment group and will include center, subject identifier, age, sex, race, weight, visit, vital sign variable and result (with abnormal values flagged as "L" or "H" accordingly). This listing will also be provided separately for the OLE and the OLE2 treatment periods.

10.4.2 Physical examination

Abnormal results of the physical examination together with details of abnormalities: abnormality clinically significant or not, will be listed by subject and visit separately for the Initial and Maintenance (SS), Open-Label Extension (OLS) and Open-Label Extension 2 (OLS2) treatment periods.

10.4.3 Electrocardiograms

ECG data will be analyzed by treatment group and visit for the Initial Treatment Period (SS), the Initial and Maintenance Treatment Period (SS), and by treatment sequence for the Open-Label Extension Period (OLS).

A summary of the number and percentage of subjects with normal and abnormal ECG results, as determined by the central reader, will be presented for all applicable visits.

The following ECG variables will be summarized (absolute values and change from Baseline) by visit: QTcF, RR, PR, QRS and QT.

QTc outliers are defined as QTcF values following dosing that are greater than 450 ms or are increases from Baseline greater than 30 ms. QTcF outliers will be highlighted in the data listings and summarized using the following categories:

- Values >450 ms, >480 ms, >500 ms
- Increase from Baseline of >30 ms, increase from Baseline of >60 ms, increase from Baseline of >90 ms
- Values >450 ms and increases of >30 ms. Values >500 ms and increases of >60 ms

The number and percentage of subjects who meet the ECG outlier criteria at any assessment post first dose will be summarized.

Two separate by-subject listing of all 12-lead ECG data will be provided based on interpretation from central reader and from site.

10.4.4 Other safety variables

10.4.4.1 Assessment and management of TB and TB risk factors

A summary of the number and percentage of subjects with negative, positive, and indeterminate IGRA (Interferon-Gamma Release Assay) results at all applicable visits will be presented for the entire study.

A by-subject listing of the "Evaluation of signs and symptoms of tuberculosis" questionnaire data and IGRA results will be provided. This listing will also be provided separately for the OLE and the OLE2 treatment periods.

A by-subject listing of the result of chest x-ray for tuberculosis will be provided by treatment.

10.4.4.2 Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

eC-SSRS questionnaire will be self-administered by the subject and assessed by trained study personnel. This scale will be used to assess suicidal ideation and behavior that may occur during the study. Results of the eC-SSRS will be summarized using the number of subject and percentage with (i) events in suicide behavior, (ii) suicidal ideation, (iii) suicidal behavior and ideation, and (iv) self-injurious behavior without suicidal intent.

Suicidal ideation is defined as an event in any of the following 5 categories:

- Wish to be dead
- Non-specific active suicidal thoughts
- Active suicidal ideation with any methods (not plan), without intent to act
- Active suicidal ideation with some intent to act, without specific plan
- Active suicidal ideation with specific plan and intent

Suicidal behavior is defined as an event in any of the following 4 categories:

- Actual attempt
- Interrupted attempt
- Aborted attempt
- Preparatory acts or behavior

Suicidal behavior or ideation is defined as an event in any of the above 9 categories.

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

The incidence of subjects with suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior will be summarized by treatment group. For events that emerged after 112 days but still within the 140 days window, those events would be classified as treatment emergent, but will be excluded from the output based on the Initial Treatment Period. However, these events will be included in the summaries for Initial Treatment Period and Maintenance Treatment Period combined. Similar summaries will be presented for the Open-Label Extension Period (OLS) by treatment sequence and visit.

A by-subject listing of the eC-SSRS questionnaire data will be provided by treatment group. This listing will also be provided separately for the OLE and the OLE2 treatment periods.

10.4.4.3 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening. The pregnancy test will be urine at all other visits.

A by-subject listing of the pregnancy test data will be provided by treatment group.

10.4.4.4 Childbearing potential and Lifestyle

Childbearing potential and lifestyle will be collected at Screening. A by-subject listing will be provided for all the subjects screened.

10.4.4.5 Patient Health Questionnaire 9 (PHQ-9)

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. The PHQ-9 scores for depression range from 0 to 27 with higher scores indicating worse state. A score of 5-9 is considered to be minimal symptoms of depression. A score of 10 to 14 is considered minor depression, dysthymia, or mild major depression. A score of 15 to 19 is considered to indicate moderately severe major depression, and a score ≥20 is considered to be severe major depression. If any of the 9 questions are missing, then the score is treated as missing.

Change from Baseline in PHQ-9 is derived as post-Baseline score minus Baseline score and will be summarized by treatment group.

Differently to other safety variables, PHQ-9 will be summarized using the MCMC/monotone regression approach described in Section 8.1.3.1. A table for the SS through Week 48 will be produced. An additional table will be produced for the OLS by treatment sequence and visit.

The number and percentage of subjects with a PHQ-9 score ≥ 15 at any point while on treatment and the number and percentage of subjects with a PHQ-9 score ≥ 20 at any point while on treatment will also be presented based on observed case data.

A by-subject listing of PHQ-9 data will be provided separately for the OLE and the OLE2 treatment periods. This listing will include site, subject number, visit, total score observed result, and total score change from Baseline value.

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12 APPENDICES

12.1 Appendix A: MedDRA algorithmic approach to anaphylaxis

The SMQ *Anaphylactic reaction* consists of three parts:

1. A **narrow search** containing PTs that represent core anaphylactic reaction terms

- Category A – core anaphylactic reaction terms
  - Anaphylactic reaction
  - Anaphylactic shock
  - Anaphylactic transfusion reaction
  - Anaphylactoid reaction
  - Anaphylactoid shock
  - Circulatory collapse
  - Dialysis membrane reaction
  - Kounis syndrome
  - Procedural shock
  - Shock
  - Shock symptom
  - Type I hypersensitivity

2. A **broad search** that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction and categorized in B, C, or D.

- Category B (Upper Airway/Respiratory terms)
  - Acute respiratory failure
  - Asthma
  - Bronchial oedema
  - Bronchospasm
  - Cardio-respiratory distress
  - Chest discomfort
  - Choking
  - Choking sensation
  - Circumoral oedema
  - Cough
  - Cough variant asthma

- Cyanosis
- Dyspnoea
- Hyperventilation
- Irregular breathing
- Laryngeal dyspnoea
- Laryngeal oedema
- Laryngospasm
- Laryngotracheal oedema
- Mouth swelling
- Nasal obstruction
- Oedema mouth
- Oropharyngeal oedema
- Oropharyngeal spasm
- Oropharyngeal swelling
- Pharyngeal oedema
- Pharyngeal swelling
- Respiratory arrest
- Respiratory distress
- Respiratory failure
- Reversible airways obstruction
- Sensation of foreign body
- Sneezing
- Stridor
- Swollen tongue
- Tachypnoea
- Throat tightness
- Tongue oedema
- Tracheal obstruction
- Tracheal oedema
- Upper airway obstruction
- Wheezing

- Category C (Angioedema/Urticaria/Pruritus/Flush terms)
  - Acquired C1 inhibitor deficiency
  - Allergic oedema
  - Angioedema
  - Circumoral swelling
  - Erythema
  - Eye oedema
  - Eye pruritus
  - Eye swelling
  - Eyelid oedema
  - Face oedema
  - Flushing
  - Hereditary angioedema with C1 esterase inhibitor deficiency
  - Injection site urticaria
  - Lip oedema
  - Lip swelling
  - Nodular rash
  - Ocular hyperaemia
  - Oedema
  - Oedema blister
  - Periorbital oedema
  - Periorbital swelling
  - Pruritus
  - Pruritus allergic
  - Rash
  - Rash erythematous
  - Rash pruritic
  - Skin swelling
  - Swelling
  - Swelling face
  - Swelling of eyelid

  - Urticaria
  - Urticaria papular
- Category D (Cardiovascular/Hypotension terms)
  - Blood pressure decreased
  - Blood pressure diastolic decreased
  - Blood pressure systolic decreased
  - Cardiac arrest
  - Cardio-respiratory arrest
  - Cardiovascular insufficiency
  - Diastolic hypotension
  - Hypotension
  - Hypotensive crisis
  - Post procedural hypotension

3. An **algorithmic approach** which combines a number of anaphylactic reaction symptoms in order to increase specificity. A case must include one of the following where both occur on either the same day as when an injection was administered or one day after, and for scenarios where two must have been reported, both events must have occurred within one day of each other:

- A narrow term or a term from Category A
- A term from Category B – (Upper Airway/Respiratory) AND a term from Category C – (Angioedema/Urticaria/Pruritus/Flush)
- A term from Category D – (Cardiovascular/Hypotension) AND [a term from Category B – (Upper Airway/Respiratory) OR a term from Category C – (Angioedema/Urticaria/Pruritus/Flush)
- Hypersensitivity events will be identified using the "Hypersensitivity (SMQ)". All TEAEs which code to a PT included in the Scope=Narrow search will be included.

12.2 Appendix B: Definition of CTCAE grades

Table 12–1: Definitions of CTCAE grades by biochemistry parameter

Parameter (unit)	Definition	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase	High	UL	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline Phosphatase	High	UL	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate Aminotransferase	High	U/L	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Bilirubin	High	umol/L	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Gamma Glutamyl Transferase	High	U/L	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Glucose	High	mg/dL	Fasting glucose value >ULN - 160 mg/dL;	Fasting glucose value >160 - 250 mg/dL;	>250 - 500 mg/dL hospitalization indicated	>500 mg/dL lifethreatening consequences
Creatinine	High	mmol/L	>ULN- 1.5 x ULN	(>1.5 – 3.0) x ULN	(>3.0 – 6.0) x ULN	6.0 x ULN
Sodium	Low	mmol/L	130- <LLN	N/A	120-<130	<120
Sodium	High	mmol/L	>ULN- 150	>150- 155	>155-160	>160
Potassium	Low	mmol/L	3.0- <LLN	3.0- <LLN	2.5-<3.0	<2.5
Potassium	High	mmol/L	>ULN- 5.5	>5.5- 6.0	>6.0-7.0	>7.0
Calcium	Low	mmol/L	2.0- <LLN	1.75- <2.0	1.5-<1.75	<1.5
Calcium	High	mmol/L	>ULN- 2.9	>2.9- 3.1	>3.1-3.4	>3.4

Magnesium	Low	mmol/L	0.5-<LLN	0.4-<0.5	0.3-<0.4	<0.3
Magnesium	High	mmol/L	>ULN-1.23	N/A	>1.23-3.30	>3.30
Total cholesterol	High	mmol/L	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92
Triglyceride	High	mmol/L	1.71 - 3.42	>3.42 - 5.7	>5.7 - 11.4	>11.4

Table 12–2: Definitions of CTCAE grades by hematology parameter

Parameter (unit)	Definition	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Hemoglobin	Low	g/L	100-<LLN	80-<100	<80	N/A
Hemoglobin	High	g/L	>0-20 above ULN	>20-40 above ULN	>40 above ULN	N/A
Platelets	Low	10^9/L	75-<LLN	50-<75	25-<50	<25
WBC	Low	10^9/L	3-<LLN	2-<3	1-<2	<1
WBC	High	10^9/L	N/A	N/A	>100	N/A
Lymphocytes	Low	10^9/L	0.8-<LLN	0.5-<0.8	0.2-<0.5	<0.2
Lymphocytes	High	10^9/L	N/A	>4-20	>20	N/A
Neutrophils	Low	10^9/L	1.5-<LLN	1.0-<1.5	0.5-<1.0	<0.5

12.3 Appendix C: Week 96 interim analyses

An additional data cut will occur approximately after the final Week 96 visit, an interim analysis will be performed focused on the Open-Label extension treatment period.

The currently anticipated date for the final Week 96 visit is 19 March 2021. The interim analyses will include:

- Efficacy data through the Week 96 visit.
- Safety data through 19 March 2021.

Selected tables, figures and listings will be produced for this Week 96 interim analysis. Study population characteristics, demographics, other baseline characteristics and measurements of treatment compliance will be presented for the OLS. The following efficacy variables will be presented for the Open-Label extension treatment period based on the OLS, this will include presentations based on the subgroup of participants switching from secukinumab to bimekizumab:

- PASI90 response
- PASI100 response
- IGA Clear or Almost Clear (with at least a 2-category improvement from Baseline)

- IGA Clear (with at least a 2-category improvement from Baseline)
- Scalp IGA Clear or Almost Clear (with at least 2 category improvement relative to Baseline)
- Palmoplantar IGA Clear or Almost Clear (with at least a 2-category improvement from Baseline)
- DLQI total score of 0 or 1
- mNAPSI90, mNAPSI100
- Absolute, change, and percent change from Baseline in PASI score
- Absolute PASI scores of ≤1, ≤2, ≤3
- Absolute and percent change from Baseline in BSA affected by PSO
- Psoriasis BSA values of 0%, ≤1%, ≤3%
- PSD response (itch, pain and scaling)
- PSD 0 or 1 (itch, pain and scaling)
- PSD 0 (itch, pain and scaling)

The following safety variables will be presented for the Open-Label extension treatment period based on the OLS:

- Extent of exposure
- TEAEs including COVID-19 and safety topics of interest
- Laboratory data focused on TEMA and CTCAE
- e-CSSRS
- PHQ-9
- COVID-19 impact

Selected analyses of TEAEs will be presented for the subgroup of participants switching from secukinumab to bimekizumab for the Open-Label extension treatment period based on the OLS. Selected analyses of TEAEs will also be presented for the BKZ Set by treatment at the time of AE onset. These tables will include AEs from both the double-blind and Open-Label treatment period.

In addition, the following tables will be produced:

- Past psoriasis medication
- Impact of COVID-19 and COVID-19 protocol deviations for Maintenance Treatment Period based on MS
- Main analysis of PASI100 Responder Rates at Week 48 plus sensitivity analyses of this variable based on hybrid approach for assessing impact of COVID-19

Laboratory data for lipid panel (Total Cholesterol, HDL Cholesterol, LDL Cholesterol, Triglycerides) for combined Initial Treatment Period and Maintenance Treatment period based on SS.

12.4 Appendix D: Efficacy analyses by data cut visit

Table 12–3: Efficacy analyses reporting

Parameter	Week 48	Week 96	Week 144/OLE[a]	Final/OLE2[b]
PASI100	X	X	X	X
PAS90	X	X	X	X
PASI75	X		X	
Absolute change and percent change from Baseline in PASI score	X	X	X	
Absolute PASI scores of ≤1, ≤2, ≤3, ≤5,	X	X	X	
Time to PASI100 response	X			
Time to PASI90 response	X			
Time to PASI75 response	X			
IGA Clear	X	X	X	X
IGA Clear or Almost Clear	X	X	X	X
IGA Change from Baseline	X			
Scalp IGA Clear or Almost Clear	X	X	X	
Palmoplantar IGA Clear or Almost Clear	X	X	X	
Change from Baseline in DLQI Total Score	X	X	X	
DLQI Total Score of 0 or 1	X	X	X	X
MCID ≥4 more in DLQI	X	X	X	
mNAPSI100	X	X	X	
mNAPSI90	X	X	X	
mNAPSI75	X	X	X	
Change from Baseline in mNAPSI score	X	X	X	
Change from Baseline in Psoriasis BSA	X	X	X	
Patient Global Assessment of PSO	X			
Absolute and percent change from Baseline in BSA affected by PSO	X	X	X	
Psoriasis BSA values of 0%, ≤1%, ≤3%, ≤5%,	X	X	X	
Absolute and percent change from Baseline in the product of IGA and BSA	X		X	
PSD response (itch, pain and scaling)	X	X	X	X
PSD 0 or 1 (itch, pain and scaling)	X	X	X	

Parameter	Week 48	Week 96	Week 144/OLE[a]	Final/OLE2[b]
PSD 0 (itch, pain and scaling)	X	X	X	
PGADA for arthritis analog scale	X		X	
PASE	X		X	
PASE (<47 versus ≥47)	X			
EQ-5D-3L	X		X	
WPAI-SHP	X		X	

[a] All Week 48 analyses will also be re-run at Week 144/OLE.
[b] All Week 48 and Week 144 analyses will also be rerun at Final/OLE2.

13 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN (SAP)

13.1 Amendment 1

Rationale of the Amendment

The main purpose of this amendment is to align the SAP with protocol amendments 3 and 4 and to achieve consistency with other SAPs of the program.

Specific Changes

Change #1

List of abbreviations

The following abbreviations have been added:

CSR	Clinical Study Report
OLE	open-label extension
OLS	open-label set

The following abbreviation has been removed:

ADR	adverse drug reaction

Change #2

1 Introduction

The SAP is based on the following study document: Protocol Amendment 1, 17 October 2018.

Has been changed to

The SAP is based on the following study document: Protocol Amendment 4, 06 Feb 2020.

Change #3

2.1.3 Other objectives

The following objectives have been added:

- **Assess the maintenance of efficacy of bimekizumab dosing Q4W versus Q8W**
- **Assess the safety and efficacy of initiating bimekizumab therapy in subjects who received secukinumab in the double-blind Treatment Period**

Change #4

2.2.1.3 Other efficacy variables

Patient Symptom Diary responses for itch, pain, and scaling has been added as a variable.

Definition of **IGA response (Clear with at least 2 category improvement relative to Baseline) and of DLQI total score** has been clarified.

Change from Baseline in Patient Health Questionnaire-9 (PHQ-9) scores was moved from this section to section **2.2.3.2 Other safety variables.**

2.2.3.2 Other safety variables

Urinalysis has been removed as a variable.

Change #5

2.3.2 Study periods

An Open-Label period has been added:

- **Open-Label Extension Period starts with the first study drug administration at or after the Week 48 visit**

Open-Label Treatment Period ends either at the Week 144 visit for subjects completing the Open-Label Treatment Period, or at PEOT Visit for subjects who discontinued early during the Open-Label Treatment Period. If a subject does not have a Week 144/PEOT visit, then the date of the last scheduled or unscheduled visit during the Open-Label Treatment Period will define the end date of the Open-Label Treatment Period.

The title of section **2.3.2.2** was changed from Double-blind Treatment Period to **Initial Treatment Period** and a separate section **2.3.2.2 Maintenance Treatment Period was created.** The following paragraphs were added:

Subjects will be classified as completing the initial treatment period if they complete the Week 16 Visit without early withdrawal from the study or if they start treatment in the maintenance treatment period. The start of the maintenance treatment period marks the end of the initial treatment period.

Subjects will be classified as completing the maintenance treatment period if they complete the Week 48 Visit without early withdrawal from the study or if they start treatment in the Open-Label extension period. The start of the Open-Label period marks the end of the maintenance treatment period.

The following section has been added:

2.3.2.4 OLE Period

After completion of the Week 48 visit assessments, subjects will be allowed to enroll in the OLE Period. All subjects enrolling in the OLE Period will sign a new ICF, and then receive the following IMP regimens as determined by the subject's treatment regimen and PASI response in the double-blind Treatment Period.

At Week 48, subjects receiving:

- **Bimekizumab 320mg Q4W who achieve PASI90 at Week 48 of the double-blind Treatment Period will be randomized 1:1 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W.**
- **Bimekizumab 320mg Q4W who do not achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q4W.**
- **Bimekizumab 320mg Q8W who do not achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q4W.**
- **Bimekizumab 320mg Q8W who achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q8W.**
- **Secukinumab who do not achieve PASI90 at Week 48 of the double-blind Treatment Period will receive bimekizumab 320mg Q4W.**
- **Secukinumab who achieve PASI90 at Week 48 of the double-blind Treatment Period will be randomized 1:1 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W.**

At Week 96, for subjects receiving bimekizumab 320mg Q4W, if PASI90 is achieved, the subject's dosing interval will change from 320mg Q4W to 320mg Q8W (default), unless, based on medical judgment, the Investigator decides differently.

During the OLE Period, subjects will attend study visits at Weeks 52, 56, 64, and 72, and then every 12 weeks. At study visits, IMP will be administered in the clinic by sc injection as applicable. In between study visits, subjects will self-inject IMP at home.

All subjects not enrolling in the Open-Label study will have the Week 48 study assessments and will enter the SFU Period.

The following bullet point was added in section **2.3.3 Study duration per subject**:

- **OLE Period: 96 weeks (final dose at Week 136 for subjects receiving bimekizumab 320mg Q8W and at Week 140 for subjects receiving bimekizumab 320mg Q4W)**

Change #6

3.1 General presentation of summaries and analyses

The following section has been added:

Per protocol, visit windows of ±3 days from the first dose to Week 24, ±7 days from Week 28 to Week 72 and ±14 days from Week 76 to Week 144 are permissible. For the SFU Visit, visit window is 20 weeks ±7 days from final dose. All by-visit summaries will contain nominal (i.e. scheduled) visits only. Unscheduled visits will not be mapped to scheduled visits except for assessments that occur within a 3-day time window of a scheduled visit. In that case, the assessment will be mapped to the corresponding scheduled visit and will be used for the analysis. This will only occur for some vendor data.

3.2 Definition of Baseline values

Unless specified otherwise, the process laid out above will always be followed to determine Baseline. An additional Baseline for the Maintenance Treatment Period will be defined for selected summaries of laboratory evaluations. This Baseline for the Maintenance Treatment Period is the latest measurement on/prior to the day of first dose in the Maintenance Treatment Period.

Has been changed to:

Unless specified otherwise, the process laid out above will always be followed to determine Baseline. An additional Baseline for the OLE Period will be defined for selected summaries of laboratory evaluations. This Baseline for the OLE Period is the latest measurement on/prior to the day of first dose in the OLE Period.

Note that for any laboratory value that occurs on the day of treatment switch, that lab value will be attributed and summarized for the treatment they were on previously.

Change #7

The following sections have been added:

3.5.6 Open-Label Set

The Open-label Set (OLS) will consist of all subjects that receive at least 1 dose of IMP at Week 48 or later in the OLE Period (including the Week 48 dose).

3.5.9 Bimekizumab Set

The Bimekizumab Set (BKZ Set) consists of all randomized subjects who received at least 1 dose of bimekizumab in the double-blind or Open-Label extension treatment period.

Change #8

3.6 Treatment assignment and treatment groups

The following has been added:

Re-randomized (Open-Label extension) treatment groups are Bimekizumab 320mg Q4W and Bimekizumab 320mg Q8W.

Change #9

3.10 Changes to protocol-defined analyses

The following has been removed as they have been updated in the latest protocol amendment are no longer changes to protocol-defined analyses:

- Percent of subjects with absolute BSA=0%, ≤1%, ≤3% and ≤5%
- Absolute and percent change from Baseline in the product of IGA and BSA (IGAxBSA)
- Shift from Baseline in PASE score suggestive of PsA (<47 versus ≥47)

For the following secondary endpoint the definition of response was added in parentheses:

- Investigators Global Assessment (IGA) response (Clear or Almost Clear with at least 2-category improvement relative to Baseline) at Week 16

All variables listed as other efficacy variables in Section 2.2.1.3 will be summarized for the RS as well as for the MS. This is a deviation from protocol Section 14.3.2.2 and is described in detail in Section 8.3.

The following has been added:

The protocol states that subgroup analyses will be performed on the primary and secondary efficacy variables that are part of the fixed sequence testing procedure. However, subgroup analyses will only be done for PASI75 and PASI100 as described in Section 4.8. Urinalysis will not be analysed in summary tables but will only be included in listings.

Urinalysis will not be analysed in summary tables but will only be included in listings.

Section 14.7 of the protocol describes how multiple imputation should be used to analyse other efficacy endpoints. It is mentioned that the imputation model will use the change from Baseline (instead of actual) values by visit. This statement was omitted from SAP Section 4.2.1.3 as actual values will be used in the imputation algorithm and change from baseline will be calculated based on the imputed values.

Also, **Patient Symptom Diary responses for itch, pain, and scaling** has been added as an endpoint that is not listed in the protocol but was added into the SAP.

Change #10

4.2.1 Handling of missing data for efficacy variables

The following has been added:

If a subject discontinues early from the study, all efficacy data that are collected later than 35 days after the last administration of study treatment will be treated as missing and subject to imputation as applicable.

Additionally, MI-MCMC/reference based imputation has been removed as a method for sensitivity analyses and LOCF has been added instead.

Change #11

4.2.1.5 Missing data overview and summary

The following has been added:

Note: for all analyses and summaries using MI, subjects with missing baseline value will be excluded.

Change #12

4.2.1.6 Missing data algorithm – MI – MCMC / Monotone Regression

Some clarifications have been made without changing the logic of the imputation method. Additionally, the following sentence was added in order to deal with imputed values that are out of range:

In addition, if values outside of the pre-defined range of values for IGA (0-4) are imputed, they will be cut off as appropriate after the multiple imputation procedure but before deriving the responder variable.

Table 4–2: Allowable ranges for imputation by variable has been added.

Further details about imputation for different analysis sets have been added as below:

Randomized Set: When programming multiple imputation based on the RS, PROC MI will be used with a separate data set for each of the 2 randomized treatment groups (bimekizumab 320mg Q4W and secukinumab) including all scheduled assessment visits from Baseline to Week 48.

Maintenance Set: When programming multiple imputation based on the MS, PROC MI will be used with a separate data set for each of the 3 Maintenance Period treatment groups (bimekizumab 320mg Q8W, bimekizumab 320mg Q4W, secukinumab) including all scheduled assessment visits from Baseline to Week 56.

Open-Label Set: When programming multiple imputation based on the OLS, PROC MI will be used with a separate data set for each of the 6 treatment sequences based on the combination of randomized treatment at Baseline, Maintenance Period treatment and OLE period treatment at Week 48 including all scheduled assessment visits from Baseline to Week 144. The summary values for the 4 treatment sequences based on the combination of randomized treatment at Baseline and OLE period treatment at Week 48 will be computed after the imputation steps

Change #13

4.3 Interim analyses and data monitoring

The first paragraph has been updated to:
After the final Week 48 visit, an interim analysis will be performed and a corresponding interim clinical study report (CSR) may be written, **data from the OLE/analysis based on the OLS will not be included in this interim analysis. For subjects that participate in the OLE period, data will be cut at the day of their Week 48 study drug administration. A final analysis will be conducted when all data for the double-blind and OLE period (including SFU) will be collected.**

4.4 Multicenter studies

However, if the model is unable to converge due to a low number of subjects at a given center, a pooling by region will be considered. Detailed strategy from Section 3.7 will be applied in order to allow the model to converge.

Has been changed to:

However, if the model is unable to converge due to a low number of subjects at a given center, a pooling by center will be considered. Detailed strategy from Section 3.7 will be applied in order to allow the model to converge. If convergence is still not achieved, a pooling by region will be applied. If convergence still cannot be achieved, this analysis will not be performed.

Change #14

4.8 Examination of subgroups

- PASI75 responders at Week 4 (yes, no) to predict PASI90/100 and IGA through Week 48
- PASI90 responders at Week 16 (yes, no) to predict PASI100 through Week 48

Has been changed to:

- **PASI75 response (OC) at Week 4 (yes, no) to predict PASI90/100 and IGA (NRI) through Week 48**
- **PASI90 response (OC) at Week 16 (yes, no) to predict PASI100 (NRI) through Week 48**

Change #15

6.2 Other Baseline characteristics

The following has been added to the list of baseline characteristics:

- **PSD items: Pain, Itch, Scaling**
- **PGADA score (=0, >0)**
- **DLQI total score (=0, >0)**

Change #16

7 MEASUREMENTS OF TREATMENT COMPLIANCE

A summary of percent treatment compliance categorized as ≤75% and >75% will be provided by treatment group and study periods (Initial Treatment Period, Maintenance Treatment Period, and the Initial and Maintenance Treatment Period).

Has been changed to:

A summary of percent treatment compliance categorized as <75% and ≥75% will be provided by treatment group and study periods (Initial Treatment Period for the SS,

Maintenance Treatment Period for the SS, Initial and Maintenance Treatment Period for the SS, and Open-Label Extension Period for the OLS).

Table 7.2 Dosing scheme, OLE Period has been added.

Change #17

8.1.2 Primary analysis of the primary efficacy variable

The following has been added:

The evaluation of superiority will use pairwise treatment comparisons based on the CMH test using the p-value for the general association. The odds ratio and associated confidence interval (CI) based on the Wald test will be presented.

To calculate the stratified Mantel-Haenszel risk difference, the method of Greenland and Robins (1985) is used. For each combination of strata, a 2x2 table of treatment group and response is created. A theoretical 2x2 table for a given stratum is shown below, where n = a+b+c+d.

	Response	
Treatment Group	**Yes**	**No**
Bimekizumab	**a**	**c**
Secukinumab	**b**	**d**

Given that structure, the stratified Mantel-Haenszel risk difference, standard error, and two-sided (1-α)*100% confidence interval may be written as follows:

$$RD_{MH} = \frac{\sum_i((a_i * (b_i + d_i)/n_i) - (b_i * (a_i + c_i)/n_i)}{\sum_i((a_i + c_i) * (b_i + d_i))/n_i}$$

$$SE_{MH} = \sqrt{\frac{\sum_i \left\{ \frac{[a_i * c_i * (b_i + d_i)^3] + [b_i * d_i * (a_i + c_i)^3]}{(a_i + c_i) * (b_i + d_i) * n_i^2} \right\}}{\left\{ \sum_i \left[\frac{(a_i + c_i) * (b_i + d_i)}{n_i} \right] \right\}^2}}$$

$$CI_{MH} = RD_{MH} \pm \text{probit}(1 - (\alpha/2)) * SE_{MH}$$

For the assessment of non-inferiority of bimekizumab to secukinumab, the lower 97.5% confidence limit for the stratified Mantel-Haenszel risk difference will be considered. If that value is greater than -10%, then non-inferiority will have been established.

Also: **An additional plot will be produced for the OLS by OLE treatment groups.**

Change #18

8.1.3.6 Sensitivity Analysis #6

The following has been added:

In order to achieve model convergence, region may be used instead of center or prior biologic exposure may be dropped from the model. If convergence still cannot be achieved, this analysis will not be performed.

Change #19

8.3 Analysis of other efficacy variables

The following paragraph has been updated:

All efficacy variables will be summarized in the manner described for Group 1 and Group 3 above. Summaries for Group 2 will be done only for a subset of efficacy variables, **namely, PASI90/100 responder rate, IGA Clear or Almost Clear.** Examination of subgroups will only be done for Group 3.

The following has been added:

Selected endpoints will be summarized for OLE Period for the OLS. Imputation methods will be identical to the respective summary for the RS.

8.3.8 Symptoms of PSO (Itch, pain, and scaling)

The following section has been added:

In addition, each of the 3 PSD scores will be characterized in terms of the percent of subjects demonstrating a specified point improvement at each visit. Subjects with a missing score will be imputed using NRI. The analysis will be limited to subjects with a Baseline PSD score at or above the applicable threshold score. The 3 threshold scores for itch, pain and scaling will be determined prior to unblinding of the data.

Cumulative distribution plots will also be provided for absolute change from Baseline PSD at Week 16 for each item.

Change #20

8.3.1.2 Time to PASI75, PASI90 and PASI100 response

The following has been added:

All visits including unscheduled visits are considered.

Subjects who discontinue study treatment without achieving a given PASI response prior to discontinuation will be censored at the date of the last observed PASI assessment on or prior to the date of treatment discontinuation. Subjects who reach the Week 48 Visit without achieving the given response will be censored at the date of the last observed PASI assessment on or prior to the Week 48 Visit. Subjects will be censored at Baseline if there is no Baseline PASI assessment or no Post Baseline PASI assessment

Change #21

8.3.11 Euro-Quality of Life 5-Dimensions, 3 levels (EQ-5D-3L)

The following clarification was added:

Responses to EQ-5D-3L will be summarized based on OC only as primary analysis. No imputation is applied **to responses to EQ-5D-3L but is applied to EQ-5D-3L VAS scores.**

Change #22

The following section has been added:

8.4 Additional statistical analysis of other efficacy variables

For selected other efficacy variables, it is of interest to perform statistical tests and to calculate inferential statistics. As these tests are not part of the multiplicity-controlled procedure, the associated p-values are considered nominal and are not controlled for multiplicity. For responder variables, the analysis will follow what was specified for the primary analysis. Specifically, a stratified Cochran-Mantel-Haenszel (CMH) test will be used, where region and prior biologic exposure (yes/no) will be stratification variables. The p-value will be based on the CMH test for a general association. Missing values will be imputed using NRI. For continuous variables, the MI – MCMC / Monotone Regression approach used for other continuous variables will be applied for the imputation model. The analysis model will be based on analysis of covariance (ANCOVA) with fixed effects of treatment, region, and prior biologic exposure and Baseline value as a covariate. Below is a list of variables for which these nominal p-values will be calculated (with the time points in parentheses). The results of these inferential tests will all be presented in a single table summarizing the testing performed outside of the multiplicity-controlled testing procedure.

- PASI90
  - Bimekizumab vs Secukinumab (Weeks 1, 2, 4, 8, 12, 16 and 48)
- IGA Clear or Almost Clear
  - Bimekizumab vs Secukinumab (Weeks 1, 2, 4, 8, 12, 16 and 48)
- PASI100
  - Bimekizumab vs Secukinumab (Weeks 4, 8, and 12)
- IGA Clear
  - Bimekizumab vs Secukinumab (Weeks 4, 8, 12, 16, and 48)
- PASI75
  - Bimekizumab vs Secukinumab (Weeks 1, 2, and 16)
- Scalp IGA Clear or Almost Clear (subjects with Baseline Scalp IGA ≥2)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- pp-IGA Clear or Almost Clear (subjects with Baseline pp-IGA ≥2)

  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- mNAPSI75 response (subjects with Baseline mNAPSI>0)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- mNAPSI90 response (subjects with Baseline mNAPSI>0)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- mNAPSI100 response (subjects with Baseline mNAPSI>0)
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- DLQI 0/1 response
  - Bimekizumab vs Secukinumab (Weeks 16 and 48)
- PASI percentage change from Baseline
  - Bimekizumab vs Secukinumab (Weeks 1, 2, 4, 8, 12, 16, and 48)
- Patient Symptom Diary responses for itch, pain, and scaling
  - Bimekizumab vs Secukinumab (Weeks 16, 32, 48)

Change #23

9.1 Pharmacokinetics

The following clarifications have been added

A separate summary table will be created for the Open-Label Extension Period for subjects that are both in the PK-PPS and the OLS.

and

A separate plot will be created for the Open-Label Extension Period for subjects that are both in the PK-PPS and the OLS.

and

If the PK sampling date is >1 day after the dosing date data points will be excluded from the PK summary tables and figures, but not from the listing.

Change #24

9.3.2 Anti-bimekizumab antibodies

Visits during the OLE period have been added.

The following paragraph has been added:

Anti-bimekizumab antibody samples are not analyzed when subjects are on a treatment other than bimekizumab. For subjects who switch from secukinumab either placebo or an active comparator to bimekizumab, samples are analyzed starting at the visit when the

switch to bimekizumab occurs. The sample at the visit when the switch occurs will act as the Baseline for that treatment group.

Additionally, adjustments in the **Subject Classification** section have been done and the rest of the section has been updated in order to align with UCB program conventions. A section about neutralizing antibodies has been added.

Change #25

10.1 Extent of exposure

The following has been added:

For the final analysis (not the interim), an additional table will be created for the BKZ set with the above categories plus the below categories. A Bimekizumab total column will be displayed only.

- **>=72 weeks**
- **>=96 weeks**
- **>=120 weeks**
- **>=144 weeks**

As the study was separated into three different periods, this section was re-written in order to provide definitions for exposure variables for the three periods and a combinations of initial and maintenance period.

The following four sections have been added:

10.1.1 Exposure during the Initial Treatment Period for SS

10.1.2 Exposure during the Maintenance Treatment Period for MS

10.1.3 Exposure during the Initial and Maintenance Treatment Period for SS

10.1.3.1 For subjects who do not switch study treatments

10.1.3.2 For subjects who switch from BKZ 320mg Q4W to Q8W at Week 16:

10.1.4 Exposure during the Open-Label Extension Period based on OLS

10.1.4.1 For subjects who do not switch study treatments

10.1.4.2 For subjects who switch from BKZ 320mg Q4W to Q8W at Week 16:

10.1.5 Exposure during the Double-blind and OLE Period based on BKZ set

10.1.5.1 For subjects who do not switch study treatments

10.1.5.2 For subjects who switch from BKZ 320mg Q4W to Q8W at Week 16:

Change #26

10.2 Adverse events

The following has been added:

For subjects who switch treatment at Week 16, Week 48, or Week 96, any adverse events that occur after initiation of the new treatment are attributable to the new treatment. If an adverse event occurs on the date of a treatment switch, the event is attributed to the original treatment. The only exception to this is if the AE fulfills any of the criteria specified below:

- **Events that fulfill the anaphylaxis criteria for acute events**
- **Events that fulfill the hypersensitivity criteria**
- **Events with an HLT of "Administration site reactions NEC"**
- **Events with an HLT of "Injection site reactions"**

Change #27

10.2.1 Data considerations

A paragraph about adverse drug reactions has been removed and the following has been added:

Selected summaries, as specified in Section 10.2.2, will include the risk difference between bimekizumab and secukinumab. The risk difference is calculated as:

$$RD = IP_{BKZ} - IP_{SEC}$$

where IP_{BKZ} is the incidence proportion for the bimekizumab-treated group and IP_{SEC} is the incidence proportion for the secukinumab group. Note that incidence proportion simply refers to the percentage of subjects within the specified treatment group that experienced a given adverse event.

The standard error for the risk difference is calculated as follows:

$$SE_{RD} = \sqrt{\left(IP_{BKZ} \times \left(\frac{1 - IP_{BKZ}}{n_{BKZ}}\right)\right) + \left(IP_{PBO} \times \left(\frac{1 - IP_{SEC}}{n_{SEC}}\right)\right)}$$

where n_{BKZ} is the number of subjects in the bimekizumab-treated group and n_{SEC} is the number of subjects in the secukinumab group.

The corresponding confidence interval for the risk difference is as follows:

$$CI_{RD} = RD \pm Z_{1-\alpha/2} \times (SE_{RD})$$

where $Z_{1-\alpha/2}$ is the Z statistic for the corresponding level of alpha. For the risk difference confidence intervals calculated in this SAP, 1.96 will be used (corresponding to a two-sided alpha of 0.05 and 95% confidence interval).

Change #28

10.2.2 AE summaries

The wording of *Adverse drug reactions* has been changed to ***related TEAEs***

The following has been added:

The following summary will be provided by treatment for the Initial Treatment Period for the SS:

- **Incidence of TEAEs Above Reporting Threshold of 5% with Risk Differences by SOC and PT**
- **Incidence of Serious TEAEs and Risk Differences by SOC and PT**

The following summary will be provided by treatment for the Open-Label Extension Period for the OLS.

- **Incidence of TEAEs Overview**
- **Incidence of TEAEs per 100 Subject-Years**

Incidence of Serious TEAEs per 100 Subject-Years In addition, all summaries of TEAEs based on "100 subject years" will include EAIR (with 95% CI) and EAER.

The tables with risk differences will also be accompanied by figures (dot plots) which show the incidence of the adverse events and corresponding 95% risk difference confidence intervals. These will be ordered by descending order of risk difference (bimekizumab vs secukinumab).

Change #29

10.2.3 Other Safety topics of interest

The following has been added:

The following outputs will be produced for the SS for the initial treatment period, for the SS for the Initial and Maintenance Treatment Period, **and for the OLS for the Open-Label Extension Period.**

Along with the tables described, there will be a table which displays the risk difference and 95% confidence intervals for each of the topics of interest during the Initial Treatment Period. A corresponding figure (with dot plots) will be prepared.

Change #30

10.2.3.1 Infections (serious, opportunistic, fungal and Tuberculosis [TB])

The steps for the identification and review of opportunistic infections have been updated.

Change #31

10.2.3.3 Major adverse cardiac event

- Incidence of Major Cardiac Event (MACE) TEAEs per 100 subject years by SOC, HLT and PT

MACE will be presented in a table. The classification of an event as MACE is determined by an external cardiovascular event adjudication committee.

Has been changed to:

- **Incidence of Major Adverse Cardiac Event (MACE) TEAEs per 100 subject years by SOC, HLT and PT**

Adjudicated MACE will be presented in a table. The classification of an event as MACE is determined by an external cardiovascular event adjudication committee.

Extended MACE events will be presented in a separate table and listing. All events which are classified by the adjudication committee as any of the following events types will be considered an extended MACE event.

Event Type Code	Event Type
1	Non-Fatal Myocardial Infarction (MI)
2	Non-Fatal Stroke: hemorrhagic
3	Non-Fatal Stroke: ischemic
4	Non-Fatal Stroke: embolic
5	Non-Fatal Stroke: undeterminable
6	Hospitalization or ER for Unstable Angina with urgent revascularization
8	Hospitalization for Heart Failure
10	Coronary Revascularization Procedures (e.g. percutaneous coronary intervention, coronary artery bypass grafting)
11	Urgent Revascularization Procedures (i.e. due to symptoms of brain ischemia or pending infarction)
18	Death due to Myocardial Infarction (MI)
19	Death due to Stroke
20	Sudden Cardiac Death
21	Other CV Death (e.g. heart failure, pulmonary embolism, cardiovascular procedure-related)
22	Cardiovascular: Undetermined Cause of Death (i.e. cause of death unknown)

A separate table and listing will present the TEAEs referred to the cardiovascular event adjudication committee by cardiovascular event type. For each cardiovascular event type (24 total), the individual PTs which fall within each event type will be summarized.

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

Change #32

10.2.3.5 Suicidal Ideation and Behavior (SIB)

- Incidence of Neuropsychiatric TEAEs per 100 subject years by SOC, HLT and PT

This table is based on the SMQ of "Depression and suicide/self-injury" (all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow).

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

Has been changed to:

10.2.3.5 Suicidal Ideation and Behavior (SIB)

- **Incidence of SIB-Adjudicated Neuropsychiatric TEAEs per 100 subject years by SOC, HLT and PT**

An external neuropsychiatric adjudication committee will evaluate potential neuropsychiatric events and determine whether any of those events were associated with suicidal ideation and behavior (SIB). If an event is adjudicated as SIB, further information will be provided. A separate listing for SIB events as determined by the adjudication committee will be included. Additionally, a listing of all events identified for potential review by the neuropsychiatric adjudication committee will be produced. This listing will indicate whether each event was escalated to the committee for formal review/adjudication.

Change #33

10.2.3.5 Neuropsychiatric events (in particular depression and suicide)

- Incidence of Neuropsychiatric TEAEs per 100 subject years by SOC, HLT and PT

This table is based on the SMQ of "Depression and suicide/self-injury" (all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow).

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

has been changed to:

10.2.3.5 Suicidal Ideation and Behavior (SIB)

- **Incidence of SIB-Adjudicated Neuropsychiatric TEAEs per 100 subject years by SOC, HLT and PT**

An external neuropsychiatric adjudication committee will evaluate potential neuropsychiatric events and determine whether any of those events were associated with suicidal ideation and behavior (SIB). If an event is adjudicated as SIB, further information will be provided. A separate listing for SIB events as determined by the adjudication committee will be included. Additionally, a listing of all events identified for potential review by the neuropsychiatric adjudication committee will be produced. This listing will indicate whether each event was escalated to the committee for formal review/adjudication.

Change #34

10.2.3.6 Inflammatory bowel disease

The following has been added:

Inflammatory bowel disease events will be summarized stratified by subjects with or without a previous medical history of inflammatory bowel disease. Previous medical history of inflammatory bowel disease will be determined using the information recorded on the Extra-Articular Assessment at Screening CRF page ("Does subject have a history of IBD?").

Change #35

10.2.3.7 Anaphylactic reaction

- Incidence of Anaphylactic Reaction TEAEs per 100 subject years by SOC, HLT and PT

This table will be prepared based on the MedDRA anaphylaxis algorithm (refer to Appendix 1 in "Bimekizumab-Safety-Topics-of-Interest.docx") for acute events (reported on the same day) and for treatment-emergent PTs including the term "hypersensitivity" reported at any time.

Furthermore, injection site reactions will be evaluated based on the any TEAE table (no separate table needed) by looking under the following HLTs: "Administration site reactions NEC" and "Injection site reactions".

has been changed to:

10.2.3.6 Hypersensitivity (including anaphylaxis)

- **Incidence of Anaphylactic Reaction TEAEs per 100 subject years by SOC, HLT and PT**

A separate table will be prepared based on the MedDRA anaphylaxis Algorithm (see Appendix A) for acute anaphylactic events (reported on the same day as when an injection was administered or one day after).

A separate table will be prepared to summarize hypersensitivity events, identified using the SMQ "Hypersensitivity (SMQ)". All TEAEs which code to a PT included in the Scope=Narrow search will be included in this table.

Furthermore, injection site reactions will be evaluated based on the any TEAE table (no separate table needed) by looking under the following HLTs: "Administration site reactions NEC" and "Injection site reactions".

Change #36

10.3 Clinical laboratory evaluations

The following has been added:

- **AST: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN**
- **ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN**
- **AST or ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN**
- Bili**rubin: >1.5xULN, >2xULN**

The following has been removed

- AST: >2xULN, >3xULN, >5xULN, >10xULN, >20xULN
- ALT: >2xULN, >3xULN, >5xULN, >10xULN, >20xULN
- AST or ALT: >2xULN, >3xULN, >5xULN, >10xULN, >20xULN
- Bilirubin: >1xULN, >1.5xULN
- ALP: >2xULN

and

- [AST ≥3xULN or ALT ≥3xULN] and Total Bilirubin ≥2xULN

Change #37

10.4.1 Vital signs

It was specified that a summary of absolute and change from baseline will be provided for the **Initial Treatment Period** and that a summary of markedly abnormal values will be provided for **the Initial Treatment Period (SS), the Initial and Maintenance Treatment Period (SS), and the open-Label Extension Period (OLS).**

Change #38

10.4.3 Electrocardiograms

It was specified that **two separate by-subject listing of all 12-lead ECG data will be provided based on interpretation from central reader and from site.**

Change #39

10.4.4.5 Patient Health Questionnaire 9 (PHQ-9)

This section has been moved to the safety section as it was previously included in the efficacy section.

The following has been added:

Change from Baseline in PHQ-9 is derived as post-Baseline score minus Baseline score **and will be summarized by treatment group.**

Differently to other safety variables, PHQ-9 will be summarized using the MCMC/monotone regression approach described in section 8.1.3.1. A table for the SS through Week 48 will be produced.

Change #40

11 REFERENCES

The following two references have been added:

Greenland S, Robins JM. Estimation of common effect parameter from sparse follow up data. Biometrics 1985;41:55-68.

Ratitch, B., Lipkovich, I., O'Kelly, M. Combining Analysis Results from Mutiply Imputed Categorical Data, PharmaSUG, 2013, SP03

13.2 Amendment 2

Rationale of the Amendment

The main purpose of this amendment is to prespecify sensitivity and supportive analyses to assess the impact of the COVID-19 pandemic on the statistical analyses methods.

Global Changes

Typographical errors were corrected and formatting was amended throughout the document.

Specific Changes

Change #1

List of abbreviations

The following abbreviations have been added:

COVID-19	Coronavirus Disease 2019
CV-CAC	Cardiovascular Clinical Event Adjudication Committee

Change #2

3.4 Protocol deviations

The following paragraph is added:

Deviations related to the Coronavirus Disease 2019 (COVID-19) global pandemic are unavoidable deviations from the protocol due to confirmed COVID-19 infection, suspected COVID-19 infection, general circumstances around COVID-19 without infection or any other deviation from the protocol due to COVID-19. COVID-19 protocol deviations will also be reviewed separately as part of the ongoing data cleaning process.

Change #3

The following section has been added:

3.10.1 Changes related to COVID-19

Change #4

4.2.1.2 Handling missing data for the secondary efficacy variables

The following paragraph has been added:

Additional methods for handling missing data to assess the impact of the COVID-19 global pandemic on planned statistical analyses are detailed in Section 4.2.1.7.

Change #5

Table 4-1 Missing data handling approach by variable priority and type

The following footnote has been added:

Note: Additional missing data handling approaches are detailed in Section 4.2.1.7 for assessing the impact of COVID-19 on the secondary efficacy variable PASI100 response at Week 48.

Change #6

The following section has been added:

4.2.1.7 Missing data methods for assessing impact of COVID-19

Change #7

4.8 Examination of subgroups

The following paragraph has been added:

Additional subgroup analyses are described in Section 4.2.1.7.2 to assess the impact of the COVID-19 pandemic on planned statistical analysis of PASI100 response at Week 48.

Change #8

5.2 Protocol deviations

The following paragraphs have been added:

A summary of number and percentage of subjects with COVID-19 protocol deviations by treatment group and visit will be provided for the MS and OLS. This summary will also be repeated by country (see Section 2.3.5 for list of countries).

A by-site, subject and visit listing of COVID-19 protocol deviations will be provided.

Change #9

8.2.3 Sensitivity analyses of the secondary efficacy variables

The following sentence has been added:

In addition, for PASI100 response at Week 48, the sensitivity analyses described in Section 4.2.1.7 will be performed.

Change #10

8.3.2 IGA response

The following text has been updated:

- IGA response (Clear) is defined when IGA score is zero (Table 8–1) with at least a two-category improvement from Baseline at visit time point.

To clarify as follows:

- IGA response (Clear) is defined when IGA score is **clear [0]** (Table 8–1) with at least a two-category improvement from Baseline at visit time point.

Change #11

8.3.8 Symptoms of PSO (Itch, pain, and scaling)

The following sentence has been deleted:

The 3 threshold scores for itch, pain and scaling will be determined prior to unblinding of the data.

The following paragraph has been added:

The PS0009 and PS0013 analyses determined a 4-point reduction as a marked within-subject clinically meaningful improvement in the weekly score each of these 3 PSD items that can be used to define different marked response to treatment over 16 weeks in patients with moderate-to-severe plaque psoriasis. Such a threshold has also been used to support

US label claims of other compounds approved in the same indication based on different PSO symptom diaries using an 11-point numeric response scale and was suggested in previous interactions with the FDA. Thus a 4-point threshold is proposed in the current study. Analyses to determine threshold for within-subject clinically meaningful improvement based on blinded PS0015 data are ongoing. In case the results differ from the 4-point threshold, sensitivity analyses with the determined thresholds may be conducted.

Change #12

10.1 Extent of exposure

The following text was updated:

Summaries for exposure will be provided. This consists of a descriptive summary of study medication duration in days. In addition, total study medication duration and time at risk will be summarized in years by treatment group

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

- >0 weeks
- >=16 weeks
- >=24 weeks
- >=48 weeks

For the final analysis (not the interim), an additional table will be created for the BKZ set with the above categories plus the below categories. A bimekizumab total column will be displayed only.

To clarify as follows:

Summaries for exposure will be provided **for the SS, MS and BKZ set**. **These** consist of a descriptive summary of study medication duration in days. In addition, total study medication duration and time at risk will be summarized in years by treatment group

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

- >0 weeks
- >=16 weeks
- >=24 weeks
- >=48 weeks

For the final analysis (not the interim), **the** table will **also** be created for the BKZ set **and will include** the above categories plus the below categories. A bimekizumab total column will be displayed only.

Change #13

The following section has been added:

10.2.1.1 COVID-19 related data considerations

Change #14

10.2.2 AE summaries

The following section has been added:

For subjects who discontinue on or prior to the final scheduled visit of the Initial Treatment Period, any AEs that emerged more than after 112 days relative to the first dose but still within the 140 days SFU window will be classified as TEAE. However these AEs will be excluded from AE summaries based on the Initial Period but included in the AE summaries for Initial and Maintenance Treatment Period. See the description of time at risk in Section 10.1.1 for further details.

Change #15

10.2.2 AE summaries

The following text was updated:

- Incidence of Related TEAEs Above Reporting Threshold of 5% by SOC and PT

To clarify as follows:

- Incidence of Related TEAEs Above Reporting Threshold of 5% **with Risk Differences** by SOC and PT

Change #16

10.2.2 AE summaries

The following text was updated:

The following summary will be provided by treatment for the Initial and Maintenance Treatment Period (combined) for the SS (only subjects treated with BKZ):

To clarify as follows:

The following summary will be provided by treatment for the Initial and Maintenance Treatment Period (combined) for the SS (only subjects treated with BKZ**, only Total BKZ will be summarized**):

Change #17

10.2.2 AE summaries

The text has been added:

- **Incidence of TEAEs per 100 subject years by SOC, HLT, and PT and by Time of Onset Relative to COVID-19 pandemic (prior to COVID-19 pandemic, during COVID-19 pandemic)**

Change #18

The terminology in the following section has been updated:

10.2.3.3 Major adverse Cardiac Events

- • Incidence of Major Adverse Cardiac Event (MACE) TEAEs per 100 subject years by SOC, HLT and PT

Adjudicated MACE will be presented in a table. The classification of an event as MACE is determined by an external cardiovascular event adjudication committee.

Extended MACE events will be presented in a separate table and listing. All events which are classified by the adjudication committee as any of the following events types will be considered an extended MACE event.

…

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

As follows:

10.2.3.3 Cardiac events

- Incidence of Major Adverse Cardiac Event (MACE) TEAEs per 100 subject years by SOC, HLT and PT

Adjudicated MACE will be presented in a table. The classification of an event as MACE is determined by **the** external **Cardiovascular Clinical Event Adjudication Committee (CV-CAC)**.

Extended MACE events will be presented in a separate table and listing. All events which are classified by the **CV-CAC** as any of the following events types will be considered an extended MACE event.

…

Additionally, a listing of all events identified for potential review by the **CV-CAC** will be produced. This listing will indicate whether each event was escalated to the committee for formal review/adjudication.

Change #19

10.3 Clinical laboratory evaluations

The following paragraph has been added:

A figure of neutrophil values over time for subjects with at least one markedly abnormal neutrophil value (CTCAE Grade 3 or 4) will also be presented.

Change #20

10.3 Clinical laboratory evaluations

The following paragraph has been added:

Spaghetti plots of AST values over time for the subset of subjects with at least one markedly abnormal AST value (CTCAE Grade 3 or 4) will also be presented. A similar set of plots will be produced for ALT values over time for the subset of subjects with at least one markedly abnormal ALT value (CTCAE Grade 3 or 4).

Change #21

10.4.4.5 Patient Health Questionnaire 9 (PHQ-9)

The following paragraph has been added:

The number and percentage of subjects with a PHQ-9 score ≥ 15 at any point while on treatment and the number and percentage of subjects with a PHQ-9 score ≥ 20 at any point while on treatment will also be presented based on observed case data.

13.3 Amendment 3

Rationale of the Amendment

The main purposes of this amendment are as follows:

- To add Section 8.4 which was accidentally omitted in Amendment 2
- To align the SAP with protocol amendment 5
- To include details of the Week 96 Interim analysis
- To describe the requirements for the Open-Label Extension period
- To update the impact due to the COVID-19 pandemic.

General Changes

Text has been added in several sections to indicate which variables will be produced for the OLE.

In addition, some texts that were accidentally omitted in previous amendment were put back (see Section 8.4).

Change #1

List of Abbreviations

Maintenance Set abbreviation (MS) has been added

Change #2

Section 2.3.2.4 OLE period

The following has been changed

From

At Week 96, for subjects receiving bimekizumab 320mg Q4W, if PASI90 is achieved, the subject's dosing interval will change from 320mg Q4W to 320mg Q8W (default), unless, based on medical judgment, the Investigator decides differently.

To

From Week 64 the subjects who are receiving bimekizumab 320mg Q4W at the time of implementation of protocol amendment 5.0 will have their dosing interval changed to bimekizumab 320mg Q8W at the next clinical site assessment as described on Table 7–2 for subjects who are receiving bimekizumab 320mg Q4W and have reached Week 96 prior to the implementation of Protocol Amendment 5.0, if PASI90 is achieved, the subject's dosing interval will change from 320mg Q4W to 320mg Q8W (default), unless, based on medical judgment, the Investigator decides differently. Otherwise if PASI90 is not achieved they will have their dosing interval changed to bimekizumab 320mg Q8W at the next clinical site assessment after implementation of protocol amendment 5.0 as detailed above.

Change #3

Section 3.2 Definition of Baseline value

The following texts (in bold) have been added

Unless specified otherwise, the process laid out above will always be followed to determine Baseline. An additional Baseline value for the OLE Period will be defined for **anti-bimekizumab antibodies for subjects initially randomized to secukinumab and** for selected summaries of laboratory evaluations. This baseline for the OLE Period is the latest measurement on/prior to the day of first dose in the OLE Period for subjects switching from secukinumab to bimekizumab.

Change #4

Section 3.6 Open-Label Set

The following texts (in bold) have been added to describe the treatment groups in the Open-Label Extension period

The following treatment sequences will be used to summarize efficacy data and specific safety data related to laboratory, ECG, PHQ-9, eC-SSRS, and vital signs assessments:

- **Subjects receiving bimekizumab in the double-blind treatment period:**
  - **Initiating OLE on bimekizumab Q8W**
  - **Initiating OLE on bimekizumab Q4W**
- **Subjects receiving secukinumab in the double-blind treatment period**
  - **Initiating OLE on bimekizumab Q8W**
  - **Initiating OLE on bimekizumab Q4W**
- **All Subjects**

Adverse event data (including for a subgroup of subjects who switched from Q4W to Q8W during OLE period) and study compliance data will be summarized in 2 treatment groups based on the dose most recently received prior to the date of the event or assessment

- **Bimekizumab 320mg Q8W**
- **Bimekizumab 320mg Q4W**
- **Bimekizumab Total**

In addition, the following key efficacy variables:

- **PASI90 response**
- **PASI100 response**
- **IGA Clear or Almost Clear (with at least a 2-category improvement from Baseline)**
- **IGA Clear (with at least a 2-category improvement from Baseline)**

will be summarized for the Open-Label Extension treatment period by the following randomized treatment sequences:

- **Bimekizumab Q4W/Q8W/Q4W for non-responder at Week 48 (<PASI90)**
- **Bimekizumab Q4W/Q4W/Q4W for non-responder at Week 48 (<PASI90)**
- **Secukinumab / Bimekizumab Q4W for non-responder at Week 48 (<PASI90)**
- **Bimekizumab Q4W/Q8W/Q8W for responder at Week 48 (>=PASI90)**
- **Bimekizumab Q4W/Q4W/Q8W for responder at Week 48 (>=PASI90)**
- **Bimekizumab Q4W/Q4W/Q4W for responder at Week 48 (>=PASI90)**
- **Secukinumab / Bimekizumab Q8W for responder at Week 48 (>=PASI90)**
- **Secukinumab / Bimekizumab Q4W for responder at Week 48 (>=PASI90)**

Change #5

Section 3.10.1 Change related to COVID-19

The following have been added due to the COVID-19 pandemic:

The following changes have been introduced due to the COVID-19 pandemic:

- COVID-19 protocol deviations have been defined in Section 3.4 and the presentation of COVID-19 protocol deviations is described in Section 5.2
- **COVID-19 impact on study visits has been assessed and are described in Section 5.1**
- **COVID-19 Disposition assessments are described in Section 5.1**

Missing data methods for assessing the impact of COVID-19 are described in Section 4.2.1.7 Data considerations for assessing the impact of COVID-19 on TEAEs are described in Section 10.2.1.1 and the associated analysis is described in Section 10.2.2

Change #6

Section 4.2.1.6 Missing data algorithm – MI – MCMC / Monotone Regression

Maintenance Set: When programming multiple imputation based on the MS, PROC MI will be used with a separate data set for each of the 3 Maintenance Period treatment groups (bimekizumab 320mg Q8W, bimekizumab 320mg Q4W, secukinumab) including all scheduled assessment visits from Baseline to Week 56.

Was changed to

Maintenance Set: When programming multiple imputation based on the MS, PROC MI will be used with a separate data set for each of the 3 Maintenance Period treatment groups (bimekizumab 320mg Q8W, bimekizumab 320mg Q4W, secukinumab) including all scheduled assessment visits from Baseline to **Week 48**.

Change #7

Section 4.2.1.7 Missing data methods for assessing impact of COVID-19

The following text in bold were added for clarifications

If the PASI assessment at Week 48 is conducted by video call or telephone, this will be treated as missing since the validity and exchangeability of these assessment modalities has not been established. This will be determined according to collection of COVID-19 protocol deviations **(including COVID-19 impact assessment)** (see Section 3.4 for further details).

Change #8

Section 4.2.1.7.3 Approach to assess the impact of out of window assessments due to COVID-19

The following clarification (in bold) for the approach to assess the impact of out of window assessments due to COVID-19 has been corrected

- Date of first dose of study drug + 315 **days >** Week 48 PASI assessment date or **Week 48 PASI assessment date >** date of first dose of study drug + 357 days

Change #9

Section 4.2.2 Handling missing data for safety variables

The following clarification (in bold) have been added to address the imputation method for Partial AE and concomitant medication start dates:

Partial **or missing** AE and concomitant medication start dates will be imputed as follows:

Imputation of Partial **or Missing** Start Dates

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

Imputation of Partial Stop Dates

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

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

- **If the year of imputed start date is the same as the year of first dose and the stop date is after the date of first dose, then set the start date to the date of first dose**
- **If the month and year of imputed start date is the same as the year and month of the first dose and the same year and month of the stop date and the stop date is prior to the date of first dose then set the start date to the 1st of the month**
- **Otherwise, set the start date to the 1st of January of the year of the start date.**

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

Change #10

Section 4.3 Interim analyses and data monitoring

The following text (in bold) has been added

An additional data cut will occur approximately after the final Week 96 visit. An interim analysis will be performed for the Open-Label treatment period using this Week 96 data cut. Selected tables, figures and listings will be produced for this interim analysis as detailed in Section 12.3 (Appendix C).

A final analysis will be conducted when all data for the double-blind and OLE period (including SFU) will be collected.

An independent Data Monitoring Committee (DMC) will periodically review and monitor the safety data from **the Double-blind treatment period** this study and advise UCB.

Cardiovascular, **Inflammatory bowel disease (IBD),** and Neuropsychiatric Adjudication Committees will also periodically review and monitor safety data from this study **including Open-label Extension treatment period** and advise UCB. Details will be provided in the DMC Charter and in the Adjudication Committee Charters.

Further details related to the DMC will be outlined in a separate analysis plan.

Change #11

Section 4.8 Examination of subgroups

The following bullet points (in bold) have been added

In addition, in order to assess whether an early response to treatment is predictive of response at later time points, subgroup analyses will be performed for the RS on PASI90/100 and IGA over time using the following early response subgroups:

- PASI75 response (OC) at Week 4 (yes, no) to predict PASI90/100 and IGA (clear or almost clear) (NRI) through Week 48
- PASI90 response (OC) at Week 16 (yes, no) to predict PASI100 (NRI) through Week 48
- **PASI90 response (OC) at Week 48 (yes, no) to predict PASI90 (NRI) during the OLE based on OLS**
- **PASI90 response (OC) at Week 48 (yes, no) to predict PASI100 (NRI) during the OLE based on OLS**
- **PASI90 response (OC) at Week 48 (yes, no) to predict IGA responder rates (clear) and IGA responder (clear or almost clear) during the OLE based on OLS.**

Change #12

Section 5.1 Subject disposition

The following texts (in bold) have been added to specify COVID-19 impact categories

The following listings for subject disposition will be provided: subjects who did not meet study eligibility criteria (all subjects screened), subject disposition (all subjects screened), study discontinuation (for RS), visit dates (for RS), subjects excluded from efficacy analysis (RS). **Summaries of visits at which subjects initiated the switch from bimekizumab 320mg Q4W to bimekizumab 320mg Q8W dosing interval in Open-Label Extension period will be presented.**

In addition, the following COVID-19 impact categories will be summarized by country and visit for the MS and OLS (see Section 2.3.5 for list of countries).

- **Visit not done**
- **Visit performed out of window**
- **Home Visit**
- **Visit performed by video call**
- **Visit performed by telephone**
- **Investigational product shipped to study participant**
- **Participant Home administration of investigational product by participant or caregiver**
- **Home administration of investigational product by a healthcare professional**
- **Missed study drug administration/dispensation**
- **Temporary discontinuation of study drug**
- **Permanent discontinuation of study drug**
- **Termination of study participation**
- **Other**

Note that home administration was permitted at certain visits (see Table 7-2) and only home administration that was not per the protocol should be captured.

A by-subject listing of COVID-19 impact categories will be provided

Change #13

Section 6.4 Prior and concomitant medication

The following texts (in bold) have been added

Medication start and stop dates will be compared to the date of first dose of treatment to allow medications to be classified as either Prior or Concomitant.

Details of imputation methods for missing or partial dates are described in Section 4.2.1.7.

Prior medications include any medications that started prior to the start date of study medication.

Concomitant medications are medications taken at least one day in common with the study medication dosing **period (defined as from first dose of study medication [including placebo] up to last dose of study medication + 28 days for the double-blind treatment period, and**

+28 days or +56 for Q4W and Q8W dosing respectively in the OLE period). Concomitant medications will be summarized separately for the double-blind Treatment Period (SS) and the OLE period (OLS).
By-subject listings of all Prior and Concomitant medications **(including COVID-19 concomitant medications)**, prior and concomitant medications glossary, and psoriasis treatment history will be
provided.
A separate listing will be produced to present viral vaccines (ATC Level 3).

Change #14

Section 7 MEASUREMENTS OF TREATMENT COMPLIANCE

The following footnotes have been added to the table 7 -2

[a] The subject's dosing interval will change from Q4W to Q8W at Week 64 or at the next scheduled clinic visit after implementation of Protocol Amendment 5.2 if the subject has already completed the Week 64 visit.

[b] Subjects whose dosing interval is changed to Q8W should be dosed at this visit and will receive kits for home administration 8 weeks later.

[c] Subjects whose dosing interval is changed to Q8W should NOT be dosed at this visit and will receive kits for home administration 4 weeks later

Change #15

Section 8.3.2 IGA response

The following texts (in bold) have been added

IGA response rate, Scalp IGA response rate, and Palmoplantar IGA response rate will be summarized for RS by treatment group and for OLS by treatment sequence and visit.

Change #16

Section 8.3.5 Dermatology Life Quality Index (DLQI)

The following texts have been added

The DLQI related efficacy variables will be summarized for the double-blind treatment visits separately for the RS and MS and for OLS by treatment sequence and visit.

Change #17

Section 8.3.6 Patient's Global Assessment of Disease Activity (PGADA) for arthritis visual analog scale (VAS)

The following texts (in bold) have been added

The absolute and change from baseline in PGADA will be summarized for the double-blind treatment visits separately for the RS and MS and OLS by treatment sequence and visit

Change #18

Section 8.3.7 Patient Global Assessment of PSO

The following sentence (in bold) has been added

The absolute value and shift from baseline in Patient Global Assessment (PGA) of PSO score will be summarized for each study period (Initial randomized, Maintenance) by treatment group and for OLE by treatment sequence and visit

Change #19

Section 8.3.8 Symptoms of PSO (Itch, pain, and scaling)

The following sentence (in bold) has been added

Absolute and percent changes from Baseline PSD item scores for each item will be summarized **for each study period (Initial randomized, Maintenance) by treatment group**

PSD response and the proportion of subjects with score of 0 (or 0/1) will be summarized for OLE Treatment Period by treatment sequence and visit.

The PS0009 and PS0013 analyses determined a 4-point reduction as a marked within-subject clinically meaningful improvement in the weekly score each of these 3 PSD items that can be used to define different marked response to treatment over 16 weeks in patients with moderate-to-severe plaque psoriasis. Such a threshold has also been used to support US label claims of other compounds approved in the same indication based on different PSO symptom diaries using an 11-point numeric response scale and was suggested in previous interactions with the FDA. **Analyses conducted on blinded PS0015 data support the 4-point threshold as indicative of marked within-subject clinically meaningful improvement that can be used for responder definition.**

Cumulative distribution plots will also be provided for absolute change from Baseline PSD at Week 16 **and Week 48** for each item

Change #20

Section 8.3.9 Modified Nail Psoriasis Severity Index (mNAPSI) score

The following sentence has been added

An mNAPSI75 responder is defined as a subject who achieved at least a 75% improvement from Baseline in the mNAPSI score. mNAPSI90 and mNAPSI100 are defined accordingly. The proportion of mNAPSI75/90/100 responders for subjects with nail PSO at Baseline over time will be summarized for each **study period (Initial randomized, Maintenance) by treatment group and OLE by treatment sequence.**

Change #21

Section8.3.10 Psoriatic Arthritis Screening and Evaluation (PASE)

The following sentence has been added

Change from Baseline in the PASE and Shift from Baseline in PASE will be summarized for each study period (Initial randomized, Maintenance) by treatment group and for OLE by treatment sequence and visit.

Change #22

Section 8.3.11 Euro-Quality of Life 5-Dimensions, 3 levels (EQ-5D-3L)

The following sentence (in bold) has been added

Responses to EQ-5D-3L will be summarized for each study period (Initial randomized, Maintenance) by treatment group and summarized **for each study period (Initial randomized, Maintenance) by treatment group and for OLE by treatment sequence and visit. The analysis will be** based on OC only as primary analysis. No imputation is applied to responses to EQ-5D-3L but is applied to EQ-5D-3L VAS scores**.**

Change #23

Section 8.3.12 Work Productivity and Activity Impairment Questionnaire – Specific Health Problem (WPAI-SHP)

The following sentence has been added

The Change from Baseline in WPAI-SHP will be summarized for each study period (Initial randomized, Maintenance) by treatment group and for OLE by treatment sequence at each visit.

Change #24

Section 8.4Additional Statistical Analysis of other Efficacy Variables

Due to a typographical error, Section 8.4 of the SAP (Additional statistical analysis of other efficacy variables) was removed from the body of the SAP. However, the analyses were described in Section 13.1 of the SAP (Amendment 1) and were performed as described. In addition nominal p-values were also produced for IGA 0 response and absolute PASI score ≤5, ≤3, ≤2, and ≤1. This change is to indicate that the Section has been put back in the SAP amendment 3.

Change #25

Section 9 Pharmacokinetics and Pharmacodynamics

The following text has been added:

- **Subjects receiving bimekizumab in the double-blind treatment period and completing the OLE period:**
  - **Bimekizumab Q4W/Q8W/Q8W**
  - **Bimekizumab Q4W/Q4W/Q4W (subjects in this group will switch to Q8W per protocol amendment 5 from Week 64 or the next scheduled clinic visit after implementation of Protocol Amendment #5 if the subject has already completed Week 64)**
  - **All other treatment sequences (this includes the treatment sequences Q4W/Q8W/Q4W, Q4W/Q4W/Q8W)**
- **Subjects receiving bimekizumab in the double-blind treatment period and not completing the OLE period (subjects that discontinued at any visit prior to Week 144)**
- **Subjects receiving secukinumab in the double-blind treatment period and completing the OLE period:**
  - **Secukinumab/Bimekizumab Q8W**
  - **Secukinumab/Bimekizumab Q4W (subjects will switch to Q8W per protocol amendment 5 from Week 64 or the next scheduled clinic visit after implementation of Protocol Amendment #5 if the subject has already completed Week 64 or the next scheduled clinic visit after implementation of Protocol Amendment #5 if the subject has already completed Week 64)**
- **Subjects receiving secukinumab in the double-blind treatment period and not completing the OLE period (subjects that discontinued at any visit prior to Week 144)**

Change #26

Section 9.1 Pharmacokinetics

The following text has been amended:

From

If the PK sampling date is >1 day after the dosing date data points will be excluded from the PK summary tables and figures, but not from the listing.

To

If the PK sampling date is >1 day after the dosing date, the plasma concentration at this visit will be excluded from the PK summary tables and figures, but not from the listing.

And the following texts have been added

If a subject misses an administration of bimekizumab, then the plasma concentration from all subsequent scheduled visits will be excluded from PK summary tables and graphs.

PK and ADAb will be summarized by treatment sequence and by visit for Initial, Maintenance, and Open-Label Extension treatment period combined:

All PK **concentration** data will be listed.

Change 27

Section 9.3.2 Anti-bimekizumab antibodies

The following texts (in bold) have been added

- Spaghetti plots of ADAb titer (y-axis) by visit (x-axis), separated by treatment **sequence (as specified above)** for all anti-bimekizumab antibody positive subjects, including Baseline positive subjects.

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

These data will be summarized by the **same** sub-group of subjects and treatment sequence as for **ADAb titer data**

Change #28

Section 10.1.4.2 For subjects who switch from bimekizumab 320mg Q4W to Q8W **during Open-Label Extension Period**

The following texts (in bold) have been added.

Following Protocol Amendment 5.0, subjects should switch to Q8W during the Open-Label extension period. (see Section 2.3.2.4 for further details).

Change #29

Section 10.1.5.2 For subjects who switch dose

The following texts (in bold) have been added.

Subjects can switch bimekizumab 320mg dose schedule up to three times during the Double-blind and Open-Label Extension Period. Switches can occur at Week 16, Week 48, and Week 96 **or at specific visit during the OLE following amendment 5.0**. See Section 2.3.2 for further details regarding switching.

Change #30

Section 10.2 Adverse Events

The following texts in (bold) have been added

- Events that fulfill the anaphylaxis criteria for acute events
- Events that fulfill the hypersensitivity criteria
- Events with an HLT of "Administration site reactions NEC"

- Events with an HLT of "Injection site reactions"

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent adverse events and treatment-emergent serious adverse events will be published.

Change #31

Section 10.2.1.1 COVID-19 related data considerations

The following texts (in bold) have been added

In order to assess the impact of the COVID-19 global pandemic on TEAEs, an additional AE summary **based on the BKZ set** will be presented for **the combined Initial, Maintenance and OLE periods.** The following data considerations are introduced to support this presentation by the following periods:

- Prior to COVID-19 pandemic
- During COVID-19 pandemic

The COVID-19 pandemic start date is defined as 11 March 2020 as it is the date the World Health Organization declared COVID-19 as a pandemic, see also Section 4.2.1.7.2. Note that the **Week 48 and Week 96** interim **analyses** will be conducted during the pandemic therefore a post COVID-19 pandemic period is not defined **for these analyses**. **If WHO declares the COVID-19 pandemic has ended prior to the final analysis, then that date may be used to support presentation of a post COVID-19 pandemic period.**

Incidence of COVID-19 TEAEs will be summarized for the OLE treatment periods based on the OLS by treatment group.

The following PTs will be used to classify COVID-19 adverse events:

- **Coronavirus infection**
- **Coronavirus test positive**

A separate by-subject listing will be produced for COVID-19 TEAEs.

Change #32

Section 10.2.2 AE summaries

The following sentences have been added

The tables with risk differences will also be accompanied by figures (dot plots) which show the incidence of the adverse events and corresponding 95% risk difference confidence intervals. These will be ordered by descending order of risk difference (bimekizumab vs secukinumab).

The following selected AEs summaries will be provided for the Open-Label Extension Period only and by treatment at time of AE onset and will be based on the OLS:

- **Incidence of COVID-19 TEAEs**
- Incidence of TEAEs Overview

- Incidence of TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs per 100 Subject-Years
- **Incidence of TEAEs Leading to Discontinuation per 100 subject-years**
- **Incidence of TEAEs Leading to Death**
- **Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by SOC and PT**
- **Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by Relationship SOC and PT**

The following summaries will be provided for the BKZ Set by treatment at the time of AE onset. These tables will include AEs from both the double-blind and Open-Label treatment period. AEs that occurred while subjects received secukinumab will not be included.

- Incidence of TEAEs Overview
- Incidence of TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs per 100 Subject-Years

In addition, all summaries of TEAEs based on "100 subject years" will include EAIR (with 95% CI) and EAER.

The following summaries will be presented for subjects who switched from secukinumab to bimekizumab at Week 48. The analyses will assign AEs according to the AE onset date relative to last secukinumab dose and accounting for approximately 5 times half-life (Onset ≤ 140 days from last secukinumab dose or Onset > 140 days from last secukinumab dose):

- **Incidence of TEAEs Overview**
- **Incidence of TEAEs per 100 Subject-Years**
- **Incidence of Serious TEAEs per 100 Subject-Years**

Change #33

Section 10.2.3 Other Safety topic of interest

The following texts (in bold) have been added

The following summaries for AEs of other safety topics of interest will be provided by actual Treatment at the time of the adverse event. The following outputs will be produced for the SS for the initial treatment period, for the SS for the Initial and Maintenance Treatment Period, and for the OLS for the Open-Label Extension Period **by treatment group (see section 3.6).**

Similar outputs for hypersensitivity events and hepatic events will also be produced for the Maintenance Treatment Period for the MS.

Additional analyses will be presented for subjects who switched from secukinumab to bimekizumab at Week 48 and the AEs will be assigned according to the onset date relative to last secukinumab dose and accounting for approximately 5 times half-life (Onset ≤ 140 days from last secukinumab dose or Onset > 140 days from last secukinumab dose).

Along with the tables described, there will be tables which displays the risk difference and 95% confidence intervals for each of the topics of interest during the Initial Treatment Period (SS) as well as for Initial and Maintenance Treatment Period combined (SS). Corresponding figures (with dot plots) will be prepared.

Change #34

Section 10.2.3.6 Inflammatory bowel disease

The following has been added

An external inflammatory bowel disease (IBD) adjudication committee will evaluate potential IBD events and will classify each one as follows:

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

A table for adjudicated definite IBD events (event type codes 3, 6, 9, 13, and 16) as determined by the adjudication committee will be produced. This table will be produced overall, as well as stratified by subjects with or without a previous medical history of IBD. Previous medical history of IBD will be determined using the information recorded on the Extra-Articular Assessment at Screening CRF page.

A table for adjudicated probable IBD events (event type codes 2, 5, 8, 12, and 15) as determined by the adjudication committee will be produced. This table will be produced overall, as well as stratified by subjects with or without a previous medical history of IBD.

A table for adjudicated possible IBD events (event type codes 1, 4, 7, 11, and 14) as determined by the adjudication committee will be produced. This table will be produced overall, as well as stratified by subjects with or without a previous medical history of IBD.

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

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

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

Change #35

Section 10.3 Clinical laboratory evaluations

The following Laboratory analytes have been added in Table 10-2

Total Cholesterol

HDL Cholesterol

LDL Cholesterol

Triglycerides

Table 13–4: Definitions of Markedly Abnormal Biochemistry Values

Parameter name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Creatinine	mg/dL	>3.0 x ULN	mmol/L	>3.0 x ULN	AH
Glucose	mg/dL	<40 >250	mmol/L	<1.7 >13.9	AL AH
Calcium	mg/dL	>12.5 <7.0	mmol/L	>3.1 <1.75	AH AL
Magnesium	mg/dL	>3.0 <0.9	mmol/L	>1.23 <0.4	AH AL
Potassium	mmol/L	>6.0 <3.0	mmol/L	>6.0 <3.0	AH AL
Sodium	mmol/L	>155 <130	mmol/L	>155 <130	AH AL

Table 13–4: Definitions of Markedly Abnormal Biochemistry Values

Parameter name	Conventional		Standard		Abnormal Designation
	Unit	Criteria	Unit	Criteria	
Total Cholesterol	**mg/dL**	**>400**	**mmol/L**	**>10.34**	**AH**
HDL Cholesterol	**mg/dL**	**<40**	**mmol/L**	**< 1.04**	**AL**
LDL Cholesterol	**mg/dL**	**≥190**	**mmol/L**	**≥ 4.90**	**AH**
Triglycerides	**mg/dL**	**>500**	**mmol/L**	**> 5.7**	**AH**

Change #36

Section 10.1.4.1 Vital signs

The following texts (in bold) have been added

The following vital signs variables should be summarized: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C) and heart rate (beats/min). The following summary will be provided for the Initial Treatment Period (SS) **for Initial and Maintenance Treatment Period, and for the Open-Label Extension Period (OLS)**

Change #37

Section 10.4.3 Electrocardiograms

The following texts (in bold) have been added

ECG data will be analyzed by treatment group and visit **for the Initial Treatment Period (SS), the Initial and Maintenance Treatment Period (SS), and by treatment sequence for the Open-Label Extension Period (OLS).**

Change #38

Section 10.4.4.2 Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

The following texts (in bold) have been added

The incidence of subjects with suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior will be summarized by treatment group. For **events** that emerged after 112 days but still within the 140 days window, those **events** would be classified as **treatment emergent**, but will be excluded from the output based on the Initial Treatment Period. However, these events will be included in the summaries for Initial Treatment Period and Maintenance Treatment Period combined. **Similar summaries will be presented for the Open-Label Extension Period (OLS) by treatment sequence and visit.**

A by-subject listing of the eC-SSRS questionnaire data will be provided by treatment group.

Change #39

Section 10.4.4.5 Patient Health Questionnaire 9 (PHQ-9)

The following texts (in bold) has been added

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. The PHQ-9 scores for depression range from 0 to 27 with higher scores indicating worse state. A score of 5-9 is considered to be minimal symptoms of depression. A score of 10 to 14 is considered minor depression, dysthymia, or mild major depression. A score of 15 to 19 is considered to indicate moderately severe major depression, and a score ≥20 is considered to be severe major depression. **If any of the 9 questions are missing, then the score is treated as missing.**

Change from Baseline in PHQ-9 is derived as post-Baseline score minus Baseline score and will be summarized by treatment group.

Differently to other safety variables, PHQ-9 will be summarized using the MCMC/monotone regression approach described in section 8.1.3.1. A table for the SS through Week 48 will be produced. **An additional table will be produced for the OLS by treatment sequence and visit.**

The number and percentage of subjects with a PHQ-9 score ≥ 15 at any point while on treatment and the number and percentage of subjects with a PHQ-9 score ≥ 20 at any point while on treatment will also be presented based on observed case data

Change #40

Section 12.2 Appendix B: Definition of CTCAE grades

The following Laboratory analytes (in bold) have been added to Table 12-1 **(see Change #34)**

Total Cholesterol has been added

Change #41

Section 12.3 has been added to describe Week 96 interim analysis

12.3 Appendix C: Week 96 interim analysis

An additional data cut will occur approximately after the final Week 96 visit, an interim analysis will be performed focused on the Open-Label extension treatment period.

The currently anticipated date for the final Week 96 visit is 19 March 2021. The interim analyses will include:

- **Efficacy data through the Week 96 visit.**
- **Safety data through 19 March 2021.**

Selected tables, figures and listings will be produced for this Week 96 interim analysis. Study population characteristics, demographics, other baseline characteristics and measurements of treatment compliance will be presented for the OLS. The following

efficacy variables will be presented for the Open-Label extension treatment period based on the OLS, this will include presentations based on the subgroup of participants switching from secukinumab to bimekizumab:

- **PASI90 response**
- **PASI100 response**
- **IGA Clear or Almost Clear (with at least a 2-category improvement from Baseline)**
- **IGA Clear (with at least a 2-category improvement from Baseline)**
- **Scalp IGA Clear or Almost Clear (with at least 2 category improvement relative to Baseline)**
- **Palmoplantar IGA Clear or Almost Clear (with at least a 2-category improvement from Baseline)**
- **DLQI total score of 0 or 1**
- **mNAPSI90, mNAPSI100**
- **Absolute, change, and percent change from Baseline in PASI score**
- **Absolute PASI scores of ≤1, ≤2, ≤3**
- **Absolute and percent change from Baseline in BSA affected by PSO**
- **Psoriasis BSA values of 0%, ≤1%, ≤3%**
- **PSD response (itch, pain and scaling)**
- **PSD 0 or 1 (itch, pain and scaling)**
- **PSD 0 (itch, pain and scaling)**

The following safety variables will be presented for the Open-Label extension treatment period based on the OLS:

- **Extent of exposure**
- **TEAEs including COVID-19 and safety topics of interest**
- **Laboratory data focused on TEMA and CTCAE**
- **e-CSSRS**
- **PHQ-9**
- **COVID-19 impact**

Selected analyses of TEAEs will be presented for the subgroup of participants switching from secukinumab to bimekizumab for the Open-Label extension treatment period based on the OLS. Selected analyses of TEAEs will also be presented for the BKZ Set by treatment at the time of AE onset. These tables will include AEs from both the double-blind and Open-Label treatment period.

In addition, the following tables will be produced:

- **Past psoriasis medication**
- **Impact of COVID-19 and COVID-19 protocol deviations for Maintenance treatment period based on MS**
- **Main analysis of PASI100 Responder Rates at Week 48 plus sensitivity analyses of this variable based on hybrid approach for assessing impact of COVID-19**

  Laboratory data for lipid panel (Total Cholesterol, HDL Cholesterol, LDL Cholesterol, Triglycerides) for combined Initial Treatment Period and Maintenance Treatment period based on SS

13.4 Amendment 4

Rationale of the Amendment

The main purposes of this amendment are as follows:

- To align the SAP with protocol amendment 5.4 and 5.5
- To include details of the Week 144 analysis
- To describe the requirements for the Open-Label Extension 2 period
- To include the analysis related to the COVID-19 vaccine.

General Changes

Texts have been added in several sections to indicate which variables will be produced for the OLE2.

Change #1

List of Abbreviation

The following abbreviations have been added: **CV-CAC, pDILI, OLE2, and OLS2, SFU2**

Change #2

Section 1 Introduction: the following text (in bold) have been added:

This statistical analysis plan (SAP) defines the scope of statistical analyses and provides a detailed description of statistical methodology for the statistical analyses to support the final clinical study report. The SAP is based on the following study document: Protocol Amendment **5.4 (US) 01 Oct 2021 and 5.5 (Canada), 08 Dec 2021**

Change #3

Section 2.3.2: Study periods. The following texts in (bold) have been added:

This study will include **5** periods, a Screening Period (2 to 5 weeks), a double-blind Treatment Period (48 weeks; final dose at Week 44), an optional Open-Label extension (OLE) Period (96 weeks, final dose at Week 136 for subjects receiving bimekizumab 320mg Q8W and at Week 140 for subjects receiving bimekizumab 320mg Q4W), **followedd by** a safety follow-up (SFU) Period (20 weeks after the final dose of IMP). **Eligible subjects from US and Canada sites who have completed the OLE Period (at Week 144), including subjects in the SFU period and subjects who have completed the SFU Period will have the option to roll over in the 48-week Open-Label Extension 2 (OLE2) Period followed by a SFU Period (SFU2, 20 weeks after the final dose of IMP administered in the OLE2).**

The double-blind treatment Period will be separated into an Initial Treatment Period (16 weeks) and a Maintenance Treatment Period (32 weeks). The end of the study is defined as the date of the last visit of the last subject in the study.

Subjects withdrawing early from the study will undergo the premature end of treatment (PEOT) Visit assessments and will enter the SFU Period. **Following completion or early withdrawal from the OLE2 Period, subjects will undergo the SFU of the OLE2 Period (SFU2) and will return for the SFU2 Visit 20 weeks after the last dose of IMP administration. in the OLE2 treatment period.**

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

- Screening Period: Prior to the date of first dose of study drug
- Initial Treatment Period is defined as the time from the first study drug administration up to the start of the Maintenance Treatment Period
- Maintenance Treatment Period starts with the first study drug administration at or after the Week 16 visit
- Open-Label Extension Period starts with the first study drug administration at or after the Week 48 visit
- SFU Period is 20 weeks after the final dose of IMP **in the double-blind Treatment Period or Open-Label Extension Period**
- **Open-Label Extension 2 Period starts with the first study drug administration at or after the Week 144 visit/OLE2 Baseline visit**
- **SFU2 Period is 20 weeks after the final dose of IMP in the OLE2**

The Open-Label Treatment Period ends either at the Week 144 visit for subjects completing the Open-Label Treatment Period, or at PEOT Visit for subjects who discontinued early during the Open-Label Treatment Period. If a subject does not have a Week 144/PEOT visit, then the date of the last scheduled or unscheduled visit during the Open-Label Treatment Period will define the end date of the Open-Label Treatment Period.

The OLE2 treatment Period ends either at the OLE2 Week 48 visit for subjects completing the OLE2 Period, or at PEOT Visit for subjects who discontinued early during the OLE2 Period. If a subject does not have an OLE2 Week 48/PEOT visit, then the date of the last scheduled or unscheduled visit during the OLE2 Period will define the end date of the OLE2 Period.

Change #4

Section 2.3.2.5 OLE2 Period has been added with the following texts

After the implementation of Protocol Amendment #5.4 and 5.5 (with the addition of a 48-week Open-Label treatment period, ie, OLE2 Period), subjects from US and Canada sites will be invited to continue or reinitiate their treatment as per the following OLE2 Groups:

- **OLE2 Group A: Subjects in the treatment phase of the OLE Period at the time of Protocol Amendment #5.4 and 5.5 implementation will attend the Week 144 Visit and directly roll over to the OLE2 Period. These subjects will continue receiving bimekizumab 320mg Q8W for 40 additional weeks, starting from the first treatment visit of the OLE2 Period (ie, Week 144/OLE2 Baseline Visit; the Week 144 Visit will coincide with the Week 144/OLE2 Baseline Visit and data collected at this visit will be used as baseline data for the OLE2 Period).**
- **OLE2 Group B: Eligible subjects who have completed the Week 144 Visit and are in the SFU or have completed the SFU of the OLE Period at the time of Protocol Amendment #5.4 and 5.5 implementation, will be eligible to reinitiate their treatment in the OLE2 Period after having undergone additional screening assessments during a 4-week OLE2 Screening Period.**
  - **The first dose of the IMP ill be administered at the OLE2 Baseline Visit and data collected at this visit will be used as baseline data for the OLE2 Period.**
  - **Subjects in OLE2 Group B with an IGA score ≥3 at the OLE2 Baseline Visit will receive bimekizumab Q4W for the first 16 weeks, and then will switch to bimekizumab 320mg Q8W.**
  - **Subjects in OLE2 Group B with an IGA score <3 at the OLE2 Baseline Visit will receive bimekizumab Q8W from the OLE2 Baseline Visit.**

Following completion or early withdrawal from the OLE2 Period, subjects will enter the SFU2 and will return for the SFU2 Visit 20 weeks after the last dose of IMP administration.

Change #5

Section 2.3.2.6: Safety Follow-Up The following texts in bold has been added:

All subjects, including those withdrawn from IMP, will have a SFU Visit 20 weeks after their final dose of IMP**.**

Two SFU Periods are considered following the implementation of Protocol Amendments #5.4 and #5.5:

- **SFU following the OLE Period that covers the initial, maintenance, and the OLE treatment periods**
- **SFU2 following the OLE2 treatment period**.

Change #6

Section 2.3.2.7 Premature End of Treatment. The following texts in bold have been added

Subjects withdrawing early from the study will undergo PEOT Visit assessments and will enter the SFU Period **or SFU2 Period depending on when subjects withdraw from the study.**

Change #7

Section 2.3.3 Study duration per subject. The following texts in bold have been added

For each subject **not entering the OLE2 treatment period**, the study will last a maximum of up to 165 weeks, as follows:

- Screening Period: 2 to 5 weeks
- Double-blind Treatment Period: 48 weeks (final dose at Week 44)
- OLE Period: 96 weeks (final dose at Week 136 for subjects receiving bimekizumab 320mg Q8W and at Week 140 for subjects receiving bimekizumab 320mg Q4W)
- Safety Follow-Up Period: an SFU Visit is planned 20 weeks after the final dose of IMP **during the OLE period (this SFU will not apply to subjects directly rolling over from the OLE to the OLE2 Period).**

The OLE2 Period will include a 48-week treatment period with a final visit at OLE2 Week 48 and a SFU2 period of 20 weeks after the final dose of IMP administered in the OLE2 Period.

For the subjects in the OLE2 Period, maximum study duration will depend on the time between their participation in the OLE until Week 144 and the start of the OLE2 Period:

- **209 weeks for subjects still being treated in the OLE Period and who will directly roll over to the OLE2 Period at Week 144**
- **225 weeks for subjects who have completed Week 144 and the SFU; these subjects will have a 4-week Screening Period before reinitiating treatment in the OLE2 Period. Note: for these subjects, the study duration will not be continuous**
- **Between 209 and 225 weeks for subjects who have completed Week 144 and are ongoing in the SFU. For these subjects, the maximum study duration will depend upon when they stop the 20-week SFU period to enter the 4-week OLE2 Screening Period.**

Change #8

Section 2.3.5 Anticipated regions and countries. The following text in bold has been added

The regions and countries planned for study conduct are North America (Canada, USA), Western Europe (Belgium, France, Germany, Netherlands, Spain, United Kingdom), Central/Eastern Europe (Poland), Asia/Australia (Australia, Turkey). **An additional OLE2 will be conducted in US and Canada only**

Change #9

Section 3.1 General presentation of summaries and analyses. The following text in bold have been added

Per protocol, visit windows of ±3 days from the first dose to Week 24, ±7 days from Week 28 to Week 72 and ±14 days from Week 76 to Week 144 are permissible. For the SFU Visit, visit window is 20 weeks ±7 days from final dose.

Per protocol, visit windows of ±14 days from the first OLE2 dose at all OLE visits except SFU2 are permissible, the SFU2 visit window is 20 weeks ±7 days from final dose in OLE2.

All by-visit summaries will contain nominal (i.e. scheduled) visits only. Unscheduled visits will not be mapped to scheduled visits except for assessments that occur within a 3-day time window of a scheduled visit. In that case, the assessment will be mapped to the corresponding scheduled visit and will be used for the analysis. This will only occur for some vendor data.

A complete set of data listings containing all documented data as well as calculated data (e.g. change from Baseline) will be generated. Separate data listings will be generated for the OLE2 period.

Change #10

Section 3.2 Definition of Baseline values. The following texts in (bold) have been added

Unless specified otherwise, the process laid out above will always be followed to determine Baseline. An additional Baseline value for the OLE Period will be defined for anti-bimekizumab antibodies for **subjects** initially randomized to secukinumab and for selected summaries of laboratory evaluations. This baseline for the OLE Period is the latest measurement on/prior to the day of first dose in the OLE Period for subjects switching from secukinumab to bimekizumab.

Note that for any laboratory value that occurs on the day of treatment switch, that lab value will be attributed and summarized for the treatment the subjects were on previously.

For subjects enrolled in OLE2, the OLE2 first dose will be administered at the Week 144/OLE2 Baseline Visit and data collected at this visit will be used as baseline data for safety data in the OLE2 Period. Efficacy data will continue to use the Week 0 Visit as Baseline.

Change #11

Section 3.5.7 Open-Label Set2 has been created with the following texts in bold

The Open-label Set 2 (OLS2) will consist of all subjects that received at least 1 dose of bimekizumab at Week 144/OLE2 Baseline Visit or later in the OLE2 Period.

Change #12

Section 3.6 Treatment assignment and treatment groups. The following texts in bold have been added

- Secukinumab / Bimekizumab Q8W for responder at Week 48 (>=PASI90)
- Secukinumab / Bimekizumab Q4W for responder at Week 48 (>=PASI90)

Safety and efficacy assessments for OLE2 period will only include subjects who entered OLE2 period and will be based on OLS2, and will be summarized by the assigned treatment as follows:

- **Subjects who roll over directly from the OLE treatment period: Group A**
  - **Bimekizumab Q8W Group A**
- **Subjects in Group B who reinitiate bimekizumab after having completed treatment in the OLE and have an IGA <3 upon entry to the OLE2): Group B.**
  - **Bimekizumab Q8W Group B**
- **Subjects in Group B who reinitiate bimekizumab after having completed treatment in the OLE and have an IGA ≥3 upon entry to the OLE2: Group B.**
  - **Bimekizumab Q4W/Q8W Group B**
- **For safety summaries only**
  - **BKZ Total.**

Change #13

Section 3.8 Coding dictionaries. The following change in bold has be made:

All medications other than study drug will be classified by WHO Anatomical Therapeutic Chemical (ATC) Classification, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and preferred term, using **World Health Organization Drug Dictionary (WHO-DD)** version **SEP 2015 for Week 48 and Week 96 analysis, and MAR 2021 for Week 144 and Final analysis**, according to UCB standard operating procedures (SOP).

Change #14

Section 3.9 Relative Day. The following texts in bold have been added

Relative day will only be computed for fully completed dates and will be missing for partial dates. **Two relative days will be used:**

- **Compared to the first dose of study drug in the Initial Treatment Period for all subjects**
- **Compared to the first dose of study drug in the Open-Label Extension 2 Period for subjects in OLS2 only**

Change #15

Section 3.10.1 Changes related to COVID-19. The following texts have been added

The following changes have been introduced due to the COVID-19 pandemic:

- COVID-19 protocol deviations have been defined in Section 3.4 and the presentation of COVID-19 protocol deviations is described in Section 5.2
- COVID-19 impact on study visits has been assessed and are described in Section 5.1
- COVID-19 Disposition assessments are described in Section 5.1
- Missing data methods for assessing the impact of COVID-19 are described in Section 4.2.1.7

Data considerations for assessing the impact of COVID-19 on TEAEs **including COVID-19 vaccine AEs** are described in Section 10.2.1.1 and the associated analysis is described in Section 10.2.2

Change #16

Section 4.2.1.6 Missing data algorithm – MI – MCMC / Monotone Regression. The following texts in bold have been added:

Table 4-2 Allowable ranges for imputation by variable. At ypo in bold has been corrected

Variable	Minimum value	Maximum value	Integer values only
PASI	0	72	No
IGA	0	4	Yes
PSD items (itch, pain, scaling)	0	10	No
Scalp IGA	0	4	Yes
mNAPSI	0	**130**	No
BSA	0	100	No
IGAxBSA	0	400	No
DLQI	0	30	Yes
PGADA	0	100	No
EQ-5D-3L VAS	0	100	Yes

Variable	Minimum value	Maximum value	Integer values only
WPAI dimension scores	0	100	No for variables: "Percent work time missed due to problem" and "Percent overall work impairment due to problem". Yes for variables: "Percent impairment while working due to problem" and "Percent activity impairment due to problem". These two variables can only take values that are multiples of 10.
PHQ-9	0	27	Yes

Maintenance Set: When programming multiple imputation based on the MS, PROC MI will be used with a separate data set for each of the 3 Maintenance Period treatment groups (bimekizumab 320mg Q8W, bimekizumab 320mg Q4W, secukinumab) including all scheduled assessment visits from Baseline to Week 48.

Open-Label Set: When programming multiple imputations based on the OLS, PROC MI will be used with a separate data set for each of the 6 treatment sequences based on the combination of randomized treatment at Baseline, Maintenance Period treatment and OLE period treatment at Week 48 including all scheduled assessment visits from Baseline to Week 144. However, the summary values for the 4 treatment sequences based on the combination of randomized treatment at Baseline and OLE period treatment at Week 48 will be computed after the imputation steps

The Open-label Set2: The analyses will be based on OC. Multiple imputation methods described above will not be applied.

Change #17

Section 4.3 Interim analyses and data monitoring. The following texts in bold have been added

The following data cuts will occur and corresponding interim analyses will be performed:

- After the final Week 48 visit, an interim analysis will be performed and a corresponding interim clinical study report (CSR) will be written, For subjects that participate in the OLE period, data will be cut at the day of their Week 48 study drug administration. Data from the OLE will not be included in this interim analysis.
- **An additional Week 96** data cut will occur approximately after **the last** Week 96 visit. **A Week 96** analysis will be performed for the Open-Label treatment period using this Week 96

data cut. Selected tables, figures, and listings **based on Week 96 data cut** will be produced for **these analyses** as detailed in Section 12.3 (Appendix C). **No corresponding CSR for these analyses was planned.**

- **In addition, a Week 144 data cut will occur after Week 144 visit and SFU. A Week 144 analysis will be performed using Week 144 and SFU data cut and a corresponding Week 144 interim CSR will be written.**
- **A final analysis will be conducted when all data for the double-blind, OLE (including SFU), and OLE2 (including SFU2) treatment periods have been collected and final CSR will be written.**

An independent Data Monitoring Committee (DMC) will periodically review and monitor the safety data from the Double-blind treatment period of this study and advise UCB.

Cardiovascular, Inflammatory bowel disease (IBD), and Neuropsychiatric Adjudication Committees will also periodically review and monitor safety data from this study including **two** Open-label Extension **(OLE and OLE2)** treatment periods and advise UCB. Details will be provided in the DMC Charter and in the Adjudication Committee Charters.

Further details related to the DMC will be outlined in a separate analysis plan.

Change #18

Section 4.5: Multiple comparisons/multiplicity. The following texts in bold have been added.

Note: Tests for H_1, H_2, H_3, and H_4 are based on all subjects initially randomized to bimekizumab compared to secukinumab. For H5 and H6, testing is based on the subjects re-randomized at Week 16 to bimekizumab 320mg Q4W, and bimekizumab 320mg Q8W, respectively, compared to secukinumab.

A table will be produced containing **the results for** all hypotheses. P-values **or confidence intervals only** will be shown **as appropriate**.

Other tables will include p-values of primary and secondary endpoints. These p-values should not be considered to evaluate hypotheses as they are not controlled for multiplicity.

Change #19

Section 4.8 Examination of subgroups. The following texts in bold have been added

Subgroup analyses will be **conducted based on Week 48 data cut only. These analyses will be** performed on the PASI75/90/100 response rates, using by visit summaries only. The following subgroups for analysis will be determined for the RS using baseline data:

Age (<40 years, 40 to <65 years, ≥65 years)

In addition, in order to assess whether an early response to treatment is predictive of response at later time points, subgroup analyses will be performed for PASI90/100 and IGA over time using the following early response subgroups:

- PASI75 response (OC) at Week 4 (yes, no) to predict PASI90/100 and IGA (clear or almost clear) (NRI) through Week 48 **Based on RS**
- PASI90 response (OC) at Week 16 (yes, no) to predict PASI100 (NRI) through Week 48 **based on RS**
- PASI90 response (OC) at Week 48 (yes, no) to predict PASI90 (NRI) during the OLE based on OLS
- PASI90 response (OC) at Week 48 (yes, no) to predict PASI100 (NRI) during the OLE based on OLS
- PASI90 response (OC) at Week 48 (yes, no) to predict IGA responder rates (clear) and IGA responder (clear or almost clear) during the OLE based on OLS.

All summaries will be based on imputed data as appropriate and will include descriptive statistics only.

Additional subgroup analyses are described in Section 4.2.1.7.2 to assess the impact of the COVID-19 pandemic on planned statistical analysis of PASI100 response at Week 48.

Change #20

Section 5.1 Subject disposition. The following texts in bold have been added

Summaries of reasons for screen failures (for all subjects screened), disposition of subjects (for all subjects screened), disposition of analysis sets (for RS, MS and OLS), disposition and discontinuation reasons (for RS, MS**, OLS, and OLS2),** as well as for the subjects who discontinued due to AEs (for RS, MS**, OLS, and OLS2)** will be produced. The disposition of subjects for all subjects screened will include the number of subjects included in each analysis set (RS, SS, FAS, MS, OLS, **OLS2,** BKZ Set, PPS and PK-PPS) overall and by site.

The following listings for subject disposition will be provided: subjects who did not meet study eligibility criteria (all subjects screened), subject disposition (all subjects screened), study discontinuation (for RS), visit dates (for RS), subjects excluded from efficacy analysis (RS). Summaries of visits at which subjects initiated the switch from bimekizumab 320mg Q4W to bimekizumab 320mg Q8W dosing interval in Open-Label Extension period will be presented.

Similar listings will be provided separately for the OLE and the OLE2 treatment periods.

In addition, the following COVID-19 impact categories will be summarized by country and visit for the MS OLS, and **OLS2** (see Section 2.3.5 for list of countries). **Separate listings of COVID-19 impact will be provided for the OLE and OLS2 treatment periods.**

A by-subject listing of COVID-19 impact categories will be provided **separately for the OLE and the OLE2 treatment periods.**

Change #21

Section 5.2 Protocol deviations. The following texts in bold have been added

A summary of number and percentage of subjects with an important protocol deviation (including a summary of subjects excluded from any analysis set due to important protocol deviations) by treatment group will be provided for the RS, MS**, OLS, and OLS2.**

A by-subject listing of important protocol deviations will be provided **separately for Initial and Maintenance treatment periods for RS. Similar listings will be provided separately for the OLE and the OLE2 treatment periods.**

A summary of number and percentage of subjects with COVID-19 protocol deviations by treatment group and visit will be provided for the MS and OLS.

A by-site, subject and visit listing of COVID-19 protocol deviations will be provided.

Separate listings of subjects with COVID-19 protocol deviations will also be provided for the OLE and the OLE2 treatment periods.

Change #22

Section 6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

All summaries detailed in this section will be performed on the RS by treatment group. Summaries for demographics and other Baseline characteristics will also be repeated on SS, MS, **OLS, and OLS2**. All these summaries **(including the OLS and the OLS2 summaries) will use the Baseline value from Week 0 of the double-blind treatment period**. If the RS and SS analysis sets are identical the summaries will not be repeated.

Change #23

Section 6.3 Medical history and concomitant diseases. The following texts in bold have been added

Previous and ongoing medical history will be summarized by treatment group(s), SOC and PT using MedDRA® version. Medical procedures are not coded.

The following listings for medical history and concomitant diseases will be provided: medical history, psoriasis history, concomitant medical procedures, previous and ongoing medical history glossary, previous and ongoing medical history conditions, and procedure history.

For subjects enrolling in OLE2 Group B, any additional medical history collected during OLE2 screening will be flagged in the medical history listing.

Change #24

Section 6.4 Prior and concomitant medications. The following texts in bold have been added

Concomitant medications are medications taken at least one day in common with the study medication dosing period (defined as from first dose of study medication [including placebo] up to last dose of study medication + 28 days for the double-blind treatment period, and +28 days or +56 for Q4W and Q8W dosing respectively in the OLE period). Concomitant medications will

be summarized separately for the double-blind Treatment Period (SS**), the OLE treatment period (OLS).**

Past psoriasis medications will be captured separately and will also be summarized by treatment group. These medications are not subject to dictionary coding. In addition, subjects who failed past psoriasis biologic treatment will be summarized by reason of failure as captured on the Psoriasis Treatment History CRF module.

The number and percentage of subjects with concomitant vaccines for COVID-19 will be summarized by treatment group, overall and by World Health Organization Drug Dictionary Standardised Drug Grouping (SDG), presenting SDG subgroup, and preferred term. The SDG subgroup Vaccines for COVID-19 will be used to identify vaccines for COVID-19 using the narrow scope; this subgroup is divided further into separate subgroups which is the level that will be presented. The number of individual occurrences of the vaccine for COVID-19 will also be summarized.

By-subject listings of all Prior and Concomitant medications (including COVID-19 concomitant medications), prior and concomitant medications glossary, and psoriasis treatment history will be **provided separately for OLE and OLE2 treatment periods. Ongoing concomitant medications from OLE to OLE2 treatment period will be flagged.**

An additional listing of concomitant vaccines for COVID-19 will be provided separately for OLE and OLE2 treatment periods.

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Change #25

Section 7 MEASUREMENTS OF TREATMENT COMPLIANCE. The following texts in bold and 7-3 have been added

A summary of percent treatment compliance categorized as <75% and ≥75% will be provided by treatment group and study periods (Initial Treatment Period for the SS, Maintenance Treatment Period for the SS, Initial and Maintenance Treatment Period for the SS, Open-Label Extension Period for the OLS **and Open-Label 2 Extension Period for the OLS2**).

A by-subject listing of treatment compliance will be provided. **Separate listings of treatment compliance will be provided for the OLE and the OLE2 treatment periods.**

Table 13–5: Dosing scheme, OLE2 Period

Visit/Week Dose Assignment	OLE2 Period									
	Week 144/OLE2 Baseline	OLE2 Week 4	OLE2 Week 8	OLE2 Week 12 [a]	OLE2 Week 16	OLE2 Week 24 [b]	OLE2 Week 32	OLE2 Week 36 [c]	OLE2 Week 40	OLE2 Week 48
	C	H	H	C	H	C	H	C	H	C
Bimekizumab 320mg Q4W/Q8W[d]	●●	●●	●●	●●	●●	●●	●●		●●	
Bimekizumab 320mg Q8W	●●		●●		●●	●●	●●		●●	

C=Clinic; H=home; IGA=Investigator's Global Assessment; IMP=investigational medication product; OLE=Open Label Extension; Q4W/Q8W=every 4 weeks for 16 weeks, followed by every 8 weeks; Q8W=every 8 week; W=week
Notes: A bimekizumab 160mg injection is depicted by black circle (●).
a Subjects will receive kits for home administration 4 weeks later.
b Subjects will receive kits for home administration 8 weeks later.
c Subjects should NOT be dosed at this visit and will receive kits for home administration 4 weeks later.
d Q4W/Q8W IMP administration only applies to those subjects who have entered the OLE2 Period as part of Group B and had an IGA ≥3 upon entry of OLE2 Period. These subjects will receive Q4W dosing for 16 weeks until OLE2 Week 16, then will change from Q4W to Q8W and will receive their next dose at the scheduled clinic visit OLE2 Week 24.

Change # 26

Section 8.1.1 Derivations of primary efficacy variable. The following texts in bold have been added

Unless otherwise specified, the Baseline value to be used in the analysis of efficacy endpoints will be the assessments from Week 0 of the double-blind treatment period of the study. A table of efficacy variables analyzed at each treatment period is provided in Section 12.4 Appendix D

Change #27

Section 8.1.2 Primary analysis of the primary efficacy variable

A line plot of the percentage improvement from Baseline in PASI score over time by treatment group will be produced by randomized treatment group for the RS and repeated for the MS. An additional plot will be produced for the OLS by OLE treatment groups.

By-subject listings of PASI and PASI responder variables will be provided. **for the Initial and the Maintenance periods combined based on RS. This listing will also be provided separately for the OLE and the OLE2 treatment periods.**

Change #28

Section 8.3: Analysis of other efficacy variables. The following texts have been added:

For variables that are part of the sequence testing procedure, summaries based on observed case data will also be provided. There may be cases where the multiple imputation model fails to converge. In such situations, the LOCF approach will instead be used to impute the missing data. Selected efficacy variables will also be summarized by visit through Week 144 for the OLE Period for the OLS. Subjects will be summarized by treatment sequence comprising randomized treatment at Baseline and OLE period treatment at Week 48.

The OC approaches will be used to summarize the following efficacy variables for subjects in the OLE2 treatment period: PASI90. PASI100, IGA (0/1), IGA (0), DLQI(0/1), and PSD responder.

Change #29

Section 8.3.1.1 PASI75, PASI90 and PASI100 response rates. The following texts in bold have been added.

A line plot of the PASI responder (PASI75, PASI90, and PASI100) rate over time, by treatment group will be produced for the RS and by randomized treatment groups. Additional plots will be produced **separately** for the MS by maintenance treatment groups, for the OLS **and for the OLS2 (excluding PASI75)** by OLE **and OLE2** treatment **sequences respectively.**

Change #30

Section 8.3.1.2 Time to PASI75, PASI90 and PASI100 response. The following texts in boldnhave been added.

Kaplan-Meier plots of time to PASI responses will also be presented by initially randomized treatment group. In these Kaplan-Meier plots, the line will start at 0 (since there are no responders at Week 0) and will increase over time, representing time to achieving the response.

Time to PASI75. PASI90, and PASI100 response analyses will not be conducted for the OLE and the OLE2 treatment periods.

Change #31

Section 8.3.1.3 PASI score. The following texts have been added.

Absolute and percent change from Baseline in PASI score is defined in Section 8.1.1.1.

The percentage of subjects with absolute PASI score ≤1, ≤2, ≤3 and ≤5 will be presented over time using NRI for the RS, the MS, and the OLS.

Absolute PASI score categories will not be summarized for the OLE2 treatment period.

Change #32

Section 8.3.2 IGA response. Table 8.3 footnote has been updated and following texts in bold have been added

Palmoplantar disease will be assessed in terms of clinical signs of redness, thickness, and scaliness using a 5-point scale as outlined in Table 8–3 below.

Table 13–6: Palmoplantar IGA

Score	Short Descriptor	Detailed Descriptor
0	Clear	Palmoplantar has no signs of PSO; post-inflammatory hyperpigmentation may be present
1	Almost clear	Palmoplantar has no thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Palmoplantar has just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Palmoplantar has clearly distinguishable to moderate thickening; dull to bright red and clearly distinguishable coloration; moderate scaling
4	Severe	Palmoplantar has severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions; numerous fissures

PSO=psoriasis.

A line plot of the IGA responder rates (both clear or almost clear and clear) over time, by treatment group will be produced for the RS and by randomized treatment groups. This plot will include assessments from the Initial and Maintenance Treatment Period. An additional plot will be produced by re-randomized maintenance treatment groups only for the Maintenance Treatment Period for the MS. **Additional plots** will be produced **based on** the OLS **and the OLS2 for (IGA clear [0] and for IGA (clear [0] or almost clear [1]) only)** by treatment sequence

Change #33

Section 8.3.3 Body Surface Area (BSA). The following texts in bold have been added.

The percent of subjects with absolute BSA=0%, ≤1%, ≤3% and ≤5% will be presented over time using NRI.

BSA results will be listed but will not be summarized for the OLE2 treatment period.

Change #34

Section 8.3.4 Body Surface Area (BSA). The following texts in bold have been added

The absolute and percentage change from baseline will be summarized for each study period (Initial randomized, Maintenance) by treatment group and visit**.**

The product of IGA and BSA will not be summarized for the OLE2 treatment period.

Change #35

Section 8.3.5 Dermatology Life Quality Index (DLQI). The following texts in bold have been added

The DLQI related efficacy variables will be summarized for the double-blind treatment visits separately for the RS and MS, and **separately** for OLS **and OLS2 [DLQI(0/1) only]** by treatment sequence respectively and visit

Change #36

Section 8.3.8 Symptoms of PSO (Itch, pain, and scaling). The following texts in bold have been added

Cumulative distribution plots will also be provided for absolute change from Baseline PSD at Week 16 and Week 48 for each item

Listings of response to individual question of the patient diary will be provided separately for the Initial., Maintenance, OLE, and the OLE2 treatment periods.

Summaries of PSD responder to Itch, Pain, and scaling symptoms will be produced for the OLE2 by treatment sequence as described in Section 3.6.

Change #37

Section 9: PHARMACOKINETICS AND PHARMACODYNAMICS The following treatment sequences and texts (in bold) have been added:

For the Week 48 Interim the following treatment groups were summarized for the Initial and Maintenance Treatment Period.

Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 16

Bimekizumab 320mg Q4W.

PK and ADAb will also be summarized through to Week 144 by the following treatment sequence and by visit for Initial, Maintenance, and Open-Label Extension treatment period combined. No PK or ADAb samples will be collected in the OLE2 treatment period.

- **Subjects receiving bimekizumab in the double-blind treatment period until treatment discontinuation:**
  - **Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 16**
  - **Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 48**
  - **Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 72 or 84**

- **Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 96 or later**
- **Bimekizumab Total (only for immunogenicity analyses).**

Subjects with any other treatment sequence groups (eg, Bimekizumab 320mg Q4W/Q8W/Q4W or Q4W/Q8W/Q4W/Q8W) will be allocated the "Bimekizumab Total" treatment sequence group for immunogenicity analysis only. All data will be included in the listings.

- **Subjects receiving secukinumab in the double-blind treatment period:**
  - **Bimekizumab 320mg Q8W from Week 48**
  - **Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 72 or 84**
  - **Bimekizumab 320mg Q4W/Q8W with switch from Q4W to Q8W occurring at Week 96 or later**
  - **Bimekizumab Total (only for immunogenicity analyses)**

Note that subjects who received Bimekizumab 320mg Q4W only, ie, those who discontinued before switching to Q8W, will be allocated to the corresponding Q4W/Q8W treatment sequence group depending on when the subject discontinued. For example, if a subject discontinued at week 68, they will be allocated to group Bimekizumab 320mg Q4W/Q8W, switch occurring at Week 72 for PK summary table and figure purposes.

Change #38

Section 9.3 Immunogenicity. The following texts in bold have been added.

The analysis of immunogenicity **for the Week 48 Interim** will be based on the SS **All other analyses will be based on the BKZ Set.**

Change #39

Section 9.3.2: Anti-bimekizumab antibodies

The following texts (in bold) have been added:

Anti-bimekizumab antibodies will be measured using a three tiered assay approach: screening assay, confirmatory assay and titration assay. Samples confirmed as positive within the confirmatory assay, will be further evaluated in a neutralizing assay to evaluate the potential of the ADAb to neutralize the activity of Bimekizumab (IL17A or IL17F, or both) in-vitro. Samples were taken at baseline, week 1, week 2, week 4, week 8, week 12, week 16, week 20, week 24, week 36, week 48, Week 72, Week 96, Week 120, Week144 (or PEOT) and at SFU which is 20 weeks after the last dose. **Due to the planned entry of some subjects to the OLE2 period, not all subjects will have an SFU period immediately following Week 144 with PK and immunogenicity samples.**

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

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

For each subject an overall ADAb status in the treatment period (Baseline to Week 144) will be derived:

- **Overall Positive is defined as having at least one value that is confirmed positive during the treatment period.**
- **Overall Negative is defined as having no values that are confirmed positive at any time up to Week 144 and at least 2/3 of the protocol scheduled post-baseline assessments up to Week 144 are evaluable (i.e. neither missing as per schedule nor inconclusive)**
- **Overall Missing is defined as having no values that are confirmed positive at any visit in the treatment period, but the subject has 1/3 or more protocol scheduled post-baseline assessments missing (or inconclusive) up to Week 144.**

This differs from the Week 48 interim analysis where all subjects were defined as either overall positive or overall negative only (a missing category was not considered). As the time on treatment is protracted in this open label extension study (up to 144 Weeks), missing data or subject discontinuation may be more prevalent and is therefore considered for the final analysis

The double-blind and OLE treatment periods do not include Baseline/pre-treatment samples or SFU.

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

1. **Pre anti-bimekizumab antibody negative – treatment emergent anti-bimekizumab antibody negative: Includes subjects who are negative at Baseline and antibody negative at all sampling points post treatment (excluding SFU)**
2. **Pre anti-bimekizumab antibody negative – treatment emergent anti-bimekizumab antibody positive: Includes subjects who are negative at Baseline and antibody positive at any sampling point post treatment (excluding SFU). This group also includes subjects who have a missing pre-treatment sample (either missing or insufficient volume) at Baseline with one or more anti-bimekizumab antibody positive post-treatment samples.**
3. **Pre anti-bimekizumab antibody positive – treatment emergent reduced anti-bimekizumab antibody: Includes subjects who are positive at Baseline, and antibody negative at all sampling points post treatment (excluding SFU).**
4. **Pre anti-bimekizumab antibody positive – treatment emergent unaffected anti-bimekizumab antibody positive: Includes subjects who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with titer values**

of the same magnitude as Baseline (ie, less than a 2.07 fold difference from the Baseline value).

5. **Pre anti-bimekizumab antibody positive – treatment emergent anti-bimekizumab antibody boosted positive: Includes subjects who are positive at Baseline and are positive at any sampling point post treatment (excluding SFU) with increased titer values compared to baseline (greater than a 2.07 fold difference increase from Baseline value which will be defined within the validation of the assay).**
6. **Inconclusive: Includes subjects who have a positive pre-treatment sample and some post-treatment samples are missing, while other post-treatment samples are anti-bimekizumab antibody negative.**
7. **Total treatment-emergent ADAb positivity (Category 7 [Categories 2 and 5 combined]): Includes study participants who are pre ADAb negative – treatment-emergent ADAb positive (Category 2) and pre ADAb positive – treatment boosted ADAb positive (Category 5).**
8. **Total prevalence of pre- ADAb positivity (Category 8 [Categories 3, 4 and 5 combined]): Study participants that are tested ADAb positive at Baseline.**
9. **Missing: Includes subjects who are antibody negative at baseline, are not positive at any post-baseline visit, and have at least one missing post-treatment scheduled assessment. Note this is also applicable to subjects who have missing baseline.**

For the Week 144 analysis, when all OLE and SFU data will be available, data from the OLE and SFU visits will be considered. That is, each instance of "excluding SFU" in the categories above, should be changed to "including SFU."

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

Analysis

- Immunogenicity will be assessed through summary tables, figures, and listing of individual results by subject. **The analysis of immunogenicity will be summarized by treatment sequence as described in Section 9 and visit.** All analyses will be run on the safety population, unless specified otherwise. Summary of anti-bimekizumab antibody status overall and by each visit separated by treatment **sequence**
- Summary of the time-point of the first occurrence of anti-bimekizumab antibody positivity during the treatment period by treatment **sequence**. A plot of the titer by time to first anti-bimekizumab antibody positivity will be prepared.
- All individual subject-level anti-bimekizumab antibody results will be listed.
- The number and percentage of subject in each of the **8** anti-bimekizumab antibody categories during the treatment period by treatment **sequence**, with an additional category combining subjects in categories 2 and 5, summarized as total treatment emergent. In addition, the count

and percentage of subjects who are pre anti-bimekizumab positive will be calculated (this is the sum of categories 3, 4, and 5).

- The prevalence of immunogenicity, separated by treatment **sequence**, and defined subcategory, will be reported by visit, defined as (cumulative) proportion of subjects having confirmed positive anti-bimekizumab antibody samples at any visit up to and including that visit. Missing samples will not be included in the denominator.
- The time to achieving treatment-emergent anti-bimekizumab antibody positivity, separated by treatment **sequence** and defined sub-category, will be analyzed based on Kaplan-Meier methods. Subjects will be considered to have an event at the time point at which treatment emergent anti-bimekizumab antibody positive is first achieved. Subjects classified as treatment-emergent anti-bimekizumab antibody negative will be censored at the time of the last available anti-bimekizumab antibody result.
- A summary of PASI 100 responders, separated by treatment sequence and defined sub-category, at weeks 16 and 48 as a function of ADAb titer will be presented graphically. This will be repeated for PASI 75 and 90 responders.
- Individual plots of Bimekizumab Concentrations/ anti-bimekizumab antibody titer and PASI score all plotted on the Y-axes by visit (x-axis) for the full treatment period (excluding SFU and OLE period for interim analyses and including SFU and OLE period for final analyses), where a patient has not progressed into the OLE. Plots should be labeled and grouped into the 7 sub-categories.
- Spaghetti plots of ADAb titer (y-axis) by visit (x-axis), separated by treatment sequence (as specified above) for all anti-bimekizumab antibody positive subjects, including Baseline positive subjects.
- Box plots Plot of ADAb titer (logscale) by time to first ADAb positivity by treatment **sequence**.

For purposes of efficacy subgroup analyses based on anti-bimekizumab antibody status, two categories will be used:

- Anti-bimekizumab antibody positive – This is defined as subjects who have anti-bimekizumab antibody levels above the specified cut point on at least 2 time points while on treatment (ie, excluding Baseline, excluding SFU).
- Anti-bimekizumab antibody negative – Subjects who are not defined as anti-bimekizumab positive (as described above) will be defined as anti-bimekizumab antibody negative.

The groups for defining anti-bimekizumab antibody status for safety subgroup analyses are as follows:

- AEs starting before first anti-bimekizumab antibody positive result
- AEs starting on or after first anti-bimekizumab antibody positive result
- AEs for subjects who were always anti-bimekizumab antibody negative

In addition to the anti-bimekizumab antibody classifications, subjects may also receive an overall neutralizing (NAb) classification for each NAb assay separately **(IL-17AA and IL-17FF),**

inclusive of Baseline and post-Baseline results, on the NAb assay results. **The classifications are as follows:**

- **NAb negative: No NAb positive samples at Baseline or post-Baseline and did not discontinue prior to Week 144. Subjects can have up to 1 missing sample.**
- **NAb positive: One or more positive samples (IL-17AA positive, IL-17FF positive, or both) at Baseline or post-Baseline (regardless of missing samples). Subjects who are NAb positive will be further classified as follows:**
  - **Positive for IL-17AA only: one or more positive samples for IL-17AA at Baseline or post Baseline. No positive samples for IL-17FF**
  - **Positive for IL-17FF only: one or more positive samples for IL-17 FF at Baseline or post Baseline. No positive samples for IL-17AA**
  - **Positive for both IL-17AA and IL-17FF: one or more positive samples for both IL-17AA and IL-17FF at Baseline or post Baseline**
- **NAb Missing: >1 relevant NAb samples are missing, eg, if subject had samples selected for NAb testing based on their anti-bimekizumab antibody levels, but there was insufficient sample left for NAb testing, or the subject discontinued prior Week 144 visit.**

A summary table covering the initial, maintenance and OLE periods combined by treatment sequence will be produced, in addition, to summarize the NAb status overall.

A listing will be produced to summarize the NAb status by visit. The listing should be sorted by treatment sequence, subject identifier, and visit and would provide the following information for each subject:

- **Visit**
  - **Study week since first BKZ dose**
  - **Sample date and time**
  - **Time since previous dose (weeks)**
- **NAb status and the corresponding bimekizumab plasma concentration (ug/mL) and the anti-bimekizumab antibody level titer at this visit**
- **IL-17AA NAb status and corresponding IL-17AA signal/negative control result IL-17FF NAb status and corresponding IL-17FF signal/negative control result**

The tables will provide the following overall summary statistics by treatment group:

- **Total number and percentage of anti-bimekizumab antibody positive, anti-bimekizumab antibody negative and missing subjects at each visit**
- **Number and percentage of subjects who are NAb positive, NAb negative and missing at each visit**
- **The number and percentage of subjects who are IL-17AA NAb positive, IL-17FF NAb positive, or both**

Change #40

Section 10.1 Extent of exposure: The following texts in bold have been added:

For **the Week 144 analysis and for** the final analysis, the table will also be created for the BKZ set and will include the above categories plus the below categories. A bimekizumab total column will be displayed.

- >=72 weeks
- >=96 weeks
- >=120 weeks
- >=144 weeks

In addition, the OLE2 exposure will be displayed as follow:

- **>0 weeks**
- **>=16 weeks**
- **>=24 weeks**
- **>=48 weeks**

Throughout this section, date of last clinical contact for each subject is defined as the maximum of (last visit date including SFU **or SFU2** visit, last imputed AE start date, date of study

Change #41

Section 10.1.4.1: For subjects who do not switch study treatments

The number of days in (bold) added to the time at risk has been changed from 140 to 141

Time at risk (days)

Study medication duration (days)

- **For subjects who receive Q4W in the Open-Label Extension Period (subjects who discontinue prior to switching to Q8W):**
  - Date of last bimekizumab dose in the Open-Label Extension Period – date of first dose in the Open-Label Extension Period + 28 days (for subjects on Q4W dosing)
- **For subjects who receive Q8W in the Open-Label Extension Period use the minimum of:**
  - Date of last bimekizumab dose in the Open-Label Extension Period – date of first dose in the Open-Label Extension Period + 56 days
  - **First dose date in Open-Label Extension 2 Period – date of first dose in the Open-Label Extension Period + 1**

Note: If date of last bimekizumab dose in the Open-Label Extension Period + 28 days (or 56 days for subjects on Q8W dosing) extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:

– Final visit date (including PEOT, but not including SFU) – date of first dose in the Open-Label Extension Period+ 1.

Note: For subjects who die, if date of last bimekizumab dose in the Open-Label Extension Period + 28 days (or 56 days for subjects on Q8W dosing) extends to a date beyond the date of death, then this calculation reverts to:

– Date of death – date of first dose in the Open-Label Extension Period+ 1.

Time at risk (days)

- For all subjects, use the minimum of the following:
  - Date of last dose in the Open-Label Extension Period – date of first dose in the Open-Label Extension Period + 140 days,
  - Date of first dose in OLE2 - date of first dose in the Open-Label Extension Period + 1 day
  - Date of last clinical contact in OLE **and** SFU – date of first dose in the Open-Label Extension Period + 1.
  - Date of death – date of OLE first dose +1

Change #42

Section 10.1.4.2: For subjects who switch from BKZ 320mg Q4W to Q8W during Open-Label Extension Period

Following Protocol Amendment 5.0, subjects **receiving Q4W** should switch to Q8W during the Open-Label extension period. (see Section 2.3.2.4 for further details).

Study medication duration (days)

- Attributed to BKZ 320mg Q4W:
  - Date of last BKZ 320mg Q4W dose in the OLE Period – date of first BKZ 320mg Q4W dose in the OLE Period + 28 days

  Note: If date of last BKZ 320mg Q4W dose in the OLE Period + 28 days extends to a date beyond the date of first BKZ 320mg Q8W dose in the OLE Period, then this calculation reverts to:
  - Date of first BKZ 320mg Q8W dose in the OLE Period – date of first BKZ 320mg Q4W dose in the OLE Period **+ 1.**
- Attributed to BKZ 320mg Q8W **use the minimum of:**
  - Date of last BKZ 320mg Q8W dose in the OLE Period – date of first BKZ 320mg Q8W dose in the OLE Period + 56 days.

- **First dose date in Open-Label Extension 2 Period – date of first BKZ 320mg Q8W dose in the Open-Label Extension Period+ 1.**

Note: If date of last bimekizumab dose in the Open-Label Extension Period + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:

- Final visit date (including PEOT, but not including SFU) – date of first BKZ 320mg Q8W dose in the OLE Period + 1.

Note: For subjects who die, if date of last bimekizumab dose in the Open-Label Extension Period + 56 days extends to a date beyond the date of death, then this calculation reverts to:

- Date of death – date of first BKZ 320mg Q8W dose in the OLE Period + 1.

- Attributed to Total BKZ
  - Sum of study medication duration in OLE period attributed to BKZ 320mg Q4W and study medication duration in OLE period attributed to BKZ 320mg Q8W – 1.

Time at risk (days)

- Attributed to BKZ 320mg Q4W:
  - Date of first BKZ 320mg Q8W dose in the OLE Period – date of last BKZ 320mg Q4W dose in the OLE Period + 1 day
- Attributed to BKZ 320mg Q8W:
  - For all subjects, use the minimum of the following:
    - Date of last BKZ 320mg Q8W dose in the OLE Period – date of first BKZ 320mg Q8W dose in the OLE Period + 140 days.
    - Date of first BKZ 320mg Q8W dose in OLE2 - date of first BKZ 320mg Q8W dose in the Open-Label Extension Period + 1 day
    - Date of last clinical contact – date of first BKZ 320mg Q8W dose in the OLE Period + 1.
    - **Date of death – date of first BKZ 320mg Q8W dose in the OLE Period + 1.**
- Attributed to Total BKZ:
  - Use the time at risk algorithm specified for subjects who do not switch study treatments in Section 10.1.4.1

Change # 43

Section 10.1.5.1 For subjects who do not switch dose

Time at risk (days)

- For all subjects, use the minimum of the following:
  - Date of last dose – date of first + 140 days.

- Date of last clinical contact – date of first dose + 1.
- **Date of death – date of first dose + 1.**

For subjects randomized to secukinumab at Baseline who initiate bimekizumab at Week 48 and continue on the same dose schedule in the OLE without switching, use the study medication duration and time at risk algorithms specified for subjects who do not switch study treatments in Section 10.1.4.1

Change #44

Section 10.1.5.2: For subjects who do not switch dose

The following texts (in bold) have been added:

Study medication duration (days)

Total study medication duration attributed to each dose will be obtained by summing the study medication duration(s) at each specific dose in each individual study period. Total study medication duration attributed to BKZ Total will be obtained by summing the study medication durations in each individual study period **and deducting n-1, where n is the number of periods covered that are being summed.**

- Attributed to BKZ 320mg Q8W
  - Date of last consecutive BKZ 320mg Q8W dose in current study period– date of first consecutive BKZ 320mg Q8W dose in current study period + 56 days

  Note: If date of last consecutive BKZ 320mg Q8W dose in current study period+ 56 days extends to a date beyond the date of first BKZ 320mg Q4W dose in the next study period, then this calculation reverts to:

  - Date of first BKZ 320mg Q4W dose in the next study period – date of first BKZ 320mg Q4W dose in the current study period.

  Note: If BKZ 320mg Q8W is the last dosing schedule received in the last study period the subject receives bimekizumab in and date of last consecutive BKZ 320mg Q8W dose in current study period+ 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU), then this calculation reverts to:

  - Final visit date (including PEOT, but not including SFU) – date of first BKZ 320mg Q8W dose in the current study period + 1.

  Note: For subjects who progress into the OLE2, if date of last bimekizumab dose in the Open-Label Extension Period + 56 days extends to a date beyond the date of first dose in the Open-Label Extension 2 Period then this calculation reverts to:

  - **First dose date in Open-Label Extension 2 Period – date of first BKZ 320mg Q8W dose in the current study period + 1.**

  Note: For subjects who die, where BKZ 320mg Q8W is the last dosing schedule received in the last study period the subject receives bimekizumab in and date of last consecutive BKZ

320mg Q8W dose in current study period+ 56 days extends to a date beyond the date of death, then this calculation reverts to:

– Date of death – date of first BKZ 320mg Q8W dose in the current study period + 1.

Time at risk (days)

Total time at risk attributed to each dose will be obtained by summing the time(s) at risk at each specific dose in each individual study period **and deducting n-1, where n is the number of non-consecutive periods covered that are being summed**. Total time at risk attributed to BKZ Total will be obtained by using the time at risk algorithms specified for subjects who do not switch study treatments in Section 10.1.5.1.

- Time at risk at each specific dose in each individual study period is calculated separately as follows:
  - Attributed to BKZ 320mg Q4W:
    - Date of first BKZ 320mg Q8W dose in the next study period – date of first BKZ 320mg Q4W dose in the current study period.

    Note: If BKZ 320mg Q4W is the last dosing schedule received in the last study period, then this calculation reverts to:
  - For all subjects, use the minimum of the following:
    - Date of last BKZ 320mg Q4W dose in the current study period – date of first BKZ 320mg Q4W dose in the current study period + 140 days.
    - Date of first BKZ 320mg Q8W dose in OLE2 - date of first BKZ 320mg Q4W dose in the Open-Label Extension Period + 1 day. The OLE and The OLE2 treatment periods should not overlap by more than 1 day
    - Date of last clinical contact – date of first BKZ 320mg Q4W dose in the OLE Period + 1.
    - **Date of death – date of first BKZ 320mg Q4W dose in the current study period + 1**
  - Attributed to BKZ 320mg Q8W:
    - Date of first BKZ 320mg Q4W dose in the next study period – date of first BKZ 320mg Q8W dose in the current study period.

    Note: If BKZ 320mg Q8W is the last dosing schedule received in the last study period, then this calculation reverts to:
  - For all other subjects, use the minimum of the following:
    - Date of last BKZ 320mg Q8W dose in the current study period – date of first BKZ 320mg Q8W dose in the current study period + 140 days.
    - Date of first dose in OLE2 - date of first BKZ 320mg Q8W dose in the Open-Label Extension Period + 1 day.

- Date of last clinical contact – date of first BKZ 320mg Q8W dose in the OLE Period + 1.

Chane #45

Section 10.1.6 Exposure during the OLE2 Period based on BKZ set

Eligible subjects from sites in the US or Canada who have completed the Week 144 Visit, or are in the SFU, or have completed the SFU of the OLE Period, can roll over to an additional OLE2 period.

Definitions for study medication duration (days) and time at risk (days) during the OLE2 Period will be provided for the following subjects:

- **Group A: Subjects who roll over directly from OLE to OLE2**
- **Group B: Subjects who reinitiate bimekizumab and who were in the SFU or had completed the SFU of the OLE Period**

Section 10.1.6.1 Group A: Subjects who roll over directly from OLE to OLE2

Study medication duration (days)

- Date of last bimekizumab dose in the OLE2 Period – date of first dose in the OLE2 Period + 56 days

  Note: If date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

  – Final visit date (including PEOT, but not including SFU2) – date of first dose in the OLE2 Period+ 1.

  Note: For subjects who die, if date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the date of death, then this calculation reverts to:

  – Date of death – date of first dose in the OLE2 Period+ 1.

Time at risk (days)

- Use the minimum of the following:
  – Date of last dose in the OLE2 Period – date of first dose in the OLE2 Period + 140 days.
  – Date of last clinical contact – date of first dose in the Open-Label Extension Period + 1.
  – Date of death – date of first dose in the OLE2 Period+1.

Section 10.1.6.2 Group B: Subjects who reinitiate bimekizumab

Section 10.1.6.2.1 Subjects reinitiated to receive BKZ Q8W at OLE2 start

- Study medication duration (days)
  – Date of last bimekizumab dose in the OLE2 period– date of first bimekizumab dose in the OLE2 + 56 days

Note: If date of last bimekizumab dose in the OLE2 + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

- Final visit date (including PEOT, but not including SFU2) – date of first dose in the OLE2 Period + 1.

Note: For subjects who die, if date of last bimekizumab 320mg Q8W dose + 56 days extends to a date beyond the date of death, then this calculation reverts to:

- Date of death – date of first dose in the OLE2 Period + 1.

- Time at risk (days)
  - Use the minimum of the following:
    - Date of last dose – date of first dose in OLE2 + 140 days.
    - Date of last clinical contact – date of first dose in OLE2 + 1.Date of death – date of first dose + 1.

Section 10.1.6.2.2 Subjects reinitiated to receive BKZ Q4W/Q8W at OLE2 start

- **Attributed to BKZ Q4W/Q8W**
  - **Date of last BKZ 320mg Q8W dose in the OLE2 Period – date of first BKZ 320mg Q4W dose in the OLE2 Period + 56 days.**

Note: If date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

- **Final visit date (including PEOT, but not including SFU2) – date of first BKZ 320mg Q4W dose in the OLE2 Period + 1.**

Note: For subjects who die, if date of last bimekizumab dose in the OLE2 Period + 56 days extends to a date beyond the date of death, then this calculation reverts to:

- **Date of death – date of first dose in the OLE2 Period + 1**

- **If the subject discontinued prior to the switch to Q8W then:**
  - **Date of last BKZ 320mg Q4W dose in the OLE2 Period – date of first BKZ 320mg Q4W dose in the OLE2 Period + 28 days.**

If date of last bimekizumab dose in the OLE2 Period + 28 days extends to a date beyond the final visit date (including PEOT, but not including SFU2), then this calculation reverts to:

- **Final visit date (including PEOT, but not including SFU2) – date of first BKZ 320mg Q4W dose in the OLE2 Period + 1.**

Note: For subjects who die prior to switch to Q8W, if date of last bimekizumab dose in the OLE2 Period + 28 days extends to a date beyond the date of death, then this calculation reverts to:

Date of death – date of first dose in the OLE2 Period + 1.

Time at risk (days)

- **Attributed to BKZ Q4W/Q8W :**
  - **Use the time at risk algorithm specified for subjects who do not switch study treatments in Section 10.1.6.1.**

Change #46

Section 10.2: Adverse events

The following text (in bold) have been added.

Adverse events will be coded according to the MedDRA. AEs will be allocated to the respective randomized treatment arm. For subjects who switch treatment at Week 16, Week 48 or **(on or after Week 64),** any adverse events that occur after initiation of the new treatment are attributable to the new treatment. If an adverse event occurs on the date of a treatment switch, the event is attributed to the original treatment. The only exception to this is if the AE fulfills any of the criteria specified below:

Change #47

Section 10.2.1 Data considerations. The PBO subscript in the following formula has been changed to SEC

$$SE_{RD} = \sqrt{\left(IP_{BKZ} \times \left(\frac{1 - IP_{BKZ}}{n_{BKZ}}\right)\right) + \left(\boldsymbol{IP_{SEC}} \times \left(\frac{1 - IP_{SEC}}{n_{SEC}}\right)\right)}$$

A separate by-subject listings of all TEAEs for the OLE and the OLE2 treatment periods will be provided.

Change #48

Section 10.2.1.1 COVID-19 related data considerations. The following texts have been added

The COVID-19 pandemic start date is defined as 11 March 2020 as it is the date the World Health Organization declared COVID-19 as a pandemic, see also Section 4.2.1.7.2. Note that the Week 48 and Week 96 interim analyses will be conducted during the pandemic therefore a post COVID-19 pandemic period is not defined for these analyses. If WHO declares the COVID-19 pandemic has ended prior **to Week 144**, then that date may be used to support presentation of a post COVID-19 pandemic period.

Incidence of COVID-19 TEAEs will be summarized for the OLE treatment periods based on the OLS by treatment group.

The following PTs will be used to **identify** COVID-19 adverse events:

- **Corona virus** infection

- **Coronavirus test** positive

By-subject listings of COVID-19 TEAEs will be produced separately for OLE and OLE2 treatment periods

To assess the impact of COVID-19 mass vaccination on TEAEs, a sensitivity analysis will present all TEAEs excluding TEAEs assessed as exclusively related to COVID-19 vaccine by the investigator. TEAEs recorded as related to both study medication and COVID-19 vaccination should not be excluded. A complementary table of TEAEs related to COVID-19 vaccine will be presented.

Another sensitivity analysis will present all TEAEs excluding TEAEs with start date on or up to 5 days after date of COVID-19 vaccine. Note that subjects may receive more than one administration of COVID-19 vaccine. A complementary table and listing of TEAEs with start date on or up to 5 days after date of COVID-19 vaccine will also be presented.

Complementary listings of TEAEs related to COVID-19 vaccine will be presented for the OLE and the OLE2 treatment periods separately.

Change #49

Section 10.2.2 AE summaries. The following texts in bold have been added

AE summaries will be provided by actual treatment at the time of the adverse event. **Separate AE summaries for OLE2 treatment period will be provided by treatment sequence as specified in Section 3.6 and will be based on OLS2.**

For subjects who discontinue on or prior to the final scheduled visit of the Initial Treatment Period, any AEs that emerged more than after 112 days relative to the first dose but still within the 140 days SFU window will be classified as TEAE. However, these AEs will be excluded from AE summaries based on the Initial Period but included in the AE summaries for Initial and Maintenance Treatment Period. See the description of time at risk in Section 10.1.1 for further details.

The following selected outputs will be produced for the SS for the Initial Treatment Period, for the MS for the Maintenance Treatment Period, for the SS for the Initial and Maintenance Treatment Period, **for the OLS for the Open-Label Extension Period**:

- Incidence of TEAEs – Overview
- Incidence of TEAEs per 100 subject years by SOC, HLT, and PT
- Incidence of Serious TEAEs per 100 subject years by SOC, HLT, and PT
- Incidence of TEAEs Leading to Discontinuation per 100 subject-years by SOC, HLT and PT
- **Incidence of TEAEs by decreasing frequency of PT**

The following selected AEs summaries will be provided **separately** for the Open-Label Extension Period, **Separate AEs summaries will be provided for the OLE2 treatment period by treatment sequence as described in Section 3.6 and will be based on the OLS2:**

- Incidence of COVID-19 TEAEs
- Incidence of TEAEs Overview
- Incidence of TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs per 100 Subject-Years
- **Incidence of Serious TEAEs by Relationship**
- Incidence of TEAEs Leading to Discontinuation per 100 subject-years
- Incidence of TEAEs Leading to Death
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by SOC and PT
- Incidence of Non-Serious TEAEs Above Reporting Threshold of 5% by Relationship SOC and PT

In addition, the following AEs summaries will be provided for the Open-Label Extension Period only by treatment at the time of AE onset and will be based on the OLS (excluding OLE2 treatment period).

- **Incidence of TEAEs Excluding TEAEs Exclusively Related to COVID-19 Vaccine by SOC, HLT, and PT**
- **Incidence of TEAEs Exclusively Related to COVID-19 Vaccine by SOC, HLT, and PT**
- **Listing of TEAEs Related to COVID-19 Vaccine**
- **Incidence of COVID-19 Vaccine Interval Censored TEAEs by SOC, HLT, and PT**
- **Incidence of COVID-19 Vaccine Interval TEAEs by SOC, HLT, and PT**
- **Listing of COVID-19 Vaccine Interval TEAEs**

The following summaries will be provided for the BKZ Set by treatment at the time of AE onset. These tables will include AEs from both the double-blind and Open-Label treatment period **(excluding OLE2** treatment period). AEs that occurred while subjects received secukinumab will not be included.

- Incidence of TEAEs Overview
- Incidence of TEAEs per 100 Subject-Years
- Incidence of Serious TEAEs per 100 Subject-Years
- **Incidence of TEAEs by decreasing frequency of PT**
- **Incidence of TEAEs per 100 subject years by SOC, HLT, and PT and by Time of Onset Relative to COVID-19 pandemic (prior to COVID-19 pandemic, during COVID-19 pandemic).**

Change #50

Section 10.2.3 Other Safety topics of interest. The following texts in bold have been added

The following summaries for AEs of other safety topics of interest will be provided by actual Treatment at the time of the adverse event. The following outputs will be produced **separately** for the SS for the initial treatment period, for the SS for the Initial and Maintenance Treatment Period, and for the OLS for the Open-Label Extension Period by treatment group (see Section 3.6).

Along with the tables described, there will be tables which displays the risk difference and 95% confidence intervals for each of the topics of interest during the Initial Treatment Period (SS) as well as for Initial and Maintenance Treatment Period combined (SS). Corresponding figures (with dot plots) will be prepared. **No safety topics of interest AE summaries will be produced for the Open-Label Extension 2 treatment period (OLS2).**

Listings of all treatment emergent adverse events of other safety topics of interest will be provided separately for the OLE and the OLE2 treatment periods.

Change #51

Section 10.2.3.1 Infections (serious, opportunistic, fungal and Tuberculosis [TB]). The following texts in bold were added.

- **Incidence of Opportunistic Infection TEAEs per 100 subject years by SOC, HLT and PT**

  Opportunistic infections (including tuberculosis) will be summarized in a stand-alone table. The table will include all **opportunistic infection** TEAEs identified using UCB-defined search criteria **which were adjudicated as opportunistic infections**

Change #52

Section 10.2.3.2 Malignancies. The following paragraphs in bold have been replaced with the updated Bimekizumab standard convention.

These events will be presented in the following tables:

- **One table will be based on the criteria (SMQ) = "Malignant or unspecified tumours (SMQ)"**
- **One table will be based on the criteria SMQ = "Malignant tumours (SMQ)".**

SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each 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. While the "Malignant tumours (SMQ)" is most relevant, "Malignant or unspecified tumours (SMQ)" must be reviewed for potential malignancies.

The output table will include 2 different overall incidence 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 (using the appropriate SMQ depending on the table), regardless of the High Level Term (HLT) it codes to**
- **The second overall incidence row will summarize "Any malignancy excluding non-melanomic skin cancers HLT" and this row will summarize the incidence of AEs flagged for inclusion in the table (using the appropriate SMQ depending on the table), excluding those which code to an HLT of "skin neoplasms malignant and unspecified (excl melanoma)".**

Change #53

Section 10.2.3.3 Cardiac events. The following paragraphs in bold have been replaced with the updated Bimekizumab standard convention.

Potential cardiovascular events are adjudicated by the independent Cardiovascular Event Adjudication Committee (CV-CAC) according to the CV-CAC Charter (version 6.0). Adjudicated events are classified by the CV-CAC to one of the event types as defined in the table below. The classification of an event as a Major Adverse Cardiac Event (MACE) is also determined by the CV-CAC. Events which are classified by the CV-CAC as any of the events types identified in the third column of the table will be considered an extended MACE. Note that extended MACE is determined programmatically and includes a broader scope definition of MACE.

MACE as determined by the CV-CAC will be presented in a table and listing. Extended MACE will be presented separately in a table and listing. Additional listings of all MACE as determined by the CV-CAC will be presented separately for the OLE and the OLE2 treatment periods.

Another table and listing will present the adjudicated cardiovascular events by type. For each cardiovascular event type, the individual PTs which fall within each event type will be summarized. This listing will indicate whether each event was determined to be a MACE and/or an extended MACE. Similar listings of the adjudicated cardiovascular events by type will be presented separately for the OLE and the OLE2 treatment periods.

Additionally, a listing of all events identified for potential review by the CV-CAC will be produced. This listing will indicate whether each event was identified by the CV-CAC Chair for full committee review. Similar listings of all events identified for potential review by the CV-CAC will be produced separately for the OLE and the OLE2 treatment periods.

Cardiovascular event classifications

Event Type Code	Event Type	Extended MACE
1	Non-Fatal Myocardial Infarction (MI)	Yes
2	Non-Fatal Stroke: hemorrhagic	Yes
3	Non-Fatal Stroke: ischemic	Yes
4	Non-Fatal Stroke: embolic	Yes
5	Non-Fatal Stroke: undeterminable	Yes
6	Hospitalization or ER for Unstable Angina with urgent revascularization	Yes
7	Hospitalization or ER for Unstable Angina without urgent revascularization	No
8	Hospitalization for Heart Failure	Yes
9	Transient Ischemic Attack (TIA)	No
10	Coronary Revascularization Procedures (e.g. percutaneous coronary intervention, coronary artery bypass grafting)	Yes
11	Urgent Revascularization Procedures (i.e. due to symptoms of brain ischemia or pending infarction)	Yes
12	Arrhythmia (not associated with ischemia)	No
13	Peripheral Arterial Event	No
14	Venous Thromboembolic Event: pulmonary embolism (PE)	No
15	Venous Thromboembolic Event: deep vein thrombosis (DVT)	No
16	Venous Thromboembolic Event: PE and DVT	No
17	Other CV Event	No
18	Death due to Myocardial Infarction (MI)	Yes
19	Death due to Stroke	Yes
20	Sudden Cardiac Death	Yes
21	Other CV Death (e.g. heart failure, pulmonary embolism, cardiovascular procedure-related)	Yes
22	Cardiovascular: Undetermined Cause of Death (i.e. cause of death unknown)	Yes
23	Non-Cardiovascular Death	No

Cardiovascular event classifications

Event Type Code	Event Type	Extended MACE
24	Non-Cardiovascular Event	No
99	Inadequate information to adjudicate	No

Change #54

Section 10.2.3.5 Suicidal Ideation and Behavior (SIB) The following paragraphs in bold have been replaced with the updated Bimekizumab standard convention.

Potential neuropsychiatric events are adjudicated by the independent Neuropsychiatric Adjudication Committee according to the Neuropsychiatric Adjudication Committee (version 8.0). Adjudicated events are classified by the Committee as Suicidal or Non-suicidal. Adjudicated events are also further classified by the Committee to one of the event types as defined in the neuropsychiatric Table below. Suicidal Ideation and Behavior (SIB) is defined as events classified by the Committee as Suicidal.

A table and listing will present SIB events. This listing will also be provided separately for OLE and OLE2 treatment periods.

Another table and listing will present the adjudicated neuropsychiatric events by type. For each neuropsychiatric event type, the individual PTs which fall within each event type will be summarized. This listing will indicate whether each event was determined to be Suicidal or Non-Suicidal. For event type suicidal ideation, the listing will also indicate if intent was present and if the suicidal ideation was clinically significant. A similar listing of the adjudicated neuropsychiatric events by type will be presented.

Additionally, a listing of all events identified for potential review by the Committee will be produced. This listing will indicate whether each event was identified by the Neuropsychiatric Event Adjudication Committee Chair for full committee review. Similar listings will be provided separately for the OLE and the OLE2 treatment periods.

Neuropsychiatric event classifications

Event Type Code	Event Classification	Event Type
1	Suicidal	Suicidal events/completed suicide
2	Suicidal	Suicide attempt
3	Suicidal	Preparatory acts toward imminent suicidal behavior

Neuropsychiatric event classifications

Event Type Code	Event Classification	Event Type
4	Suicidal/Non-suicidal[c]	Suicidal ideation
7	Non-suicidal	Nonsuicidal Self-injurious behavior
8	Non-suicidal	Nonsuicidal Other
99	Not applicable	Inadequate information to adjudicate

Suicidal ideation event types can be classified by the Neuropsychiatric Adjudication Committee as Suicidal or Non-suicidal depending on whether intent to die was present

Change #55

10.2.3.6 Inflammatory bowel disease. The following paragraphs in bold have been replaced with the updated Bimekizumab standard convention.

- **Incidence of Inflammatory Bowel Disease TEAEs per 100 subject years by SOC, HLT and PT**

Selected gastrointestinal events are adjudicated by the independent Inflammatory Bowel Disease (IBD) Adjudication Committee (IBD-CAC) according to the IBD-CAC Charter (version 3.0). Adjudicated events are classified by the IBD-CAC into one of the diagnostic types as defined in the IBD event classifications Table below. The events will further be classified as definite, probable or possible IBD.

An overview of adjudicated IBD events will be stratified by subjects with or without a previous medical history of IBD. Previous medical history of IBD will be determined using the information recorded on the Extra-Articular Assessment at Screening CRF page ("Does subject have a history of IBD?"). This overview table will present events adjudicated by the IBD-CAC as either possible, probable or definite IBD. Definite and probable IBD will also be aggregated and summarized in this table. In addition, this table will summarize each IBD event classification (possible, probable or definite) separately.

Another table and listing will present the adjudicated IBD events by type. For each IBD event type, the individual PTs which fall within each event type will be summarized. Similar listings of the adjudicated IBD events by type will be presented separately for OLE and OLE2 treatment periods.

Additionally, a listing of all events identified for potential review by the IBD-CAC will be produced. This listing will indicate whether each event was identified by the IBD-CAC Chair for full committee review. Similar listings of all events identified for potential review by the IBD-CAC Chair for full committee review will be produced separately for the OLE and the OLE2 treatment periods.

A further supportive listing will present the individual diagnostic criteria met for each adjudicated IBD event. This listing will also be presented separately for the OLE and the OLE2 treatment periods combined

IBD event classifications

Event Type Code	Event Type (Classification and diagnosis)	Classification
1	Possible Inflammatory Bowel Disease – Crohn's Disease	Possible
2	Probable Inflammatory Bowel Disease – Crohn's Disease	Probable
3	Definite Inflammatory Bowel Disease – Crohn's Disease	Definite
4	Possible Inflammatory Bowel Disease – Ulcerative Colitis	Possible
5	Probable Inflammatory Bowel Disease – Ulcerative Colitis	Probable
6	Definite Inflammatory Bowel Disease – Ulcerative Colitis	Definite
7	Possible Inflammatory Bowel Disease – type unclassified	Possible
8	Probable Inflammatory Bowel Disease – type unclassified	Probable
9	Definite Inflammatory Bowel Disease – type unclassified	Definite
10	Symptoms not consistent with Inflammatory Bowel Disease	Not applicable
11	Possible Inflammatory Bowel Disease – Microscopic Colitis	Possible
12	Probable Inflammatory Bowel Disease – Microscopic Colitis	Probable
13	Definite Inflammatory Bowel Disease – Microscopic Colitis	Definite
14	Possible Inflammatory Bowel Disease – no further differentiation possible	Possible
15	Probable Inflammatory Bowel Disease – no further differentiation possible	Probable
16	Definite Inflammatory Bowel Disease – no further differentiation possible	Definite
99	Not enough information to adjudicate	Not applicable

IBD=inflammatory bowel disease.
Note: IBD diagnoses of "microscopic colitis" and "no further differentiation possible" were added in an adjudication charter amendment, accounting for the event type numbering.

Change #56

10.2.3.7 Hypersensitivity (including anaphylaxis). The following paragraphs in bold have been replaced with the updated Bimekizumab standard convention.

- **Incidence of Anaphylactic Reaction TEAEs per 100 subject years by SOC, HLT and PT**

A separate table will be prepared based on the MedDRA anaphylaxis Algorithm (see Appendix 1) for acute anaphylactic events (reported on the same day as when an injection was administered or one day after). An AE glossary table will also be produced to summarize the MedDRA coding for these events. The glossary table will include the following fields: reported term, PT, LLT, HLT, and SOC.

A separate table will be prepared to summarize hypersensitivity events, identified using the SMQ "Hypersensitivity (SMQ)". All TEAEs which code to a PT included in the Scope=Narrow search will be included in this table. In addition, a separate table will be prepared to summarize serious hypersensitivity events, identified using the SMQ "Hypersensitivity (SMQ)". All serious TEAEs which code to a PT included in the Scope=Narrow search will be included in this table. An AE glossary table will also be produced to summarize the MedDRA coding for these events. The glossary table will include the following fields: reported term, PT, LLT, HLT, and SOC.

Furthermore, a separate table will be prepared to summarize injection site reactions, identified using the HLTs: "Administration site reactions NEC" and "Injection site reactions".

Change #57

Section 10.2.3.8 Hepatic events. The following paragraphs in bold have been replaced with **the updated Bimekizumab standard convention.**

- **Incidence of hepatic events TEAEs per 100 subject years by SOC, HLT and PT**

A table for hepatic events will be created based on the SMQ of "Drug related hepatic disorders - comprehensive search (SMQ)". However, these 2 sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps) (SMQ)" and "Liver neoplasms, malignant and unspecified (SMQ)". For each of the above SMQs, include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow.

Note that all AEs meeting the above criteria are to be included. It should not be limited to events that the investigator determined to be related to study drug.

Cases of Hy's Law will be reported separately in a liver function test table. Section 10.3

A by-subject listing of all AEs of safety topics of interest by type of safety topics of interest will be provided.

Change #58

Section 10.3 Clinical laboratory evaluations. The following texts in bold have been added

- A shift table of the number and percentage of subjects experiencing CTCAE grade 0, 1, 2, 3, or 4 values (as applicable) at Baseline to minimum/maximum post-Baseline CTCAE grade, by laboratory variable and treatment group. Two separate tables will show results for the initial treatment period (for the SS) and the Initial and Maintenance Treatment Period (for the

MS). An additional table for the OLE period will be provided for the OLS by treatment the subjects were receiving at the time of the assessment of the value with the given CTCAE grade. **A lipid profile table of treatment emergent markedly abnormal laboratory data will be provided for Initial and Maintenance Treatment Period (SS) and Open-label Extension treatment period (OLS) separately**.

In addition, a shift table of number and percentage of subjects experiencing post-Baseline HDL Low risk (≧ 1.55 mmol/L), Intermediate risk (≥ 1.04 - < 1.55 mmol/L) and High risk (< 1.04 mmol/L) compared to baseline will be provided for then Initial and Maintenance Treatment Period (SS) and the Open-Label Extension Treatment Period (OLS).

A figure of neutrophil values over time for subjects with at least one markedly abnormal neutrophil value (CTCAE Grade 3 or 4) will also be presented.

A by-subject listing of all laboratory data (including urinalysis) will be provided. **Separate by-subject listings for the OLE and the OLE2 treatment periods will be provided. These** listings will be presented by treatment group and will include: center, subject identifier, age, sex, race, weight, visit, laboratory variable, result (with abnormal values flagged as "L" or "H" accordingly) and unit.

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In addition, a table will be produced to summarize potential Hy's Law cases. The following two definitions will be used in that table:

- **[AST ≥3xULN or ALT ≥3xULN] and**
- **Total Bilirubin ≥2xULN in the absence of ALP ≥2xULN**

In order to meet the above criteria, a subject must experience the elevation in bilirubin and ALT or AST (and the absence of ALP elevation, if applicable) at the same visit. For example, a subject who experiences a ≥2 x ULN elevation of bilirubin at one visit and a ≥3xULN elevation in ALT (or AST) at a subsequent visit has not fulfilled the Hy's law criteria.

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

A table for potential drug induced liver injuries (pDILI) will be presented by treatment group for subjects with at least one post-Baseline liver laboratory assessment. Number and percentage of subjects meeting laboratory criteria for pDILI for at least 1 visit and reporting at least 1 symptom potentially associated with hepatitis or hypersensitivity according to the Investigator on the pDILI CRF will be presented. All criteria must be met at the same visit for subjects who potentially meet Hy's law criteria at least 1 time during exposure to be counted as potential Hy's Law.

Change #59

Section 10.4.1 Vital signs. The following texts in bold have been added

The following vital signs variables should be summarized: systolic blood pressure (mmHg), diastolic blood pressure (mmHg), body temperature (°C) and heart rate (beats/min). The following summary will be provided for the Initial Treatment Period (SS) for Initial and Maintenance Treatment Period, and for the Open-Label Extension Period (OLS). **Vital signs will not be summarized for the OLE2.**

- A summary of the absolute and change from Baseline value for each vital sign variable by treatment group and visit.
- **A shift from Baseline to Post-Baseline systolic and diastolic blood pressure values based on the following categorization will be provided for the Initial and Maintenance Treatment Period (SS), and the Open-label Extension Period (OLS):**
  - **Hypotension: systolic blood pressure <90 mmHg *or* diastolic blood pressure <60**
  - **Normal: systolic blood pressure ≥90 and <120 mmHg *and* diastolic blood pressure ≥60 and <80 mmHg**
  - **Elevated: systolic blood pressure between 120-129 mmHg *and* diastolic blood pressure <80**
  - **Stage 1: systolic blood pressure between 130-139 mmHg *or* diastolic blood pressure between 80-89**
  - **Stage 2: systolic blood pressure ≥140 and ≤180 mmHg *or* diastolic blood pressure ≥90 and ≤120 mmHg**
  - **Hypertensive crisis: systolic blood pressure >180 mmHg *and/or* diastolic blood pressure >120 mmHg.**

A by-subject listing of all vital signs data will be provided. This listing will be presented by treatment group and will include: center, subject identifier, age, sex, race, weight, visit, vital sign variable and result (with abnormal values flagged as "L" or "H" accordingly). **This listing will also be provided separately for the OLE and the OLE2 treatment periods.**

Change #60

Section 10.4.2 Physical examination. The following texts in bold have been added.

Abnormal results of the physical examination together with details of abnormalities: abnormality clinically significant or not, will be listed by subject and visit **separately for the Initial and Maintenance (SS), Open-Label Extension (OLS) and Open-Label Extension 2 (OLS2) treatment periods.**

Change 61

Section 10.4.3 Electrocardiograms. The following texts in bold have been added

Two separate by-subject listing of all 12-lead ECG data will be provided based on interpretation from central reader and from site.

Change #62

Section 10.4.4.2 Assessment and management of TB and TB risk factors. The following texts in bold have been added

A by-subject listing of the "Evaluation of signs and symptoms of tuberculosis" questionnaire data and IGRA results will be provided. **This listing will also be provided separately for the OLE and the OLE2 treatment periods.**

A by-subject listing of the result of chest x-ray for tuberculosis will be provided by treatment.

Change #63

Section 10.4.4.2 Electronic Columbia Suicide Severity Rating Scale (eC-SSRS. The following texts in bold have been added

A by-subject listing of the eC-SSRS questionnaire data will be provided by treatment group. **This listing will also be provided separately for the OLE and OLE2 treatment periods.**

Change #64

Section 10.4.4.3 Pregnancy testing. The following texts in bold have been added.

A by-subject listing of the pregnancy test data will be provided by treatment group.

Change #65

Section 10.4.4.5 Patient Health Questionnaire 9 (PHQ-9) . The following texts in bold have been added

The number and percentage of subjects with a PHQ-9 score ≥ 15 at any point while on treatment and the number and percentage of subjects with a PHQ-9 score ≥ 20 at any point while on treatment will also be presented based on observed case data.

A by-subject listing of PHQ-9 data will be provided separately for the OLE and the OLE2 treatment periods. This listing will include site, subject number, visit, total score observed result, and total score change from Baseline value.

Change #66

Section 12.2 Apendix B

Table 13–1: Definitions of CTCAE grades by biochemistry parameter

The CTCAE grades (1-4) for the following Lab parameters in bold have been added to Table 12.1:

Parameter (unit)	Definition	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Alanine Aminotransferase	**High**	**UL**	**>ULN - 3.0 x ULN**	**>3.0 - 5.0 x ULN**	**>5.0 - 20.0 x ULN**	**>20.0 x ULN**
Alkaline Phosphatase	**High**	**UL**	**>ULN - 2.5 x ULN**	**>2.5 - 5.0 x ULN**	**>5.0 - 20.0 x ULN**	**>20.0 x ULN**
Aspartate Aminotransferase	**High**	**U/L**	**>ULN - 3.0 x ULN**	**>3.0 - 5.0 x ULN**	**>5.0 - 20.0 x ULN**	**>20.0 x ULN**
Bilirubin	**High**	**umol/L**	**>ULN - 1.5 x ULN**	**>1.5 - 3.0 x ULN**	**>3.0 - 10.0 x ULN**	**>10.0 x ULN**
Gamma Glutamyl Transferase	**High**	**U/L**	**>ULN - 2.5 x ULN**	**>2.5 - 5.0 x ULN**	**>5.0 - 20.0 x ULN**	**>20.0 x ULN**
Glucose	**High**	**mg/dL**	**Fasting glucose value >ULN - 160 mg/dL;**	**Fasting glucose value >160 - 250 mg/dL;**	**>250 - 500 mg/dL hospitalization indicated**	**>500 mg/dL lifethreatening consequences**
Creatinine	High	mmol/L	>ULN-1.5 x ULN	(>1.5 – 3.0) x ULN	(>3.0 – 6.0) x ULN	6.0 x ULN
Sodium	Low	mmol/L	130-<LLN	N/A	120-<130	<120
Sodium	High	mmol/L	>ULN-150	>150-155	>155-160	>160
Potassium	Low	mmol/L	3.0-<LLN	3.0-<LLN	2.5-<3.0	<2.5
Potassium	High	mmol/L	>ULN-5.5	>5.5-6.0	>6.0-7.0	>7.0
Calcium	Low	mmol/L	2.0-<LLN	1.75-<2.0	1.5-<1.75	<1.5
Calcium	High	mmol/L	>ULN-2.9	>2.9-3.1	>3.1-3.4	>3.4
Magnesium	Low	mmol/L	0.5-<LLN	0.4-<0.5	0.3-<0.4	<0.3

Magnesium	High	mmol/L	>ULN-1.23	N/A	>1.23-3.30	>3.30
Total cholesterol	High	**mmol/L**	**>ULN-7.75**	>7.75-10.34	>10.34-12.92	>12.92
Triglyceride	**High**	**mmol/L**	**1.71 - 3.42**	**>3.42 - 5.7**	**>5.7 - 11.4**	**>11.4**

Change #67

12.1 Appendix A: MedDRA algorithmic approach to anaphylaxis. The Table has been replaced with the following texts

Appendix A: MedDRA algorithmic approach to anaphylaxis

The SMQ *Anaphylactic reaction* consists of three parts:

1. A **narrow search** containing PTs that represent core anaphylactic reaction terms

- Category A – core anaphylactic reaction terms
  - Anaphylactic reaction
  - Anaphylactic shock
  - Anaphylactic transfusion reaction
  - Anaphylactoid reaction
  - Anaphylactoid shock
  - Circulatory collapse
  - Dialysis membrane reaction
  - Kounis syndrome
  - Procedural shock
  - Shock
  - Shock symptom
  - Type I hypersensitivity

2. A **broad search** that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction and categorized in B, C, or D.

- Category B (Upper Airway/Respiratory terms)
  - Acute respiratory failure
  - Asthma
  - Bronchial oedema

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

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

- Pruritus allergic
- Rash
- Rash erythematous
- Rash pruritic
- Skin swelling
- Swelling
- Swelling face
- Swelling of eyelid
- Urticaria
- Urticaria papular

- Category D (Cardiovascular/Hypotension terms)
  - Blood pressure decreased
  - Blood pressure diastolic decreased
  - Blood pressure systolic decreased
  - Cardiac arrest
  - Cardio-respiratory arrest
  - Cardiovascular insufficiency
  - Diastolic hypotension
  - Hypotension
  - Hypotensive crisis
  - Post procedural hypotension

3. An **algorithmic approach** which combines a number of anaphylactic reaction symptoms in order to increase specificity. A case must include one of the following where both occur on either the same day as when an injection was administered or one day after, and for scenarios where two must have been reported, both events must have occurred within one day of each other:

- A narrow term or a term from Category A
- A term from Category B – (Upper Airway/Respiratory) AND a term from Category C – (Angioedema/Urticaria/Pruritus/Flush)
- A term from Category D – (Cardiovascular/Hypotension) AND [a term from Category B – (Upper Airway/Respiratory) OR a term from Category C – (Angioedema/Urticaria/Pruritus/Flush)
- Hypersensitivity events will be identified using the "Hypersensitivity (SMQ)". All TEAEs which code to a PT included in the Scope=Narrow search will be included.

Change #68

The following Section 12.4 Appendix D has been added:

Appendix D: Efficacy analyses by data cut visit

Table 13–2: Efficacy analyses reporting

Parameter	Week 48	Week 96	Week 144/OLE[a]	Final/OLE2[b]
PASI100	X	X	X	X
PAS90	X	X	X	X
PASI75	X		X	
Absolute change and percent change from Baseline in PASI score	X	X	X	
Absolute PASI scores of ≤1, ≤2, ≤3, ≤5,	X	X	X	
Time to PASI100 response	X			
Time to PASI90 response	X			
Time to PASI75 response	X			
IGA Clear	X	X	X	X
IGA Clear or Almost Clear	X	X	X	X
IGA Change from Baseline	X			
Scalp IGA Clear or Almost Clear	X	X	X	
Palmoplantar IGA Clear or Almost Clear	X	X	X	
Change from Baseline in DLQI Total Score	X	X	X	
DLQI Total Score of 0 or 1	X	X	X	X
MCID ≥4 more in DLQI	X	X	X	
mNAPSI100	X	X	X	
mNAPSI90	X	X	X	
mNAPSI75	X	X	X	
Change from Baseline in mNAPSI score	X	X	X	
Change from Baseline in Psoriasis BSA	X	X	X	
Patient Global Assessment of PSO	X			
Absolute and percent change from Baseline in BSA affected by PSO	X	X	X	
Psoriasis BSA values of 0%, ≤1%, ≤3%, ≤5%,	X	X	X	

Parameter	Week 48	Week 96	Week 144/OLE[a]	Final/OLE2[b]
Absolute and percent change from Baseline in the product of IGA and BSA	X		X	
PSD response (itch, pain and scaling)	X	X	X	X
PSD 0 or 1 (itch, pain and scaling)	X	X	X	
PSD 0 (itch, pain and scaling)	X	X	X	
PGADA for arthritis analog scale	X		X	
PASE	X		X	
PASE (<47 versus ≥47)	X			
EQ-5D-3L	X		X	
WPAI-SHP	X		X	

[a] All Week 48 analyses will also be re-run at Week 144/OLE.

[b] All Week 48 and Week 144 analyses will also be rerun at Final/OLE2

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

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

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