STATISTICAL ANALYSIS PLAN

Study: PA0009

Product: Bimekizumab

A MULTICENTER, PHASE 2B, OPEN-LABEL, FOLLOW-UP STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BIMEKIZUMAB IN SUBJECTS WITH PSORIATIC ARTHRITIS

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Confidentiality Statement

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LIST OF ABBREVIATIONS

ACP	above the cut point
ACR	American College of Rheumatology
ACR20,50,70	American College of Rheumatology 20, 50, 70% response criteria
ADAb	anti-bimekizumab antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BCP	below the cut point
BKZ	bimekizumab
BLQ	below the limit of quantification
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CCP	cyclic citrullinated peptide
CI	confidence interval
COVID-19	Coronavirus Disease 2019
CP	confirmed positive
CRP	high-sensitivity C-reactive protein Note: High-sensitivity CRP is referred to as CRP throughout the SAP and is therefore abbreviated as CRP.
CTCAE	Common Terminology Criteria for Adverse Events
CV (%)	coefficient of variation
DAS28(CRP)	Disease Activity Score-28 joint count C-reactive protein
DIP	distal interphalangeal joint
DMARD	disease modifying anti-rheumatic drug
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
ES	Enrolled Set
ET	Early Termination
EV	entry visit
FAS	Full Analysis Set
GGT	gamma glutamyltransferase
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression
HAQ-DI	Health Assessment Questionnaire – Disability Index
HLGT	high level group term
HLT	high level term
HRQoL	health-related quality of life

IBD	Inflammatory bowel disease
IGRA	interferon-gamma release assay
IMP	investigational medicinal product
IP	interphalangeal
IXRS	interactive voice or web response system
LD	loading dose
LDH	lactate dehydrogenase
LDI	Leeds Dactylitis Index
LLOQ	lower limit of quantification
MASES	Maastricht Ankylosing Spondylitis Enthesitis Index
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov-Chain Monte Carlo
MCP	metacarpophalangeal
MCS	Mental Component Summary
MCV	mean corpuscular volume
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MRD	minimum required dilution
MTP	metatarsophalangeal
MTX	methotrexate
n	number of observations
NCP	not confirmed positive
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
OC	observed case
OLE	open-label extension
PASI	Psoriasis Area and Severity Index
PASI75, PASI90, PASI100	Psoriasis Area and Severity Index 75%, 90%, 100%
PCS	Physical Component Summary
PDILI	potential drug-induced liver injury
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PIP	proximal interphalangeal
PsA	psoriatic arthritis
PsAID-9	Psoriatic Arthritis Impact of Disease-9
PT	preferred term
PtAAP	Patient's Assessment of Arthritis Pain
Q4W	every 4 weeks (monthly)
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event

SAP	statistical analysis plan
sc	subcutaneous(ly)
SD	standard deviation
SF-36	Short-Form 36-item Health Survey
SFU	Safety Follow-up
SIB	suicidal ideation and behavior
SJC	swollen joint count
SMQ	standardized MedDRA query
SOC	system organ class
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required statistical analysis for PA0009. It also defines the summary tables, figures, and listings to be generated in the clinical study report according to the protocol.

The SAP is based on the following study documents:

- Final protocol, 15 May 2017.
- Protocol Amendment 1, 27 June 2017.
- Protocol Amendment 2, 09 Mar 2018.
- Protocol Amendment 3, 11 Dec 2019.

The content of this SAP is compatible with the International Council for Harmonisation/Food and Drug Administration E9 Guidance documents (1998).

2 PROTOCOL SUMMARY

PA0009 is a multicenter, open-label extension (OLE) study evaluating the long-term safety, tolerability, and efficacy of bimekizumab (also known as UCB4940) in subjects with psoriatic arthritis (PsA). Only subjects who complete PA0008, a Phase 2b study, are eligible for enrollment into PA0009. At Week 48 of PA0008, all subjects continuing into PA0009 will undergo the final PA0008 study assessments and any nonoverlapping PA0009 entry assessments and will then receive their first open label dose of bimekizumab.

PA0008 was a multicenter, Phase 2b, randomized, double blind, placebo-controlled, parallel group, dose ranging study to evaluate the efficacy and safety of bimekizumab in 200 subjects with active PsA.

In the PA0009 OLE study, bimekizumab will be administered at a dose of 160mg every 4 weeks (Q4W) subcutaneously (sc) for all subjects regardless of treatment received in PA0008.

Up to 200 subjects from PA0008 may be enrolled into this study at any of the sites participating in PA0008.

The study duration for each subject is estimated to be up to a maximum of 120 weeks: an Open Label Treatment Period of up to 100 weeks (~2 years), followed by a Safety Follow up (SFU) Visit 20 weeks after the final dose of bimekizumab.

2.1 Study objectives

2.1.1 Primary objective

The primary objective of this open-label study is to assess the long-term safety and tolerability of bimekizumab administered over a period of up to 100 weeks (~2 years).

2.1.2 Secondary objective

The secondary objectives of the study are as follows:

- To assess the long-term efficacy of bimekizumab

2.1.3 Other objectives

The other objectives are:

- To assess the impact on dactylitis and enthesitis
- To assess the impact on patient-reported quality of life
- To assess plasma concentrations of bimekizumab
- To assess the immunogenicity of bimekizumab

2.2 Study variables

2.2.1 Safety variables

2.2.1.1 Primary safety variables

The primary safety variables are the incidences of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs). The latter is measured by the incidence of serious TEAEs.

2.2.1.2 Secondary safety variables

The secondary safety variable is the withdrawal due to TEAEs. This is measured by the incidence of TEAEs leading to study discontinuation and/or permanent withdrawal of study medication.

2.2.1.3 Other safety variables

Other safety variables are listed below:

- Change from PA0009 Laboratory Baseline (defined as the earliest date in PA0009 at or prior to PA0009 Week 12) for clinical laboratory variables (hematology and biochemistry, excepting high-sensitivity C-reactive protein [CRP]) at each visit (PA0009 Week 24, 36, 48, 60, 72, 84, 96, 100, 104, SFU).
- Change from Baseline of PA0008 in vital signs (pulse, temperature, and blood pressure) (PA0009 Entry Visit [EV], Week 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 100, 104, SFU) and body weight (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104, SFU).

2.2.2 Efficacy variables

2.2.2.1 Primary efficacy variable

There is no primary efficacy variable for this study because the primary objective is to assess long-term safety and tolerability.

2.2.2.2 Secondary efficacy variables

The secondary efficacy variables are:

- American College of Rheumatology (ACR) 20% response criterion (ACR20), ACR 50% response criterion (ACR50), and ACR 70% response criterion (ACR70) response at PA0009 Week 48, relative to PA0008 Baseline.
- Change from Baseline of PA0008 in Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) at PA0009 Week 48.

- Change from Baseline of PA0008 in the Leeds Dactylitis Index (LDI) at PA0009 Week 48.
- Psoriasis Area and Severity Index (PASI) 75% (PASI75) and PASI 90% (PASI90) response at PA0009 Week 48, relative to PA0008 Baseline.

2.2.2.3 Other efficacy variables

The other efficacy variables are listed below and will be evaluated at scheduled visits in accordance with the schedule of study assessments in Table 2-1:

- ACR20, ACR50, and ACR70 response at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104), relative to PA0008 Baseline.
  - ACR20, ACR50 and ACR70 response will also be reported at each post-PA0008 Baseline visit in PA0008 through to PA0009 Week 104 (PA0008 Week 2, 4, 8, 12, 16, 20, 24, 36 and PA0009 EV [PA0008 Week 48], Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104), for subjects who were responders at PA0008 Week 12. These are additional variables to those specified in the protocol and will be used to assess maintenance of response.
- PASI75, PASI90 and PASI100 response at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104), relative to PA0008 Baseline.
  - PASI75, PASI90 and PASI100 response will also be reported at each post-PA0008 Baseline visit in PA0008 through to PA0009 Week 104 (PA0008 Week 2, 4, 8, 12, 24 and 36 and PA0009 EV [PA0008 Week 48], Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104), for subjects who were responders at PA0008 Week 12. These are additional variables to those specified in the protocol and will be used to assess maintenance of response.
  - BSA at each visit in PA0009 will also be reported. This is additional to the protocol and was added as an additional method of assessing response in order to provide information at visits where the PASI data may be missing.
- Minimal Disease Activity (MDA) at each visit (PA0009 EV, Week 12, 24, 36, 48, 72, 96, 104).
- Change from Baseline of PA0008 value in Disease Activity Score-28 based on C-reactive protein (DAS28[CRP]) at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104).
- Change from Baseline of PA0008 in MASES at each visit (PA0009 EV, Week 12, 24, 36, 48, 72, 96, 104).
- Change from Baseline of PA0008 in the LDI at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104).
- Change from Baseline of PA0008 in Psoriatic Arthritis Impact of Disease-9 (PsAID-9) at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104).
- Change from Baseline of PA0008 in Short Form 36-item Health Survey (SF-36) at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104).

- Change from Baseline of PA0008 in Hospital Anxiety and Depression Scale (HADS)-Anxiety (HADS-A) and HADS-Depression (HADS-D) scores at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104).
- Depression and anxiety status 'normal' as defined by HADS-D and HADS-A<8 at each visit (PA0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 100, 104).

2.2.3 Pharmacokinetic/pharmacodynamic variables

2.2.3.1 Other pharmacokinetic variable

The pharmacokinetic (PK) variable is the plasma concentration of bimekizumab evaluated at scheduled visits up to 104 weeks (2 years) in accordance with the schedule of study assessments in Table 2-1 (PA0009 EV, Week 12, 24, 36, 48, 72, 96, 104, SFU).

No pharmacodynamic variables are defined.

2.2.4 Other pharmacogenomic variables

No analyses of genomic, genetic, proteomic, or metabolomic biomarkers relevant to disease biology and progression, response to therapy, and the inflammatory and immune response processes are specified.

2.2.5 Other immunological variable

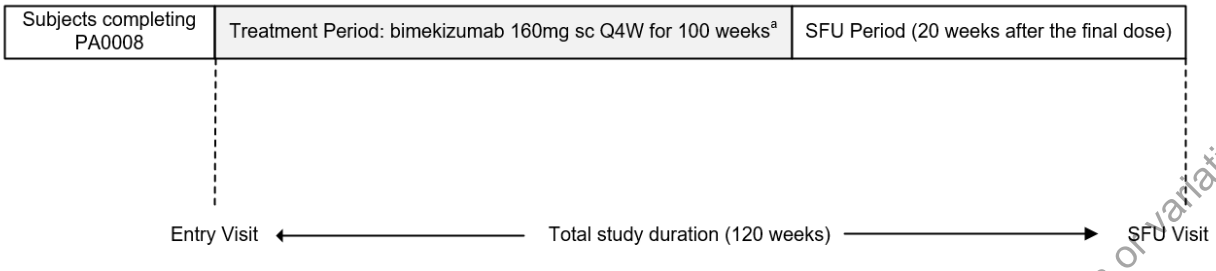
The immunological variable is the anti-bimekizumab antibody (ADAb) detection evaluated at scheduled visits up to 104 weeks (2 years) in accordance with the schedule of study assessments in Table 2-1 (PA0009 EV, Week 12, 24, 36, 48, 72, 96, 104, SFU).

2.3 Study design and conduct

PA0009 is a multicenter OLE study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult subjects with PsA who completed the Phase 2b study PA0008. At Week 48 of PA0008, all eligible subjects continuing into PA0009 will undergo their final PA0008 study assessments and any nonoverlapping PA0009 entry assessments and will then receive their first open-label dose of bimekizumab.

The OLE study will assess the safety, tolerability, and efficacy of bimekizumab administered for a period of up to 100 weeks (~2 years). Bimekizumab will be administered at a dose of 160mg Q4W upon entry into PA0009, regardless of the dose received in PA0008. Additionally, other treatments may be used in addition to bimekizumab per Investigator discretion. Subjects not responding to treatment may be withdrawn from the treatment and study at the discretion of the Investigator. A study schematic diagram of PA0009 is provided in Figure 2–1.

Figure 2–1: Schematic Diagram



Q4W=every 4 weeks; sc=subcutaneous; SFU=Safety Follow-up
Note: Self-administration will be allowed after 3 months of treatment (from PA0009 Week 16 onwards) as described in Table 2-1.
[a] Subjects will receive their final dose of study drug on PA0009 Week 100 and the SFU Visit will be conducted 20 weeks after the last dose of investigation medicinal product (IMP).

A schedule of study assessments is provided in Table 2-1.

Table 2-1: Schedule of Study Assessments

Protocol activity	Treatment Period																		SFU
Weeks[a]	**EV[b]**	**4**	**12**	16	**24**	28	**36**	40	**48**	52	**60**	64	**72**	76	**84**	88	**96**	**100**	**W104/**	
		8		20		32		44		56		68		80		92			**ET**	
Visit[a]	**1**	**2/3**	**4**	H[c]	**5**	H[c]	**6**	H[c]	**7**	H[c]	**8**	H[c]	**9**	H[c]	**10**	H[c]	**11**	**12**	**13**	
Informed consent	X[d]																			
Inclusion/exclusion	X[e]																			
Concomitant medications	X[f]	X	X		X		X		X		X		X		X		X	X	X	X
Adverse events	X[f]	X	X		X		X		X		X		X		X		X	X	X	X
eC-SSRS	X[e,f]	X	X		X		X		X		X		X		X		X	X	X	X
HADS	X[e,f]		X		X		X		X		X		X		X		X	X	X	
HAQ-DI	X[e,f]		X		X		X		X		X		X		X		X	X	X	
SF-36	X[e,f]		X		X		X		X		X		X		X		X	X	X	
PGADA	X[e,f]		X		X		X		X		X		X		X		X	X	X	
PtAAP	X[e,f]		X		X		X		X		X		X		X		X	X	X	
PsAID-9	X[e,f]		X		X		X		X		X		X		X		X	X	X	
TB questionnaire	X[e,f]		X		X		X		X		X		X		X		X	X	X	X
Vital signs (pulse, temperature, BP)[g]	X[e]	X	X		X		X		X		X		X		X		X	X	X	X
Body weight	X[e,f]		X		X		X		X		X		X		X		X	X	X	X
Physical examination[h]	X[e,f]								X								X		X	X
TJC (78) and SJC (76)	X[e,f]		X		X		X		X		X		X		X		X	X	X	
BSA affected by PSO (BSA palm method)	X[e,f]		X		X		X		X		X		X		X		X	X	X	
PASI[i]	X[e,f]		X		X		X		X		X		X		X		X	X	X	
MASES	X[e,f]		X		X		X		X				X				X		X	

Table 2-1: Schedule of Study Assessments

Protocol activity	Treatment Period																		SFU
Weeks[a]	**EV**[b]	**4**	**12**	16	**24**	28	**36**	40	**48**	52	**60**	64	**72**	76	**84**	88	**96**	**100**	**W104/**	
		8		20		32		44		56		68		80		92			**ET**	
Visit[a]	**1**	**2/3**	**4**	H[c]	**5**	H[c]	**6**	H[c]	**7**	H[c]	**8**	H[c]	**9**	H[c]	**10**	H[c]	**11**	**12**	**13**	
LDI	X[e,f]		X		X		X		X		X		X		X		X	X	X	
PhGADA	X[e,f]		X		X		X		X		X		X		X		X	X	X	
ECG	X[e,f]								X								X		X	
Hematology/biochemistry/ urine pregnancy[j,k]	X[e,f]		X		X		X		X		X		X		X		X	X	X	X
Blood Sample for CRP[k]	X[e,f]		X		X		X		X		X		X		X		X	X	X	X
Blood sample for bimekizumab plasma concentrations[k]	X[e,f]		X		X		X		X				X				X		X	X
Blood sample for anti-bimekizumab antibodies[k]	X[e,f]		X		X		X		X				X				X		X	X
IGRA TB test[l]	X[e]								X								X			X
IXRS	X	X	X		X		X		X		X		X		X		X	X	X	X
Bimekizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

BP=blood pressure; BSA=body surface area; CRP=C-reactive protein; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; ET=Early Termination; EV=Entry Visit; H=home; HADS=Hospital Anxiety and Depression Scale; HAQ-DI=Health Assessment Questionnaire—Disability Index; IGRA=interferon-gamma release assay; IXRS=interactive voice or web response system; LDI=Leeds Dactylitis Index; MASES= Maastricht Ankylosing Spondylitis Enthesitis Score; PASI=psoriasis area severity index; PGADA=Patient's Global Assessment of Disease Activity; PhGADA=Physician's Global Assessment of Disease Activity; PsAID=Psoriatic Arthritis Impact of Disease; PSO=psoriasis; PtAAP=Patient's Assessment of Arthritis Pain; SF-36=Short Form 36-item Health Survey; SFU=Safety Follow-Up; SJC=swollen joint count; TB=tuberculosis; TJC=tender joint count

Note: The SFU it Visit will occur 20 weeks after the final dose of study medication.

[a] Visit windows are ±7 days from the scheduled visit day (relative to the first dose) with a minimum of 21 days and a maximum of 35 days in between doses at all visits except the SFU Visit. For the SFU Visit (20 weeks after the final dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

Table 2-1: Schedule of Study Assessments

Protocol activity	Treatment Period																			SFU
Weeks[a]	**EV**[b]	**4**	**12**	16	**24**	28	**36**	40	**48**	52	**60**	64	**72**	76	**84**	88	**96**	**100**	**W104/**	
		8		20		32		44		56		68		80		92			**ET**	
Visit[a]	**1**	**2/3**	**4**	H[c]	**5**	H[c]	**6**	H[c]	**7**	H[c]	**8**	H[c]	**9**	H[c]	**10**	H[c]	**11**	**12**	**13**	

[b] PA0009 entry will occur at the end of the lead-study PA0008. At Week 48 of PA0008, all subjects continuing into PA0009 will undergo the final PA0008 study assessments and any nonoverlapping PA0009 entry assessments before receiving their first open-label dose of bimekizumab.
[c] From the Entry Visit onwards, self-administration training will be provided to the subject/caregivers/appropriate designee by the study nurse. At Week 8 and Week 12, the subject/caregiver/appropriate designee will perform administrations under the supervision of the site staff to ensure that study medication is being properly and safely injected.
[d] Ensure that a separate Informed Consent form was completed by the subject for PA0009 prior to study entry.
[e] To be performed prior to the first dose of open-label bimekizumab.
[f] Assessment will be performed at Week 48 of the lead-in study PA0008 and will be used as the PA0009 Entry Visit value.
[g] At PA0009 study entry collect pulse and BP prior to drug administration and then at 30 minutes and 1 hour after dosing. At all other visits collect pulse and BP prior to drug administration and once after dosing.
[h] Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.
[i] If the BSA affected by PSO was ≥3% at Baseline of PA0008, determine the PASI.
[j] If there has been a delay in menses, perform a urine pregnancy test.
[k] All blood samples are to be taken prior to dosing.
[l] It is recommended that the QuantiFERON TB Test be performed. This assessment will be performed at study entry, unless an IGRA negative result is available less than 6 weeks prior to the first dose of open-label bimekizumab.

2.4 Determination of sample size

There is no formal sample size calculation for this study. The sample size is determined by the number of subjects eligible for PA0009 and rolling over from PA0008. Up to 200 subjects from PA0008 could be enrolled into this study.

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

All computations and generation of outputs will be performed using SAS® Version 9.3 or later.

UCB uses SAS in a 64-bit Windows environment, and it is well-documented that in this environment the maximum accuracy of any numeric value is 15 significant digits. However, SAS by default does not limit the accuracy of numeric values to 15 significant digits which, in certain instances, may result in inaccurate representation of the data and cause errors when used in subsequent calculations, particularly when comparing a value to a chosen threshold. This, in turn, could potentially result in a change in classification of a subject from a responder to a nonresponder (and vice versa) if these values occur on a threshold used in the evaluation of response (or a critical laboratory value for example).

Therefore, in order to avoid issues caused by inaccurate floating point representation of numeric values, temporary variables are created (ie, for absolute values, change and percentage change from Baseline) during programming which are rounded to 12 decimal places prior to comparison to a specific threshold in the derivation of a response parameter. This does not imply inherent rounding on the ADaM variables AVAL (absolute value), CHG (change) or PCHG (percentage change) which are retained unrounded in the final ADaM dataset. Thus, rounding is applied exclusively during the derivation of new response parameters or critical value variables, and the rounded values are created on a temporary basis only.

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 categorical variables, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects included in the respective analysis set. For observed case (OC) summaries, or summaries of data where no imputation is made for missing data, subjects with missing data will be accounted for by including 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. Percentages will be presented to 1 decimal place. If the percentage is 100%, no decimal will be presented. If the percentage is 0, no percentage will be presented. The % sign will be presented in the column header, but not with each individual value.

For continuous variables, descriptive statistics will include number of subjects with available measurements (n), mean, standard deviation (SD), median, minimum, and maximum. Decimal places for descriptive statistics will apply the following rules:

- "n" will be an integer.
- Arithmetic and geometric mean, SD, and median will use 1 additional decimal place compared to the original data.

- Coefficient of variation (CV [%]) will be presented with 1 decimal place.
- Minimum and maximum will have the same number of decimal places as the original value.

The number of decimal places used for derived efficacy variables is shown in Table 3-1.

Table 3-1: Decimal places for derived efficacy variables

Variable	Decimal places used for minimum and maximum	Decimal places used for mean, SD and median
MASES	1	2
LDI	0	1
SJC, TJC	0	1
DAS28(CRP)	2	3
PsAID-9	2	3
SF-36 MCS	2	3
SF-36 PCS	2	3
HADS-A	0	1
HADS-D	0	1
HAQ-DI	2	3

DAS28(CRP)=Disease Activity Score 28 joint count C-reactive protein; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; HAQ-DI=Health Assessment Questionnaire - Disability Index; LDI=Leeds Dactylitis Index; MASES=Maastricht Ankylosing Spondylitis Enthesitis Index; PsAID-9=Psoriatic Arthritis Impact of Disease-9; SD=standard deviation; SF-36 MCS=Short Form 36-Item – Mental Component Summary; SF-36 PCS=Short Form 36-Item – Physical Component Summary; SJC=swollen joint count; TJC=tender joint count.

The abbreviation BKZ will be used for bimekizumab in table and listings headers.

All data will be presented in by-subject data listings sorted by planned (randomized) treatment group at completion of PA0008 (for efficacy listings) or actual treatment group at completion of PA0008 (for all other listings), site, subject number, variable (where applicable), and visit (where applicable). All listings will include scheduled, repeated and unscheduled measurements in chronological order. Dates will be presented in the format 'YYYY-MM-DD' and times will be presented in 24-hour clock format as 'hh:mm'.

In all listings (where applicable) the subject level demographic information (ie, gender, age, race, weight) will be based on the data reported at PA0008 Baseline.

3.2 General study level definitions

3.2.1 Relative day

Two relative days will be calculated, these will be relative to the following *reference dates*; the first relative to the start date of study medication (placebo or bimekizumab) in PA0008 and the second relative to the start date of study medication in PA0009. Relative day will be calculated as:

$$Current\ date - reference\ date + 1 \quad (1)$$

for dates on or after the reference date, and:

$$Current\ date - reference\ date \quad (2)$$

for dates before the reference date.

Additional character relative day variables will be derived for inclusion in listings:

$$Current\ date - reference\ date + 1 \quad (3)$$

for dates on or after the reference date and on or before the end date of study medication (no prefix),

$$Current\ date - reference\ date \quad (4)$$

for dates before the reference date ('-' prefix), and:

$$Current\ date - end\ date\ of\ study\ medication\ in\ PA0009 \quad (5)$$

for dates after the end date of study medication (with '+' prefix).

Relative day will not be calculated if dates are partial or missing.

3.2.2 Study periods

The following study periods are defined:

- Treatment Period: The Treatment Period (100 weeks) starts at the start date of study medication in PA0009 and ends at the end date of study medication.
- Dosing period: The dosing period starts at the start date of study medication in PA0009 and ends at 1 dosing interval (28 days) after the end date of study medication.
- SFU Period: The SFU Period starts on the day after the end date of study medication and ends at the SFU visit scheduled for 20 weeks after the end date of study medication.

3.3 Definition of Baseline values

The Baseline value defined in the PA0008 database will be used as a Baseline for PA0009, without additional derivation. The change from PA0008 Baseline will be calculated.

Due to a change in laboratory vendor between PA0008 and PA0009, laboratory values (with the exception of CRP) will use the PA0009 Laboratory Baseline, defined as the earliest post-EV value recorded in PA0009 at or prior to PA0009 Week 12). Change from PA0009 Laboratory Baseline will be calculated for these parameters.

The CRP values from the 2 analyzing laboratories have been calibrated, so change from PA0008 Baseline will be calculated for CRP.

3.4 Protocol deviations

Important protocol deviations are defined as those likely to have a meaningful impact on study conduct or on the safety or efficacy outcomes for an individual subject. The criteria for identifying protocol deviations and classifying them as important will be defined within the appropriate protocol-specific document. All potential protocol deviations will be reviewed as part of the ongoing data cleaning process and documented prior to database lock.

All deviations will be identified and classified as important or not important. Important protocol deviations will be identified and classified by the deviation types:

- Inclusion criteria deviation
- Exclusion criteria deviation
- Withdrawal criteria deviation
- Prohibited concomitant medication use
- Incorrect treatment or dose
- Treatment non-compliance
- Procedural non-compliance

The process for identifying and categorizing prohibited medications is described in Section 6.5.

The impact of the COVID-19 pandemic on study procedures/conduct (eg, missed visits, remote visits, interruption of study treatment) will be documented using the information collected on a dedicated eCRF page, the details for which are included in Section 12.6.

3.5 Mapping of assessments

Study assessments at an Early Termination (ET) visit where the visit date is within the protocol-defined visit window of a scheduled site visit will be mapped to that scheduled site visit (this does not include home visits). Visit windows will be calculated relative to the date of first dose in PA0009 (planned at the PA0009 EV), but if the dose was missed at that visit, the date of the PA0009 EV will be used instead. The following rules will also be applied:

- If there is an existing scheduled site visit in the window and the specific assessment was performed at that scheduled visit, then the relevant assessments at the ET visit will be

mapped to the next scheduled site visit (regardless of whether this is within the protocol-defined visit window for that site visit).

- Study assessments at an ET visit that does not fall into the protocol-defined visit window of a scheduled site visit will be assigned to the next scheduled site visit after the date of the ET visit (regardless of whether this is within the protocol-defined visit window for that site visit).
- Mapping of an assessment to a scheduled visit will occur regardless of whether the assessment was planned to be conducted at that visit (with the exception of ADAb). For ADAb however, data will only be mapped to scheduled site visits where ADAb levels are planned to be measured. Any PK samples taken at the same ET visit will be mapped to the same scheduled visit as the ADAb.
- Additional rules regarding visit windows for PK and ADAb summaries are included in Section 9.1 and Section 9.2.

Unscheduled assessments where the visit date is within the protocol-defined visit window of a scheduled site visit will be mapped to that scheduled site visit (this does not include home visits). Visit windows will be calculated relative to the date of first dose in PA0009, but if the dose was missed at that visit, the date of the PA0009 EV will be used instead. The following rules will also be applied:

- If there is an existing assessment with a non-missing response (from a scheduled site visit or ET visit) in the window, the assessment will be left as unscheduled.
- Unscheduled assessments which do not fall within a protocol-defined visit window based on time since first dose (or date of PA0009 EV if the first dose was missed) will be left as unscheduled.
- Unscheduled assessments obtained at specific time points (eg, vital signs) will only be mapped to a scheduled site visit for the equivalent time point. Thus, if an assessment falls within the protocol-defined visit window of a scheduled site visit but the scheduled visit does not have a corresponding time point, the measurement will be left as unscheduled (eg, if the unscheduled time point was '1 HOUR POST DOSE' this will not be mapped to a visit at which only 'PRE DOSE' time points are scheduled).
- Unscheduled PK and ADAb assessments may also be mapped to a scheduled site visit if the visit date is within the protocol-defined visit window of that visit. For ADAb this will only apply to scheduled site visits where ADAb levels are planned to be measured. For any PK samples obtained at the same unscheduled visit, these will be mapped to the same scheduled visit as the ADAb.

If there are multiple unscheduled assessments in a specific visit window, the first non-missing assessment will be mapped to the scheduled visit and used for summary statistics or frequency counts. Similarly, if there are multiple scheduled assessments performed on the same visit date, the first non-missing assessment will be used for summary statistics or frequency counts.

Assessments will be reported according to the planned Schedule of Assessments (Table 2-1) and each scheduled visit summary will include actual data and any data mapped from an ET visit to

that scheduled visit. The final visit will be labeled "Week 104". Data obtained at scheduled visits will be reported as per the database (ie, these will not be remapped as described above).

Assessments mapped to visits at which the assessment was not planned and unscheduled assessments that are not mapped to a scheduled visit at which the assessment was planned will be listed only.

3.6 Analysis sets

Three analysis sets will be defined for this study.

3.6.1 Enrolled Set

The Enrolled Set (ES) will consist of all subjects who have given informed consent for PA0009.

3.6.2 Safety Set

The Safety Set (SS) will consist of all subjects in the ES who received at least one dose of study medication in PA0009.

All safety variables will be summarized for the SS. Pharmacokinetic and immunological variables will also be summarized on the SS.

Two Sub-populations of the SS will be defined for this study: SS Sub-population 1 will consist of all subjects in the SS who took no concomitant rescue medication in PA0009, and SS Sub-population 2 will consist of all subjects in the SS who took concomitant rescue medication in PA0009, as outlined in Section 6.5. Rescue medications will be identified in the study database using the flag collected in the electronic case report form (eCRF). Concomitant medications are defined in Section 6.4.

Selected summaries of the primary and secondary safety variables will be repeated for both SS Sub-populations only in the event that the number of subjects receiving rescue medication is ≥10% of the total number of subjects in the SS.

3.6.3 Full Analysis Set

The Full Analysis Set (FAS) will consist of all subjects in the ES who received at least 1 dose of study medication in PA0009 and have a valid measurement for at least 1 efficacy variable after PA0009 EV.

Secondary and other efficacy variables will be summarized for the FAS. Immunological variables will also be summarized on the FAS where specified in Section 9.2.

3.7 Treatment assignment and treatment groups

This is an open label, single arm study.

Treatment group at the completion of PA0008 (presented as 'BKZ 160mg' or 'BKZ 320mg') and an overall 'BKZ Total' column will be used to summarize data in PA0009.

The endpoints assessing maintenance of ACR and PASI response over time will be summarized by treatment sequence across PA0008 and PA0009. Treatment sequences take the form 'A/B/C', where A is the treatment in the first 12 weeks of PA0008, B is the treatment from Week 12 to Week 48 of PA0008, and C is the treatment in PA0009. The seven planned treatment sequences are as follows:

- Placebo/BKZ 160mg/BKZ 160mg.
- Placebo/BKZ 320mg/BKZ 160mg.
- BKZ 16mg/BKZ 160mg/BKZ 160mg.
- BKZ 16mg/BKZ 320mg/BKZ 160mg.
- BKZ 160mg loading dose (LD)/BKZ 160mg/BKZ 160mg.
- BKZ 160mg/BKZ 160mg/BKZ 160mg.
- BKZ 320mg/BKZ 320mg/BKZ 160mg.

For safety summaries the following will be presented:

- Safety summaries including PA0009 data only will be presented by treatment group at the completion of PA0008 and overall.
- Safety summaries including data from both PA0008 and PA0009 combined will be presented for ‘BKZ 160mg’, ‘BKZ 320mg’, and 'BKZ Total’. The assignment of each of the sequences to the columns in this table is presented in Table 3-2.
  - The ‘BKZ 160mg’ treatment column in these tables will include subjects in both the BKZ 160mgLD and BKZ 160mg treatment groups.
  - For each column, only those periods for which the specified treatment is received will contribute to the summary ie, for sequence BKZ 16mg/BKZ 320mg/BKZ 160mg, the 16mg period will contribute to the BKZ Total column only, the BKZ 320mg period will contribute to the BKZ 320mg column and the BKZ Total column only, and the BKZ 160mg period will contribute to the BKZ 160mg column and the BKZ Total column only.

Table 3-2: Treatment sequence assignment for safety summaries

Sequence	BKZ 160mg	BKZ 320mg	BKZ Total
Placebo/BKZ 160mg/BKZ 160mg	X		X
Placebo/BKZ 320mg/BKZ 160mg	X	X	X
BKZ 16mg/BKZ 160mg/BKZ 160mg	X		X
BKZ 16mg/BKZ 320mg/BKZ 160mg	X	X	X
BKZ 160mg LD/BKZ 160mg/BKZ 160mg	X		X
BKZ 160mg/BKZ 160mg/BKZ 160mg	X		X
BKZ 320mg/BKZ 320mg/BKZ 160mg	X	X	X

BKZ=bimekizumab; LD=loading dose.

- For all safety summaries, subjects who took bimekizumab 320mg during PA0008 will contribute to all 3 columns. Subjects who did not take 320mg in PA0008 will contribute to the 'BKZ 160mg' and 'BKZ Total' columns.
- The combined summaries will include all data from PA0008 in addition to PA0009 only for subjects who were enrolled in PA0009.
- The PA0009 only summaries will include only data collected in PA0009 (unless otherwise stated).

Subjects will be summarized based on the actual/received treatment or the planned treatment for different analysis sets as follows:

- ES: planned treatment.
- SS and SS Sub-populations: actual treatment.
- FAS: planned treatment.

For actual and planned treatments in PA0008, the data will be used directly from the PA0008 analysis database without any rederivation of treatment assignments in each period.

In PA0009 it will be assumed that all subjects received the correct treatment as the dose level of bimekizumab is the same for all subjects and throughout the study (160mg). If a subject missed a dose at PA0008 Week 48, they will also be considered to have received the planned treatment. Thus for all subjects in PA0009, the actual treatment will be the same as the planned treatment.

3.8 Center pooling strategy

Centers at PA0008 Baseline will be grouped into the geographic regions of North America (county code USA) and Europe (country codes CZE, DEU, HUN, POL, RUS) for use as a

covariate in statistical analyses and for subgroup analyses (see Section 4.1 and Section 8.4). An additional region grouping of North America (county code USA), Eastern Europe (country codes CZE, HUN, POL, RUS) and Western Europe (country code DEU) will be derived in the datasets for possible use in future integration.

3.9 Coding dictionaries

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0. Medical history conditions and will be classified by primary system organ class (SOC) and preferred term (PT). AEs will be classified by primary system organ class (SOC), high level term (HLT) and preferred term (PT).

Prior and concomitant medications will be coded using version SEP2015 of the World Health Organization Drug Dictionary and will be classified by Anatomical Main Group, Pharmacological Subgroup, and PT.

Medical procedures will not be coded.

3.10 Changes to protocol-defined analyses

The following changes have been made to the protocol-defined analyses:

- Summaries of ACR20, ACR50, ACR70, PASI75, PASI90, and PASI100 response at each post-PA0008 Baseline visit have been added for subjects who were responders at PA0008 Week 12. These summaries include all post-Baseline PA0008 visits through to PA0009 Week 104 and will be used to assess maintenance of response.
- Summaries of BSA at each visit in PA0009 have been added as an additional method of assessing response in order to provide information at visits where the PASI data may be missing.
- Summaries by randomized treatment in PA0008 will not be produced, as subjects will have been on a constant dose of bimekizumab 160mg or 320mg for at least 36 weeks prior to PA0009 entry. Maintenance of response displays will be split by treatment sequence across PA0008 and PA0009. Safety displays using PA0008 information will incorporate exposure in PA0008.
- The protocol stated that all safety analyses would be performed for both SS Sub-populations; instead only key safety analyses will be repeated by SS Sub-population as identified in Section 10. These analyses will be performed only in the event that the number of subjects receiving rescue medication is ≥10% of the total number of subjects in the SS.
- The protocol stated that figures presenting the relationship between ACR20 response and ADAb positivity over time would be produced. This has been changed to use the ACR50 response instead as this is considered to be the key efficacy endpoint with respect to ACR.

3.10.1 Changes related to COVID-19

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

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

- Subject disposition, including details of impacted visits and effects on collection and reporting of efficacy data (Section 5.1.1)
- Adverse events (Section 10.2.4)

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

All multiple imputation (MI) models (see Section 4.2.1) will include the following covariates:

- Geographic region at PA0008 Baseline (North America, Europe), as defined in Section 3.8.
- Previous (past) tumor necrosis factor (TNF) inhibitor agent exposure in PA0008. The value in the PA0008 database for past anti-TNF therapy (as collected on the eCRF) will be used for PA0009, without additional derivation.

Missing efficacy data will be handled as described in Section 4.2.1. No imputation will be made for missing safety or background data, except as described in Section 4.2.3 and Section 4.2.4.

4.2 Handling of missing data

4.2.1 Handling of missing data for efficacy analysis

Calculation of derived efficacy variables in the presence of missing data is described in individual subsections of Section 8.1. All derived efficacy variables will be calculated using observed data, and any resulting missing data will be handled as described in this section. All nonresponder imputation (NRI) and MI imputation as described below will be performed only for subjects in the FAS for PA0009.

Additional methods for deriving the PASI response in the presence of missing data are described in Section 4.2.2.

For assessments missing during PA0008, which were to be used in PA0009 for reporting maintenance of response, the following approach will be used:

- For summaries of binary data following NRI, the imputed value from the PA0008 database will be used.
- For summaries of non-imputed (OC) data, the assessment will be left as missing.

For all visits in PA0009 (including PA0009 EV), missing values for binary secondary/other efficacy variables (ACR20, ACR50, ACR70, PASI75, PASI90, PASI100, MDA) or values, which cannot be constructed (eg, for ACR either tender joint count [TJC]/swollen joint count [SJC] are missing or >2 out of the 5 remaining core set measures are missing) will be imputed using NRI. For each visit, subjects with missing data or who have dropped out of the study will be counted as nonresponders. This includes any subjects with missing Baseline values. For PASI response, NRI will be implemented only for subjects with BSA ≥3% at PA0008 Baseline.

For missing continuous secondary/other efficacy variables an MI approach will be used. This will be performed for the following endpoints:

- TJC and SJC

- Psoriasis Area and Severity Index (PASI)
  - For PASI the MI model will be restricted to subjects with a BSA affected by psoriasis of ≥3% at PA0008 Baseline. Subjects with a BSA affected by psoriasis of <3% at PA0008 Baseline will be excluded prior to performing the procedure outlined below.
- Patient's Global Assessment of Disease Activity (PGADA)
- Physician's Global Assessment of Disease Activity (PhGADA)
- Patient's Assessments of Arthritis Pain (PtAAP)
- Health Assessment Questionnaire – Disability Index (HAQ-DI)
- CRP
  - For CRP, the rules for handling measurements that are below the limit of quantification should be followed as per Section 8.1.7. Thus, if any imputed values are <0.16mg/L, these will be replaced with 0.08mg/L prior to any subsequent reporting.
- MASES
  - For MASES, the MI model will be restricted to subjects with a MASES score >0 at PA0008 Baseline. Subjects with a MASES score of 0 at PA0008 Baseline will be excluded prior to performing the procedure outlined below.
- LDI
  - For LDI, the MI model will be restricted to subjects with LDI scores >0 at PA0008 Baseline. Subjects with LDI scores of 0 at PA0008 Baseline will be excluded prior to performing the procedure outlined below.
- DAS28[CRP]
- PsAID-9
- SF-36
  - For SF-36, this will be performed for the Physical Component Summary (PCS) score and Mental Component Summary (MCS) score only.
- HADS-A and HADS-D
  - Incidence of normal HADS-A and HADS-D scores (defined as having HADS-D<8 and HADS-A<8 at the same visit) will be derived at each visit using the values for HADS-A and HADS-D obtained after MI

The missing absolute value (not the change from Baseline) will be replaced by one of a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. The basic assumption in MI is that the underlying missing data mechanism is ignorable, eg, the missing data are missing at random.

All MI procedures will be performed using data from both PA0008 and PA0009 such that missing data across both studies will be imputed (in general, only data from PA0009 will be presented in the summary tables, with the exception of the summaries of maintenance of response where all visits in PA0008 and PA0009 will be presented). Any previous imputation

(MI or last observation carried forward [LOCF] or other imputation) performed in PA0008 will not be considered for PA0009 such that the procedure will use OC data only across both studies. Thus, the results presented in the maintenance tables for visits in PA0008 may differ from those previously reported as part of the PA0008 clinical study report.

As the PA0008 Week 48 time point is synonymous with the PA0009 EV time point, this will be incorporated once only into the model.

The SAS® PROC MI procedure will be used for the imputation.

The MI consists of 3 steps:

- The missing data are imputed m times to create m complete datasets.
- The m datasets are summarized.
- The results of the m summaries are combined into a single result.

The MI method will be applied as follows:

Step 1

- Create a data set, sorted by treatment group at completion of PA0008, of subjects with observed values and missing values needing imputation. Missing values will be separated into non-monotone (ie, intermittent missing values between completed assessments) and monotone (ie, missing values after the subject dropped out). The procedure will sequentially estimate an imputation model for the efficacy variable at each post-PA0008 Baseline visit where efficacy variables are collected, with PA0008 Baseline, geographic region, and past TNF inhibitor exposure (as collected on the eCRF in PA0008 for past anti-TNF exposure) as covariates, separately for each treatment group at the completion of PA0008.
- Intermittent missing data will be imputed by draws from the imputation model using the Markov-Chain Monte Carlo (MCMC) method with multiple chains and monotone imputing. A total number of imputations will be 100. The seed used for these imputations will be 2017.

  Note: All MI procedures described in this SAP will use the same seed.
- The post-PA0008 Baseline values will be specified in chronological order in the imputation model so that the SAS® PROC MI imputes variables from left to right. If a PA0008 Baseline raw value is missing, the study participant will be excluded. The imputation model based on the MCMC method will only allow multivariate normal variables as predictors. Therefore, past TNF inhibitor exposure and geographic region will be re-coded as indicator variables. For past TNF exposure, this will be 0 for no past exposure and 1 for past TNF exposure. Similarly, for region, this will be 1 for subjects from Europe and 0 for all other subjects. The order for the covariates in the model will be as follows: region indicator variable (Europe = 1, North America = 0), past TNF exposure (Yes = 1, No = 0), Baseline value, and visit variables.
- Once the intermittent missing data are imputed, the monotone missing data will be imputed including covariates as defined above, based on the datasets created by the intermittent missing data MI. Since this dataset already has 100 imputed values at each visit, only 1 imputation will be performed.

Step 2

The dataset with the imputed results for each treatment arm will be combined into 1 complete dataset including each of the 100 imputations. If any imputed value is less than the lower limit of the allowable range for that parameter (as shown in Table 4–1), it will be changed to the lower limit of the range, and similarly for values higher than the allowable range. This dataset will be used to calculate the change from PA0008 Baseline variable where appropriate.

Table 4–1: Allowable ranges for continuous efficacy variables

Variable	Minimum	Maximum
MASES	0	13
PASI	0	72
LDI	0	NA
DAS28(CRP)	0.988[a]	NA
CRP[b]	0.08	NA
PsAID-9	0	10
SF-36 MCS	-3.33	80.09
SF-36 PCS	5.02	79.78
HADS-A	0	21
HADS-D	0	21
TJC	0	78
SJC	0	76
HAQ-DI	0	3
PtAAP	0	100
PhGADA	0	100
PGADA	0	100

CRP=high sensitivity C-reactive protein; DAS28(CRP)=Disease Activity Score 28 joint count C-reactive protein; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; HAQ-DI=Health Assessment Questionnaire - Disability Index; LDI=Leeds Dactylitis Index; LLOQ=lower limit of quantification; MASES=Maastricht Ankylosing Spondylitis Enthesitis Index; NA=not applicable; PASI=Psoriasis Area and Severity Index; PGADA=Patient's Global Assessment of Disease Activity; PhGADA=Physician's Global Assessment of Disease Activity; PsAID-9=Psoriatic Arthritis Impact of Disease-9; PtAAP=Patient's Assessment of Arthritis Pain; SF-36 MCS=Short Form 36-Item – Mental Component Summary; SF-36 PCS=Short Form 36-Item – Physical Component Summary; SJC=swollen joint count; TJC=tender joint count.

[a] For the purpose of the analysis, the actual minimum value will be set to the calculated value of 0.36*ln(CRP+1) +0.96 using the minimum CRP of 0.08mg/L.

[b] For the purpose of the MI any numerical CRP values obtained in PA0009 that were <0.16 mg/L will be substituted with half the lower limit of quantification (LLOQ) LLOQ from PA0008 (ie, 0.08 mg/L) prior to performing the MI. Subsequently any imputed values of <0.16mg/L will be replaced by the value of 0.08mg/L for the purpose of summaries based on imputed data. Listings will display the original result. Any CRP values of ≥500mg/L will be

set to missing prior to performing the MI procedure; the subsequently imputed CRP value will be included in the summary tables.

Step 3 (Excluding CRP)

The 100 imputed datasets 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 (median, minimum and maximum), Rubin's rules do not apply. Multiple imputation estimates will be computed by calculating arithmetic means of the estimates from the multiple repetitions of the imputation algorithm. Thus, for median, minimum and maximum the following approach will apply:

- The data will be summarized by treatment, visit and imputation and the summary statistics will be computed.
- Results will be summarized by taking the mean value of each summary statistic at each visit across all imputations.

The number of decimal places will remain the same as the original for display purposes (ie, if the mean was presented to 1 decimal place, the mean of the means will also be presented to 1 decimal place).

Step 3 (CRP only)

The CRP data will be presented using the geometric mean, 95% confidence interval (CI) for the geometric mean, median, Q1, Q3, minimum and maximum. The change from Baseline will be expressed as the ratio to Baseline in the summaries. The following approach will be applied:

- Following the MI procedure the ratio to Baseline will be calculated for any of the imputed values
- The natural logarithm of the absolute values and of the ratios to Baseline will be calculated
- The logged values will be summarized by treatment, visit and imputation
- The datasets will be combined using PROC MIANALYZE in order to get the mean and 95% CI estimates from the absolute values and ratios to Baseline (based on logged data) across imputations
- The estimates of the mean and 95% CI will be back-transformed to obtain the geometric mean and 95% CI on the original scale
- For the median, Q1, Q3, minimum and maximum the procedure outlined above for the other endpoints will be followed

As a sensitivity analysis, certain efficacy variables will be summarized based on observed data (see Section 8).

As a further sensitivity analysis for ACR and PASI responses, the response variables will be derived following MI of the individual components for ACR or following MI of the overall PASI score. The ACR and PASI responses will then be derived for each subject and each imputation (where each imputation is performed across all individual components for ACR) and the number and percentage of subjects with each ACR and PASI response in each imputation will be

calculated. The mean value (across imputations) for the percentage of subjects with each ACR or PASI response will be reported.

A similar approach will be followed for the calculation and summary of the number and percentage of subjects with normal HADS scores (defined as having HADS-D and HADS-A <8 at the same visit) based on the HADS-D and HADS-A values after MI.

Primary and sensitivity analyses are summarized in Table 4–2. All summaries presenting data following MI will include only visits from PA0009 EV onwards (although the MI procedure will incorporate data from both PA0008 and PA0009).

Table 4–2: Missing data handling

Variable	Type	Missing data handling approach		
		NRI	MI/MCMC (monotone regression)	OC
ACR20, 50, 70	Responder	P	S[a]	S
MASES	Continuous		P	S
LDI	Continuous		P	S
PASI75, 90, 100	Responder	P	S[a]	S
MDA	Responder	P		S
DAS28 (CRP)	Continuous		P	
CRP	Continuous		P	
PsAID-9	Continuous		P	
SF-36 PCS, MCS	Continuous		P	
HADS-A, HADS-D	Continuous		P	
Incidence of normal depression/anxiety status (using HADS)	Responder		P[a]	
TJC, SJC	Continuous		P	
HAQ-DI	Continuous		P	
PtAAP	Continuous		P	
PGADA	Continuous		P	
PhGADA	Continuous		P	

ACR=American College of Rheumatology 20, 50, 70% response criteria; CRP=high sensitivity C-reactive protein; DAS28(CRP)=Disease Activity Score 28 joint count C-reactive protein; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; HAQ-DI=Health Assessment Questionnaire - Disability Index; LDI=Leeds Dactylitis Index; LLOQ=lower limit of quantification; MASES=Maastricht Ankylosing Spondylitis Enthesitis Index; MCMC=Markov-Chain Monte Carlo; MDA=Minimal Disease Activity; MI=multiple imputation; NRI=nonresponder imputation; OC=observed case; P=primary method; PASI 75, 90, 100=Psoriasis Area and Severity Index 75%, 90% and 100%; PGADA=Patient's Global Assessment of Disease Activity; PhGADA=Physician's Global Assessment of Disease Activity; PsAID-9=Psoriatic Arthritis Impact of Disease-9; PtAAP=Patient's Assessment of Arthritis Pain; S=secondary method;

SF-36 MCS=Short Form 36-Item – Mental Component Summary; SF-36 PCS=Short Form 36-Item – Physical Component Summary; SJC=swollen joint count; TJC=tender joint count.

[a] Imputation method is applied on continuous data, and response variable is derived from the continuous data based on complete dataset.

In the event that the MI model fails to converge or will not run for other reasons (eg, data issues, data distribution), alternative approaches may be considered including LOCF and /or OC summaries as appropriate. For some efficacy endpoints, these approaches may be planned already as part of the existing analyses or sensitivity analyses, and therefore it may not be necessary in all cases to provide additional summaries.

4.2.2 Additional rules for handling missing data for derivation of PASI response

Supplementary supporting analyses will be performed for the PASI response in order to take into account missing PASI data during the study. PASI data are known to be missing for some subjects/visits due to an error in the original protocol schedule of events which stated that PASI would only be determined at a given visit if the BSA affected by psoriasis at that visit was ≥3%. The protocol was subsequently updated (Amendment 3) to correct the schedule of events such that PASI is assessed at all visits for subjects with BSA affected by psoriasis of ≥3% at PA0008 Baseline.

These supporting analyses will be performed in addition to those described in Section 4.2.1 and will utilize the BSA assessments to provide surrogate information regarding the PASI response. Two different approaches will be used in this regard:

- For any visit where the derived total PASI score is missing the subject will be considered as a PASI responder if the corresponding BSA assessment at the same visit is 0%. A BSA of 0% will therefore be considered to meet the criteria for PASI75, PASI90, and PASI100 responses.
- For any visit where the derived total PASI score is missing, the PASI response will be imputed using LOCF (based on OC data) only if the BSA has not worsened at any interim time point or the current time point compared to the last visit at which both PASI response and BSA were non-missing (including unscheduled/repeat assessments).

  For example, if the PASI score is missing at Visit 4 (Week 12), the response (PASI75, PASI90, or PASI100) at Visit 1 EV will be carried forward and used in the summary, if BSA at Visit 4 ≤BSA at Visit 1. If BSA at Visit 4 >BSA at Visit 1, the response will be left as missing.

  – If the data at the PA0009 EV are missing the LOCF will be taken from the last available assessment obtained in PA0008 (based on OC data).
  – The approach above will be followed regardless of the BSA value at the corresponding visit, ie, if the BSA=0% at the visit, the previous PASI response will be carried forward for each variable (PASI75, PASI90, and PASI100) and may be Yes or No.

For both approaches above, the rules will be applied to PA0009 data only and only for subjects in the FAS. In addition, this will be implemented only for subjects with BSA ≥3% at PA0008 Baseline.

4.2.3 Handling of missing data for adverse events

A complete date must be established to correctly identify the AE as treatment-emergent. For purposes of imputing missing components of partially reported start and stop dates for AEs, the algorithms listed below will be followed. Start and stop dates of AEs will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listings).

Partial or missing start dates for events recorded during PA0008 (including those which were ongoing at the start of PA0009) will be imputed using the imputed start date from the PA0008 database.

Imputation of partial AE start dates for events reported in PA0009 only will follow the rules below (treatment switching rules refer to PA0008 only and data were used directly from the PA0008 database):

- If only the month and year of the AE start date are specified, and the month and year of the start date of study medication in PA0009 are not the same as the month and year of the AE start date, and the subject did not switch treatment during that month and year, then use the 1st of the month of the AE start date.
- If only the month and year of the AE start date are specified, and the month and year of the start date of study medication in PA0009 are not the same as the month and year of the AE start date, and the subject switched treatment during the month and year of the AE start date, then use the date of treatment switch.
- If only the month and year of the AE start date are specified, and the month and year of the start date of study medication in PA0009 are the same as the month and year of the AE start date, then use the start date of study medication in PA0009 (regardless of treatment switching). If this results in a start date after a known end date use the 1st of the month of the AE start date.
- If only the year of the AE start date is specified, and the year of the start date of study medication in PA0009 is not the same as the year of the AE start date, and the subject did not switch treatment during the year of the AE start date, then use the 1st of January of the year of the AE start date.
- If only the year of the AE start date is specified, and the year of the start date of study medication in PA0009 is not the same as the year of the AE start date, and the subject switched treatment during the year of the AE start date, then use the date of treatment switch.
- If only the year of the AE start date is specified, and the year of the start date of study medication in PA0009 is the same as the year of the AE start date, then use the start date of study medication in PA0009 (regardless of treatment switching). If this results in a start date after a known end date use the 1st of January of the year of the AE start date.
- If only the year and day of the AE start date are specified, and the year of the start date of study medication in PA0009 is not the same as the year of the AE start date, then use January of the year of the AE start date together with the known day.
- If only the year and day of the AE start date are specified, and the year of the start date of study medication in PA0009 is the same as the year of the AE start date, then use the start month of study medication in PA0009 together with the known day.

  - If this results in a start date after a known end date use January of the year of the AE start date together with the known day.
  - If this results in a start date prior to the start date of study medication in PA0009 (in the imputed month) the event will be considered to be treatment-emergent.

- If the AE start date is completely unknown and the AE stop date is unknown or not prior to the start date of study medication in PA0009, then use the start date of study medication in PA0009.

Imputation of partial AE stop date:

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

In the event of ambiguity or incomplete data which makes it impossible to determine whether the AE was treatment-emergent, the AE will be considered treatment-emergent. For subjects who may have died during the study, imputed dates will be truncated at the date of death.

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

If the seriousness of an AE is unknown, no imputation will be performed. Such events will therefore be excluded from any listings or summaries of SAEs.

4.2.4 Handling of missing data for prior and concomitant medication

A complete start and stop date must be established to correctly identify the medication as prior or concomitant. For purposes of imputing missing components of partially reported start and stop dates for medications, the algorithms listed below will be followed. Start and stop dates of medications will be displayed as reported in the subject data listings (ie, no imputed values will be displayed in data listings).

Partial start dates for medications which started during PA0008 and were ongoing at the start of PA0009 will be taken from the PA0008 database based on the dedicated eCRF page for imported medications in PA0009.

Imputation of all partial start dates for medications (including those reported on the 'imported' page) will follow the rules below (treatment switching rules refer to PA0008 only):

- If only the month and year of the medication start date are specified, and the month and year of the start date of study medication in PA0009 are not the same as the month and year of the medication start date, and the subject did not switch treatment during that month and year, then use the 1st of the month of the medication start date.
- If only the month and year of the medication start date are specified, and the month and year of the start date of study medication in PA0009 are not the same as the month and year of the medication start date, and the subject switched treatment during the month and year of the medication start date, then use the date of treatment switch.

- If only the month and year of the medication start date are specified, and the month and year of the start date of study medication in PA0009 are the same as the month and year of the medication start date, then use the start date of study medication in PA0009 (regardless of treatment switching). If this results in a start date after a known end date use the 1st of the month of the medication start date
- If only the year of the medication start date is specified, and the year of start date of study medication in PA0009 is not the same as the year of the medication start date, and the subject did not switch treatment during the year of the medication start date, then use the 1st of January of the year of the medication start date.
- If only the year of the medication start date is specified, and the year of the start date of study medication in PA0009 is not the same as the year of the medication start date, and the subject switched treatment during the year of the medication start date, then use the date of treatment switch.
- If only the year of the medication start date is specified, and the year of the start date of study medication in PA0009 is the same as the year of the medication start date, then use the start date of study medication in PA0009 (regardless of treatment switching). If this results in a start date after a known end date use the 1st of January of the year of the medication start date.
- If only the year and day of the medication start date are specified, and the year of the start date of study medication in PA0009 is not the same as the year of the medication start date, then use January of the year of the medication start date together with the known day.
- If only the year and day of the medication start date are specified, and the year of the start date of study medication in PA0009 is the same as the year of the medication start date, then use the start month of study medication in PA0009 together with the known day.
  - If this results in a start date after a known end date use January of the year of the medication start date together with the known day.
  - If this results in a start date prior to the start date of study medication in PA0009 (in the imputed month) the medication will be considered to be concomitant.
- If the medication start date is completely unknown and the medication stop date is unknown or not prior to the start date of study medication in PA0009, then use the start date of study medication in PA0009.

Imputation of partial medication stop dates:

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

In the event of ambiguity or incomplete data which makes it impossible to determine whether the medication was prior or concomitant, the medication will be considered concomitant. For

subjects who may have died during the study, imputed dates will be truncated at the date of death.

There will be no imputation of any other missing data for concomitant medications.

4.2.5 Handling of partial treatment end dates

The date of last study drug administration in PA0009 may be completely unknown (eg, if the subject is lost to follow-up) or partially known. In the latter case, it is possible to enter a known month and year into the database but to leave the day as missing (ie, YYY-MMM-XX) on the study termination page of the eCRF.

Missing or partial treatment end dates will be handled according to the following rules:

- For subjects for whom the treatment end date is completely missing on the study termination page, the date of last dose in PA0009 will be the date/time of the last known dose as reported on the study medication administration page of the eCRF.
- For subjects for whom the treatment end date is partially missing (ie, only the month and year are known) the following rules will be applied:
  - The treatment end date will be imputed as date of last known study medication administration + 28 days (ie, equivalent to the dosing interval), assuming this gives an imputed date in the known month and year
  - If the above rule results in an imputed date that is not in the known month and year the following will apply:
    - If the date of last known study medication +28 days results in a month PRIOR to the month of the partial date, then the imputed date of last dose will be set to the 1st of the known month ie, YYYY-MMM-01.
    - If the date of last known study medication +28 days results in a month AFTER the month of the partial date, then the imputed date of last dose will be set to the last day of the known month eg, YYYY-MM-31 (modified according to the calendar month).

In the listings the date of last study drug administration will be displayed as received in the data ie, without imputation.

4.3 Interim analyses and data monitoring

No formal interim analysis is planned for this study. Additional data cuts may be prepared following regulatory requests or for publication purposes.

A snapshot of data will be taken after the final subject has reached PA0009 Week 60 and used to create displays in this SAP, based on one year's exposure in the study. No change to study conduct is expected as a result.

4.4 Multicenter studies

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

Centers will be grouped into the geographic regions of North America and Europe as described in Section 3.8 for use as a covariate in statistical analyses and for subgroup analyses.

4.5 Multiple comparisons/multiplicity

Not applicable.

4.6 Use of an efficacy subset of subjects

Not applicable.

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

Subgroup summaries of the efficacy variables of ACR20, ACR50, ACR70 and PASI75 and PASI90 response at PA0009 Week 48 will be performed. The following subgroups will be used:

- Geographic region at PA0008 Baseline (North America, Europe), as defined in Section 3.8.
- Previous (past) TNF inhibitor agent exposure in PA0008. The value in the PA0008 database for past anti-TNF therapy (as collected on the eCRF) will be used for PA0009, without additional derivation.
- Disease duration at start of PA0008 (<2 years, ≥2 years). The value in the PA0008 database will be used for PA0009, without additional derivation.
- Concomitant DMARD status at start of PA0008 (yes, no). The value in the PA0008 database will be used for PA0009, without additional derivation.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

Subject disposition (date of first and last subject visit, number of subjects included in each analysis set [ES, SS, and FAS]) will be presented overall, by region and for each site, and by treatment group at completion of PA0008 and overall for the ES.

The number and percentage of subjects in each analysis set (ES, SS and SS Sub-populations, and FAS) will be presented by treatment group at completion of PA0008 and overall.

The number and percentage of subjects who started, completed and discontinued the study, along with the primary reason for discontinuation will be presented by treatment group at completion of PA0008 and overall for the SS (a subject will be considered to have completed the study if they attended Visit 13 [Week 104]). For the purposes of the summaries the data will be taken directly from the eCRF page for study termination.

The number and percentage of subjects who started, completed and discontinued study medication, along with the primary reason for medication discontinuation will be presented by treatment group at completion of PA0008 and overall for the SS (a subject will be considered to have completed study treatment if they received a dose at Visit 12 [Week 100]). For the purposes of the summaries the data will be taken directly from the eCRF page for study medication discontinuation.

For any subjects where the data on the study termination and study medication discontinuation eCRF pages are inconsistent, the data reported on the study termination page will be considered

as primary ie, if a subject is reported as discontinuing from the study, they will be regarded as discontinuing study medication as well (regardless of whether this is reported in the eCRF).

Discontinuations due to AEs will be summarized by treatment group at completion of PA0008 and overall for the SS.

Subjects who did not meet the eligibility criteria and the inclusion and/or exclusion criteria not met will be listed for the ES.

Subject disposition (subject status, date of informed consent, date of enrollment into PA0009, treatment sequence across PA0008 and PA0009, treatment received at the completion of PA0008, start and end date/time and relative days of study medication in PA0009, date of premature study discontinuation and date of final contact) will be listed for the ES. Days relative to the start date of study medication in PA0008 and to the start of study medication in PA0009 will be included for the end date of study medication.

Subject inclusion in each analysis set will be listed for the ES.

Subjects excluded from at least 1 analysis set, with reason for exclusion, will be listed for the ES. Subjects who were excluded from the SS will have a reason of 'Subject did not receive at least one dose of study medication during PA0009', and subjects who were excluded from the FAS will have a reason of 'Subject did not have a valid measurement of at least one efficacy variable after PA0009 study entry'.

Study and treatment discontinuation reasons and the name of any subsequent treatment will be listed for the ES. Total days on study medication from the start date in PA0008 and from the start date in PA0009 will be included. These will be calculated as described below:

$$Total\ days\ on\ study\ medication\ from\ start\ date\ in\ PA0009 = (Date\ of\ last\ dose\ in\ PA0009 - Date\ of\ first\ dose\ in\ PA0009) + 1 \quad (6)$$

$$Total\ days\ on\ study\ medication\ from\ start\ date\ in\ PA0008 = (Date\ of\ last\ dose\ in\ PA0009 - Date\ of\ first\ dose\ in\ PA0008) + 1 \quad (7)$$

For the total days on study medication in PA0008 this will be calculated from the first dose of any medication received regardless of treatment assignment.

Visit dates, including the day relative to the start of study medication in PA0008 and in PA0009, will be listed for the ES.

5.1.1 Impact of COVID-19

A listing of all visits affected by COVID-19 will be presented based on the Enrolled Set including the visit, date of visit, relationship to COVID-19, impact category and a narrative (short description) of the event. This data will be summarized by treatment group at completion of PA0008, and overall for the ES for the following:

- Impact of COVID-19 for any reason
- Impact of COVID-19 for any reason by country

In addition, in order to assess the potential impact of COVID-19 on the collection and reporting of efficacy data a separate listing and summary will be presented to display missing data and data collected via an alternative modality (eg, phone, video call). For the purpose of these displays, missing data will be presented only for visits affected by COVID-19 (as reported on the dedicated eCRF page) ie, missing data at other visits and for other reasons will not be included.

The following efficacy assessments may be collected remotely:

- HADS
- HAQ-DI
- SF-36
- PGADA
- PtAAP
- PsAID-9

For visits conducted remotely (as reported on the dedicated eCRF page), it is not possible to assess MASES, PhGADA, BSA, PASI, LDI, TJC or SJC, and therefore these assessments will be missing at the specified visit. In addition, for any missed visit or a visit conducted remotely, the CRP assessment will also be missing. Such assessments will be considered to be missing as a result of COVID-19. For these visits, it will therefore not be possible to assess DAS28(CRP) and may not be possible to classify the subject as an ACR responder or nonresponder.

A listing will be presented showing each impacted visit based on the FAS. This will include the planned visit, the visit date, and details of the assessments conducted remotely and/or those missing as a result of COVID-19.

These data will be presented in a summary table by treatment group at completion of PA0008 and overall for the FAS.

For both the listing and the summary table, only visits at which efficacy assessments are scheduled will be included.

5.2 Protocol deviations

The number and percentage of subjects with an important protocol deviation and with each category of important protocol deviation (as described in Section 3.4) will be presented by treatment group at completion of PA0008 and overall for the ES.

Important protocol deviations, including deviation type and description, will be listed for the ES.

A separate listing of COVID-19 related important protocol deviations will be presented, based on the ES. COVID-19 related important deviations will be identified by the prefix of 'COVID' in the deviation verbatim text.

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Demographic variables (age [at time of informed consent], gender, racial group, ethnicity, weight, height, body mass index [BMI], country, and geographic region) will be summarized by treatment group at completion of PA0008 and overall for the SS.

One summary table will be produced for PA0008 Baseline values. Age, sex, weight and BMI will be collected at EV or recalculated in PA0009 and will be listed only.

Age and BMI will be summarized as continuous and as categorical variables:

Age will be categorized as:

- ≤18, 19 to <65, ≥65 years (clinicaltrials.gov requirement).
- 18-<65, 65 to <85, ≥85 years (EudraCT requirement).
- 18 to <45, ≥45 to <65, ≥65 years (bimekizumab program conventions).

BMI (kg/m^2) is calculated based on the height (in m) and the weight (in kg) using the formula:

$$BMI = \frac{weight}{height^2} \quad (8)$$

Even if available in the database, BMI will be re-calculated. BMI is rounded to 1 decimal place. BMI will be categorized as follows: <25, 25 to <30, ≥30 kg/m^2.

Demographic data, including PA0008 Baseline and PA0009 EV values for the repeated variables, will be listed for the ES.

6.2 Other baseline characteristics

PsA history (date of first diagnosis, time since first diagnosis of PsA [at time of enrolment in PA0008 and at time of enrolment in PA0009], age at first diagnosis date, and PsA subtype [polyarticular – symmetric arthritis, oligoarticular – asymmetric arthritis, distal interphalangeal, joint predominant, spondylitis predominant, arthritis mutilans]) will be summarized by treatment group at completion of PA0008 and overall for the SS.

Time since first diagnosis of PsA will be summarized as a continuous variable and as a categorical variable. Time since first diagnosis of PsA at time of enrolment in PA0008 will be taken from the PA0008 database. Time since first diagnosis of PsA at time of enrolment in PA0009 will be calculated as below, where date of diagnosis will be taken from the PA0008 database:

$$\begin{aligned} &Time\ since\ first\ diagnosis \\ &\quad = date\ of\ informed\ consent\ in\ PA0009 \\ &\quad - \ date\ of\ first\ diagnosis\ in\ PA0008 \end{aligned} \quad (9)$$

Time since first diagnosis for each study will be categorized as: <2, ≥2 years.

Age at first diagnosis will be taken from the PA0008 database.

PsA history will be listed for the ES.

The following Baseline characteristics will be summarized by treatment group at completion of PA0008 and overall for the SS:

- TJC.
- SJC.
- CRP.
- Rheumatoid factor (Positive, Negative).
- Anti-cyclic citrullinated peptide (CCP) antibodies (Positive, Negative).
- NSAID therapy prior to first dose in PA0008 (yes, no). The value in the PA0008 database for past NSAID therapy (as collected on the eCRF) will be used for PA0009, without additional derivation.
- Anti-TNF therapy prior to first dose in PA0008 (yes, no). The value in the PA0008 database for past anti-TNF therapy (as collected on the eCRF) will be used for PA0009, without additional derivation.
- Psoriasis BSA category (<3%, ≥3% to <10%, ≥10%).
- Nail psoriasis (yes, no).
- Dactylitis (yes, no).
- Enthesitis (yes, no).
- Current number of NSAID therapies (0, 1, 2, ≥3).
- Current synthetic DMARDs (methotrexate [MTX], sulfasalazine, hydroxychloroquine) (yes, no).

One summary table will be produced for PA0008 Baseline values and another for PA0009 EV values. Rheumatoid factor, anti-CCP antibodies, nail psoriasis, dactylitis and NSAID and anti-TNF therapy prior to first dose in PA0008 will be based on data collected in PA0008 and will be included in the PA0008 Baseline table only.

TJC, SJC, CRP, psoriasis BSA and current NSAID and synthetic DMARD therapy will be included in both tables. CRP values at PA0009 EV will be taken from the Week 48 record in the PA0008 database. For the summary of PA0009 EV data, current NSAID and synthetic DMARD therapy are defined as medications that are ongoing at the PA0009 EV, or that started on the date of the PA0009 EV. This does not include medications that were stopped on the date of the PA0009 EV.

Baseline characteristics, including PA0008 Baseline and PA0009 EV values for the repeated variables, will be listed for the ES.

6.3 Medical history and concomitant diseases

Medical history and ongoing medical conditions collected prior to the start date of study medication in PA0008 and any additional conditions collected prior to the start date of study medication in PA0009 will be summarized together. The number and percentage of subjects

with any condition, and with each condition in each MedDRA SOC and PT, will be presented by treatment group at completion of PA0008 and overall, for the SS.

Medical history and ongoing medical conditions, including the start date and end date (or ongoing if applicable), will be listed for the SS. The listing will indicate whether the condition was reported in PA0009.

A glossary of all medical history conditions including the reported term, PT, and SOC will also be presented.

The number and percentage of subjects with a history of each category of extra-articular manifestations (uveitis, inflammatory bowel disease [IBD], psoriasis, peripheral arthritis, enthesitis, dactylitis) will be summarized by treatment group at completion of PA0008 and overall, for the SS, based on data collected at the PA0009 EV. The number and percentage of subjects with an occurrence of extra-articular manifestations (uveitis, IBD) post-PA0009 EV will be summarized by treatment group at completion of PA0008 and overall, for the SS. Extra-articular assessments will be listed for the SS.

6.4 Past, prior and concomitant medications

Only medications that were ongoing at the end of PA0008 or were started during PA0009 will be reported.

Concomitant medications are medications taken on at least 1 day in common with the dosing period of PA0009 (as defined in Section 3.2.2). A medication is classed as concomitant if the start date is no later than the end date of study medication in PA0009 + 28 days, and the stop date is either missing or on or after the start date of study medication in PA0009. This includes medications that started prior to dosing in PA0009 and continued after.

For the purposes of the analysis, past medications are medications that started and stopped prior to dosing in PA0008. This includes past TNF therapy as used for subgroup analyses, MI modelling and Baseline characteristics and past NSAID therapy (for Baseline characteristics).

Missing or partial medication start and stop dates will be imputed as described in Section 4.2.3. Imputations will be performed before calculation of relative study days and classification as concomitant.

The number and percentage of subjects taking concomitant medications will be summarized by anatomical therapeutic chemical (ATC) class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and PT in separate tables for PsA concomitant medications and other concomitant medications, by treatment group at completion of PA0008, and overall for the SS. The complete list of PsA concomitant medications is included in the protocol Section 7.8.1 and includes: NSAIDS, corticosteroids, DMARDs, (MTX, sulfasalazine, leflunomide and apremilast), and joint injections.

PsA concomitant medications will be identified following the procedure outlined in Section 6.5.

All medications reported in PA0009, including flags to identify concomitant, PsA and rescue medications, start and stop days relative to the start date of study medication in PA0008, and start and stop days relative to the start of study medication in PA0009, will be listed for the ES.

A glossary of all medications including the Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3) PT and reported term will also be presented, based on the ES.

6.5 Prohibited medication and rescue therapy

The following medication categories will be identified:

- Rescue medications as defined below. Subjects in the category 'Any concomitant rescue therapy in PA0009' will be considered SS Sub-population 2 and other subjects will be considered SS Sub-population 1. Rescue medications will be identified in the study database using the flag collected in the eCRF.
- DMARDs to identify subgroups/covariates.
- PsA medications as defined in the protocol Section 7.8.1 (this includes DMARDs).
- Prohibited medications.

Rescue medication, DMARDs, and PsA medications will be classified into subcategories for reporting purposes. These will be reviewed and confirmed by the study physician in order to ensure that the classifications are correct.

The number and percentage of subjects who receive the following categories of rescue medication will be summarized by treatment group at completion of PA0008 and overall for the SS.

- Any rescue medication in PA0009 that is classified as a concomitant medication as defined in Section 6.4.
- NSAID at PA0009 EV.
- No NSAID at PA0009 EV.
  - No NSAID at PA0009 EV and initiate NSAID [but not Cox-2 inhibitors] in PA0009 (only the initiation of NSAIDs that are classified as concomitant medications as defined in Section 6.4 will be included).
  - No NSAID at PA0009 EV and initiate Cox-2 inhibitors in PA0009 (only the initiation of Cox-2 inhibitors that are classified as concomitant medications as defined in Section 6.4 will be included).
- Use of MTX, sulfasalazine, leflunomide, apremilast or DMARD combinations in PA0009 (with the exception of MTX and leflunomide together). Only concomitant medications will be included as defined in Section 6.4. For the programming of combination medications the following rules will be applied:
  - If any combination of DMARDs is taken at least once during the study the subject will be counted in the 'combination of DMARDs' main category

- If LEF and MTX are taken in combination (with or without another DMARD) at least once during the study the subject will be counted in the 'combination of LEF and MTX' subcategory
- If LEF is taken in combination with another DMARD (not MTX) at least once during the study the subject will be counted in the 'combination of DMARDs (except LEF and MTX together)' subcategory
- If MTX is taken in combination with another DMARD (not LEF) at least once during the study the subject will be counted in the 'combination of DMARDs (except LEF and MTX together)' subcategory
- If any other combination of DMARDs is taken (not including LEF or MTX) at least once during the study the subject will be counted in the 'combination of DMARDs (except LEF and MTX together)' subcategory
- For all the above, medications taken in combination will be defined as those with at least one concomitant study day in common (after imputation of partial dates as described in Section 4.2.4) and both classified as concomitant medications
- If more than 1 DMARD medication is taken but the dates are not overlapping, these will be counted in both the relevant individual categories in the table only (eg, LEF and MTX individual categories)

Subjects will be counted in all applicable categories and subcategories in the table ie, if a subject receives both LEF and apremilast and these have at least 1 study day in common, these will be counted in both the combination rows and the individual medication rows. Subjects will be counted only once in each category.

- Intra-articular corticosteroid in PA0009 that is classified as a concomitant medication as defined in Section 6.4.
- Oral corticosteroid in PA0009 that is classified as a concomitant medication as defined in Section 6.4.
- Analgesics in PA0009 that are classified as concomitant as defined in Section 6.4.

Rescue therapy category and medication name, start date, and day relative to start of study medication in PA0008 and PA0009 will be listed for the SS.

PRN analgesic and PRN opioid analgesic use within 24 hours prior to study visits will be listed for the ES, based on the dedicated eCRF page for prohibited medications.

6.6 Concomitant medical procedures and procedure history

A listing of concomitant medical procedures and a separate listing of procedure history will be presented for the ES.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

Compliance will be summarized using the number of doses received relative to the number of doses expected:

$$Percent\ treatment\ compliance = 100 * \frac{\text{Number of doses received}}{\text{Number of doses expected}} \quad (10)$$

where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes treatment 26 doses are expected (EV and every fourth week afterwards until PA0009 Week 100). If a subject discontinues early, then the number of expected doses is based on the time of study discontinuation relative to the planned dosing visits (taking into account the permitted visit window). If the date of study discontinuation is missing the final contact date (as reported on the eCRF) will be used instead.

A summary of percent treatment compliance, both continuous and categorized as ≤75% and >75%, will be provided by treatment group at completion of PA0008 and overall for the SS.

Treatment compliance will be listed for the SS. A separate listing of study medication administration (including injection dates and times, kit numbers, who performed the injection and the location of the injection) will be presented.

8 EFFICACY ANALYSES

Missing efficacy data will be imputed as described in Section 4.2.1 prior to reporting. As a sensitivity analysis, summaries will be repeated based on non-imputed (OC) data for the following variables:

- ACR20, ACR50 and ACR70 response relative to PA0008 Baseline at each visit in PA0009.
- PASI75, PASI90 and PASI100 response relative to PA0008 Baseline at each visit in PA0009.
- MDA at each visit in PA0009.
- Change from PA0008 Baseline in MASES at each visit in PA0009.
- Change from PA0008 Baseline in LDI at each visit in PA0009.

A further sensitivity analysis will be performed for ACR20, ACR50 and ACR70, PASI75, PASI90 and PASI100 responses relative to PA0008 Baseline at each visit. The response endpoint will be re-derived and summarized based on the mean value (across multiple imputations) of the ACR component scores or PASI total score after imputation for missing data.

Efficacy variables will be summarized and listed (including individual raw data and derived domain and total scores, where applicable) for the FAS. Summaries of MASES will be restricted to subjects with a MASES >0 at PA0008 Baseline, of LDI will be restricted to subjects with a LDI >0 at PA0008 Baseline, and of PASI responses will be restricted to subjects with a BSA affected by psoriasis of ≥3% at PA0008 Baseline. Maintenance of response summaries will be restricted to subjects with a response at PA0008 Week 12 for the specific endpoint (where response at PA0008 Week 12 is taken directly from the PA0008 datasets).

Responder variables (eg, ACR20 response) will be derived relative to the PA0008 Baseline and summarized using n and percentage at each visit, by treatment group at completion of PA0008 and overall.

Maintenance of response will be assessed for ACR20, ACR50, ACR70, PASI75, PASI90 and PASI100. The responses will be derived relative to PA0008 Baseline and summarized using n and percentage at each post-PA0008 Baseline visit, by treatment sequence across PA0008 and PA0009. These summaries will therefore include PA0008 Week 2, 4, 8, 12, 16 (for ACR only), 20 (for ACR only), 24, and 36 and PA0009 EV [PA0008 Week 48], Week 12, 24, 36, 48, 60, 72, 84, 96, 100, and 104, for subjects who were responders at PA0008 Week 12.

Absolute and change from PA0008 Baseline for all continuous efficacy variables will be summarized descriptively by visit, by treatment group at completion of PA0008, and overall.

In the event that the MI model fails to converge or will not run for other reasons, alternative approaches may be considered as described in Section 4.2.1 and additional outputs will be provided. The planned MI tables will be retained in the final delivery outputs with the following text included in the table body: 'Multiple imputation procedure was not possible to perform due to insufficient data and/or data distribution issues'.

8.1 Derivation of efficacy variables

Derived efficacy variables at PA0008 Baseline will be taken from the PA0008 database. Derivations described below will only be performed for data in the PA0009 database (which includes PA0008 Week 48 relabeled as PA0009 EV).

For composite endpoints, component assessments will be combined based on the visit assignment following any mapping as described in Section 3.5. Assessments from the same assigned visit will be used, regardless of actual assessment date.

8.1.1 78/76-joint evaluation for ACR response

The following joints are assessed for tenderness:

- Temporomandibular joints (x2)
- Sternoclavicular joints (x2)
- Acromioclavicular joints (x2)
- Shoulder joints (x2)
- Elbow joints (x2)
- Wrist joints (x2)
- Carpometacarpal joints of the thumb (x2)
- Metacarpophalangeal (MCP) joints of the hands (x10)
- Proximal interphalangeal (PIP) joints of the hands (x8) and interphalangeal (IP) joints of the thumbs (x2)
- Distal interphalangeal (DIP) joints of the hands (x8)
- Hip joints (x2)
- Knee joints (x2)
- Talotibial (ankle) joints (x2)

- Tarsal joints (x2)
- Metatarsophalangeal (MTP) joints of the feet (x10)
- PIP joints of the feet (x8) and IP joints of the big toes (x2)
- DIP joints of the toes (x8)

All, except for the hips, are assessed for swelling.

The swelling and tenderness grading criteria are summarized in Table 8–1 .

Table 8–1: Swelling and tenderness grading criteria

Grade	Swelling response (76)	Tenderness response (78)
0	None	Not tender
1	Detectable synovial thickening with or without loss of bony contours, or bulging synovial proliferation with or without cystic characteristics	Positive response to questioning (tender), spontaneous response elicited (tender and winced) or withdrawal by subject on examination (tender, winced, and withdrew)

Table 8-2 summarizes the joint categorization and derived tenderness and swelling categories at each visit.

Table 8-2: Joint categorization and derived tenderness and swelling

Joint Category		Swelling category	Tenderness category
-1	Missing/not recorded.	Missing	Missing
0	No symptoms.	0	0
1	Pain/tender only.	0	1
2	Swollen only.	1	0
3	Pain/tender and swollen.	1	1
4	Permanently not evaluable.	Missing	Missing
5	Temporarily not evaluable.	Missing	Missing
6	Injection.	1	1

For the purposes of calculating total tender and swollen joint counts, joints will be handled as follows:

- Category 4 joints will be considered missing for both tender and swollen joint counts at the visit at which the category was recorded and all subsequent visits. Joints in category 4 at any

time in PA0008 will be considered missing for both tender and swollen joint counts at all visits in PA0009.

- Category 6 joints will be considered tender and swollen at the visit at which the category was recorded and subsequent visits up to 364 days following the date of the visit. Joints that were in category 6 in PA0008 will be considered tender and swollen at all PA0009 visits up to 364 days following the date of the assessment in PA0008.

The TJC and SJC are weighted joint counts. If there are missing observations in the tender or swollen joint assessments, then the remaining observations will be assessed and weighted by the number of the assessed joints:

$$SJC = n * \sum_{i=1}^{n} SJ \Big/ \sum_{i=1}^{n} AJ \quad (11)$$

$$TJC = n * \sum_{i=1}^{n} TJ \Big/ \sum_{i=1}^{n} AJ \quad (12)$$

where n is the total number of joints, SJ is a swollen joint, TJ is a tender joint and AJ is an assessed joint.

If more than 50% of the planned tender joint assessments (ie, more than 39 assessments) or more than 50% of the planned swollen joint assessments (ie, more than 38 assessments) are missing at a visit, then the TJC or SJC will be set to missing for that visit.

8.1.2 28-joint evaluation for determination of Disease Activity Score-28 (C-reactive Protein)

The following 28 joints will be used for calculation of the DAS28(CRP).

- Shoulder joints (x2)
- Elbow joints (x2)
- Wrist joints (x2)
- MCP joints of the hands (x10)
- PIP joints of the hands (x8) and IP joints of the thumbs (x2)
- Knee joints (x2)

Joints will be categorized and handled in the same way as for the 76/78-joint evaluation (Section 8.1.1).

8.1.3 Patient's Global Assessment of Disease Activity

Subjects will complete the PGADA using a visual analog scale (VAS) where 0mm is "very good, no symptoms" and 100mm is "very poor, severe symptoms". The subject should be asked to consider both joint and skin components in their response to this question.

8.1.4 Physician's Global Assessment of Disease Activity

The Investigator will complete the PhGADA by assessing the overall status of the subject with respect to their PsA signs and symptoms and functional capacity (considering both joint and skin components) using a VAS where 0mm is "very good, asymptomatic and no limitation of normal activities" and 100mm is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities".

8.1.5 Patient's Assessment of Arthritis Pain

The PtAAP VAS is part of the ACR core set of measures in arthritis (Felson et al, 1993). Subjects will assess their arthritis pain using a VAS where 0mm is "no pain" and 100mm is "most severe pain".

8.1.6 Health Assessment Questionnaire-Disability Index Score

The HAQ-DI contains 20 items divided into 8 domains that measure: dressing and grooming (2 items), arising (2 items), eating (3 items), walking (2 items), hygiene (3 items), reach (2 items), grip (3 items), and common daily activities (3 items). Subjects are required to indicate the degree of difficulty they have experienced in each domain in the past week on a 4-point scale that ranges from 0 (without difficulty) to 3 (unable to do).

Each category is given a score by taking the maximum score of each question (the question in each category with the highest score is the score for that category).

If the maximum score equals 0 or 1, but a device related to that category is used, or help from another person is provided for the category, then the category score is increased to 2. If the category score is already a 2, and a device related to that category is used, or help from another person is provided for the category, the score for that category remains 2.

The association of each aid and device with the category scores is shown in Table 8-3. The use of devices classed as 'Other' will not be accounted for in the final score.

Table 8-3: Aid or device associated with health assessment questionnaire-disability index domain

[redacted]

If all questions within a given category are unanswered, no score will be provided for that category (this rule applies even if aids and devices are non-missing).

The HAQ-DI score (range 0 to 3) will be calculated by dividing the sum of the highest score in each category (0 to 24) by the number of categories with at least 1 question answered. If fewer than 6 categories have responses, no HAQ-DI score will be calculated. A lower HAQ-DI score indicates an improvement in function.

8.1.7 High-sensitivity C-reactive protein levels

Note that high sensitivity C-reactive protein is referred to as CRP throughout this SAP. CRP levels will be analyzed by the central laboratory.

Due to a change in laboratory vendor between PA0008 and PA0009, CRP values from the PA0009 laboratory have been calibrated to match those from the PA0008 laboratory, and these values will be used for all CRP summaries and listings.

In PA0008, the LLOQ was 0.16mg/L; however, in PA0009, it was possible to measure concentrations below this value and report these as a numeric result. The LLOQ in PA0008 will therefore be applied to the PA0009 data in order to retain consistency in reporting across the studies. Thus, numeric values of less than 0.16mg/L (<0.16mg/L) in PA0009 will be imputed with half the LLOQ from PA0008 (ie, 0.08mg/L) prior to summary reporting or any derivation of composite parameters. The original values will be included in the listing.

Any CRP values ≥500mg/L will be set to missing prior to performing the MI procedure (Table 4–1) as these are considered to be extreme outliers.

CRP values at PA0008 Baseline and PA0009 EV will be taken from the PA0008 database (Baseline and Week 48 records respectively).

8.1.8 American College of Rheumatology Response Criteria

ACR20 response is defined as at least a 20% improvement (decrease) from PA0008 Baseline values for each of the following:

- TJC (based on 78 joints).
- SJC (based on 76 joints).
- At least 3 of the 5 remaining core set measures:
  - Disease activity as assessed by PGADA.
  - Disease activity as assessed by PhGADA.
  - Pain as assessed by PtAAP.
  - Physical function as assessed by the HAQ-DI.
  - Acute phase response as assessed by the CRP.

ACR response will be assessed using component assessments from the same analysis visit, ie, after applying any visit mapping as outlined in Section 3.5.

The following rules will be applied:

- For component scores with a Baseline value of 0, the percentage improvement is not calculable and will be considered as not having met the criteria for improvement at each visit. This will be applied and considered to be part of the OC analysis.
- In the case of partial data at a specific visit, if there are sufficient data to calculate a response eg, if results are available for TJC, SJC and at least 3 of the remaining core set assessments and these fulfil the criteria for percentage improvement (eg, 20% improvement for ACR20), this subject will be included in the summary of OC results as an ACR20 responder at the specific visit.
- Similarly, if there are sufficient data to calculate nonresponse regardless of missing data, this subject will be included in the summary of OC results as a nonresponder at the specific visit.
- For all non-missed visits, if it is not possible to determine response or nonresponse due to missing component scores, this subject will be excluded from the OC analysis at the specific visit, and regarded as a nonresponse in the NRI analysis.

Further details regarding these calculation algorithms and rules for handling missing components are provided in Section 12.1.

ACR50 and ACR70 are defined similarly, using a 50% or 70% improvement from Baseline, respectively. An ACR70 responder at a given visit is therefore also an ACR50 and an ACR20 responder.

8.1.9 Body surface area affected by psoriasis

The BSA palm method will be used for the evaluation of BSA affected by psoriasis. The subject's hand, including the palm, fingers, and thumb, is used as the reference point for measuring how much of their skin is affected by psoriasis, representing roughly 1% of the body's surface. The full and regional BSA percentage affected will be calculated as multipliers of the percentage of the palm affected as follows:

- Head and neck=10% (10 palms)
- Upper extremities=20% (20 palms)
- Trunk=30% (30 palms)
- Lower extremities=40% (40 palms)
- Total BSA=100% (100 palms).

8.1.10 Psoriasis Area and Severity Index Response

The PASI is the most commonly used and validated assessment for grading the severity of psoriasis in clinical studies (Feldman, 2004). The PASI quantifies the severity and extent of the disease and weights these with the percentage of BSA involvement.

The body is divided into 4 sections as described in Table 8-4. Each of these sections is scored by itself, and then the 4 scores are combined into the final PASI.

For each section, the percent of area of skin affected (A), is estimated and then transformed into a grade from 0 to 6:

– 0: 0% of area affected.

- 1: < 10% of area affected.
- 2: 10-<30% of area affected.
- 3: 30-<50% of area affected.
- 4: 50-<70% of area affected.
- 5: 70-<90% of area affected.
- 6: ≥90% of area affected.

Table 8-4: Body areas for calculation of psoriasis area and severity index

Body area	Details of area	BSA	Degree of involvement of body area[a]
Head (h)	Face, back of head	10%	0 to 6
Upper limbs (u)	Left, right, upper lower, flexor surface, extensor surface	20%	0 to 6
Trunk (t)	Front, back, groin	30%	0 to 6
Lower limbs (l)	Left, right, upper lower, flexor surface, extensor surface, including buttocks	40%	0 to 6
Total		100%	

BSA =- body surface area.
[a] Where 0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6= ≥90% affected.

Within each body area, the severity is estimated by 3 clinical signs: redness (R), thickness (T), and scaliness (S) (each on a 5-point scale: 0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked). The PASI is a measure of the average redness, thickness, and scaliness of the psoriatic skin lesions, multiplied by the involved psoriasis area score of the respective section, and weighted by the percentage person's skin for the respective section:

$$PASI = 0.1 * Ah * (Rh + Th + Sh) + 0.2 * Au * (Ru + Tu + Su) + 0.3 * At * (Rt + Tt + St) + 0.4 * Al * (Rl + Tl + Sl) \quad (13)$$

where

- Rh, Ru, Rt, and Rl is the redness score of plaques on the head, upper limbs, trunk, and lower limbs;
- Th, Tu, Tt, and Tl is the thickness score of plaques on the head, upper limbs, trunk, and lower limbs;

- Sh, Su, St, and Sl is the scaliness score of plaques on the head, upper limbs, trunk, and lower limbs;
- Ah, Au, At, and Al is the degree of involvement for the head, upper limbs, trunk, and lower limbs.

The PASI score ranges from 0 to 72 with a higher score indicating increased disease severity.

The following calculation rules will be applied:

- If 2 or fewer severity (redness, thickness, or scaliness) measurements are missing for a certain region, the average of the remaining non-missing assessments will be utilized to substitute the missing assessment(s).
- If the area of affected skin and/or all severity measurements for 2 or fewer body areas are missing, the missing (R+T+S) x A for a body area will be substituted by the average of the available (R+T+S) x A. Otherwise the PASI will be set to missing.

The percent improvement in PASI scores from PA0008 Baseline will be computed as follows:

$$Percent\ improvement = 100 * \frac{baseline\ PASI - PASI}{baseline\ PASI} \qquad (14)$$

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.

The PASI75, PASI90, and PASI100 responses will be 1 if there was at least 75%, 90%, and 100% (respectively) improvement from PA0008 Baseline in the PASI score, and 0 if there was less than the cut-off value. A PASI100 responder at a given visit is therefore also a PASI90 and a PASI75 responder.

If BSA affected by psoriasis (determined by the BSA palm method described in Section 8.1.9) is <3% at PA0008 Baseline (or BSA at PA0008 Baseline is missing) then the PASI response will be set to missing.

Summaries of PASI responses will be restricted to subjects with a BSA affected by psoriasis of ≥3% at PA0008 Baseline.

8.1.11 Minimal Disease Activity

Minimal disease activity is a state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations. Criteria have been developed to determine whether a patient has reached MDA based on key outcome measures in PsA.

MDA will be assessed using component assessments from the same analysis visit, ie, after applying any visit mapping as outlined in Section 3.5. MDA will only be assessed for visits at which all assessments (with the exception of BSA and PASI, see below) were planned to be collected.

A subject will be considered as having MDA if 5 or more of the following 7 criteria are fulfilled:

- TJC≤1
- SJC≤1

- PASI≤1 or BSA≤3
- PtAAP≤15mm
- PGADA≤20mm
- HAQ-DI≤0.5
- Tender enthesial joints≤1

The following additional rules will be applied:

- PASI or BSA
  - The criteria "PASI ≤1 or BSA ≤3" will be considered to be met if either of the 2 subcriteria are satisfied, even if the other assessment is missing. Note that a separate rule (as defined below) is applied for subjects with BSA affected by psoriasis of <3% at PA0008 Baseline.
  - The criteria "PASI ≤1 or BSA ≤3" will be considered as a missing component (for OC) if only 1 subcriterion is available and this does not meet the condition for MDA
  - A subject with BSA affected by psoriasis of <3% at PA0008 Baseline will always be considered to have met the criteria "PASI ≤1 or BSA ≤3". This is the case because PASI and BSA are not planned to be measured at post-Baseline visits for subjects with BSA <3 at PA0008 Baseline. However, if for some reason, PASI or BSA are measured post-PA0008 Baseline for such subjects, and the results indicate a PASI>1 or BSA>3, then this criterion will be considered as not having been met.
- The MASES items will be used to assess whether a subject has ≤1 tender enthesial joint: if the total derived MASES score is ≤1 then the criterion will be considered met.
- If any component is missing then the criteria for that component will be considered to have not been met.
- In the case of partial data at a specific visit, if there are sufficient data to derive MDA as having been met eg, if results are available for 5 out of the 7 assessments and these fulfill the criteria above, this subject will be counted as having achieved MDA in the summary of observed case results. Similarly, if there are sufficient data to calculate non-response regardless of missing data, this subject will be included in the summary of OC results as not having MDA at the specific visit

Further details regarding these calculation algorithms and rules for handling missing components are provided in Section 12.2).

8.1.12 Disease Activity Score-28 based on C-reactive Protein

The components for DAS28(CRP) include the TJC and SJC based on 28 joints (see Section 8.1.2), CRP (mg/L), and the PGADA (mm). Any CRP values less than 0.16mg/L will be substituted as described in Section 8.1.7 prior to calculating the DAS28(CRP) score.

If more than 50% of the planned joint assessments (ie, more than 14 assessments) are missing at a visit, then the TJC or SJC will be set to missing for that visit for the purposes of DAS28(CRP) calculation.

DAS28(CRP) is calculated as follows (where 'ln' represents the natural logarithm function):

$$DAS28(CRP) = 0.56 * \sqrt{TJC} + 0.28 * \sqrt{SJC} + 0.014 * PGADA + 0.36 * \ln(CRP + 1) + 0.96 \quad (15)$$

DAS28 (CRP) will be assessed using component assessments from the same analysis visit, ie, after applying any visit mapping as outlined in Section 3.5.

If any individual component score is missing, the DAS28(CRP) will be missing.

8.1.13 Maastricht Ankylosing Spondylitis Enthesitis Index

The MASES Index comprises six two-sided and one one-sided item (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest and proximal insertion of the achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each scored as 0 = not tender or 1 = tender and then summed for a possible score of 0 to 13, with higher scores indicating worse enthesitis.

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

Summaries of MASES will be restricted to subjects with a MASES >0 at PA0008 Baseline.

8.1.14 Leeds Dactylitis Index

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation, is a characteristic of inflammatory spondyloarthropathies, including PsA. Presence of dactylitis will be assessed using the LDI basic, which evaluates for a ≥10% difference in the circumference of the affected digit compared to the opposite digit (Healy and Helliwell, 2007, Helliwell, 2005).

The percent difference in circumference (mm) between each affected digit and its opposite will be multiplied by a tenderness score for the affected digit (0 for non-tender, 1 for tender). The results from each digit with dactylitis will be summed to produce a final score at each visit.

If matching digits are both affected, the circumference of each digit will be compared to the normative value in Table 8-5. If both digits have a difference in circumference from the normative value of ≥10%, then both digits will contribute to the LDI score (if they are both tender).

If the circumference of the affected digit is smaller than the unaffected digit, then the affected digit will be compared to the normative value. If a digit is affected and the circumference of the opposite digit is missing, the affected digit will be compared with the normative value.

Table 8-5: Normative values for Leeds Dactylitis Index (mm)

	Digit	Men	Women
Hand	Thumb	70	58
	Index	63	54
	Middle	63	54

Table 8-5: Normative values for Leeds Dactylitis Index (mm)

	Digit	Men	Women
	Ring	59	50
	Little	52	44
Foot	Great toe	82	72
	Second	52	46
	Middle	50	44
	Fourth	50	44
	Little	52	45

Summaries of LDI will be restricted to subjects with LDI scores >0 at PA0008 Baseline. PA0008 Baseline LDI will be taken directly from the PA0008 database without derivation. Digits that are included in the calculation of the LDI score (both tender and non-tender) will be flagged in the relevant analysis dataset.

8.1.15 Hospital Anxiety and Depression Scale

The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with chronic plaque psoriasis (Langley et al, 2010; Dauden et al, 2009). The HADS consists of 14 items, each scored from 0 to 3.

HADS-A will be calculated as the sum of the scores for items 1, 3, 5, 7, 9, 11, 13, and HADS-D will be calculated as the sum of the scores for items 2, 4, 6, 8, 10, 12, 14. Each score ranges from 0 to 21 with higher scores indicating a worse state. A score below 8 is considered normal and a score of 15 and above is considered severe (Snaith and Zigmund, 1994). If any of the 7 items required to calculate the HADS-A or HADS-D are missing, then the HADS-A or HADS-D will be treated as missing.

A flag to identify "normal" depression and anxiety status at each visit (defined as having HADS-D <8 and HADS-A<8 at the same visit) will be derived.

8.1.16 Psoriatic Arthritis Impact of Disease-9

The PsAID-9 is a patient-reported outcome measure for assessing the impact of PsA in 9 physical and psychological domains, including pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, and anxiety/fear/uncertainty.

Each domain is assessed with a single question using a 0 to 10 numerical rating scale. Each domain score is multiplied by a weighting factor and the results are then summed to provide the total score.

$$\begin{aligned} PsAID-9 = {} & Pain * 0.174 + Fatigue * 0.131 + Skin * 0.121 \\ & + Work\ and/or\ Leisure\ Activities * 0.110 + Function \\ & * 0.107 + Discomfort * 0.098 + Sleep * 0.089 + Coping \\ & * 0.087 + Anxiety * 0.085 \end{aligned} \quad (16)$$

The total score ranges from 0 to 10, with higher scores indicating a worse status. A score below or equal to 4 out of 10 is considered a patient-acceptable status. A decrease of 3 or more points from PA0008 Baseline is considered a minimal clinically important difference (MCID).

If 1 of the 9 domains is missing, the missing value is imputed using the mean of the raw values (prior to weighting) from the 8 other (non-missing) domains. If 2 or more of the domains are missing, the PsAID-9 score will be missing.

8.1.17 Short Form – 36 Items Health Survey

The SF-36 (Version 2, standard recall) is a 36 item generic health-related quality of life (HRQoL) instrument that uses a recall period of 4 weeks. Items are grouped into 8 component scales as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and a further unscaled single item (Question 2) for perceived stability or change in health (Health Transition) during the last year. The concepts represented by these scales contribute to physical, mental, and social aspects of HRQoL. The classification of the questionnaire items to the health scales is shown in Section 12.3.

The SF-36 PCS score and MCS score are used to measure the 2 broad components, or aspects, of health: physical and mental. PCS and MCS scores are based on the aggregate of the 8 health concepts described above and all of the 8 health scales are used to score both components.

For the calculation of the SF-36 scale scores and the component summary scores PCS and MCS, the scoring software Optum's PRO CoRE will be used (Version 1.4). The norm-based scores (based on the US 2009 general population) will be utilized for analysis. The latest updates to the software use improved methods for missing data estimation through the following:

- Dropping the previous 'half-scale' rule, so that scale scores (except the Physical Functioning scale) will be estimated when the respondent has provided a response to at least one item in the same scale.
- Using item response theory to develop a model for estimating a score on the Physical Functioning scale.
- Using regression methods to estimate the PCS and MCS on the basis of the available scales.

8.2 Statistical analysis of secondary efficacy variables

The following secondary efficacy variables will be summarized for the FAS, by treatment group at the completion of PA0008 and overall:

- ACR20, ACR50, and ACR70 response relative to PA0008 Baseline at PA0009 Week 48.
- Change from PA0008 Baseline value in MASES at PA0009 Week 48.
  - Only subjects with MASES >0 at PA0008 Baseline will be included.
- Change from PA0008 Baseline value in LDI at PA0009 Week 48.
  - Only subjects with LDI >0 at PA0008 Baseline will be included.
- PASI75 and PASI90 response relative to PA0008 Baseline at PA0009 Week 48.
  - Only subjects with BSA affected by psoriasis ≥3% at PA0008 Baseline will be included.

For ACR and PASI responses, one set of summaries will be produced using data following NRI and another set using OC data. For MASES and LDI, summaries will be produced using data following MI.

8.3 Statistical analysis of other efficacy variables

The following other efficacy variables will be summarized for the FAS at scheduled visits in accordance with the schedule of study assessments in Table 2-1, by treatment group, at the completion of PA0008 and overall:

- ACR20, ACR50, and ACR70 response at each visit in PA0009, relative to PA0008 Baseline.
- PASI75, PASI90 and PASI100 response at each visit in PA0009, relative to PA0008 Baseline.
  - Only subjects with BSA affected by psoriasis ≥3% at PA0008 Baseline will be included.
- BSA at each visit in PA0009
  - The number and percentage of subjects with a BSA in the following categories at each visit will be summarized based on OC data: 0%, 1 to 3%, >3 to 10%, >10 to 20%. >20 to 30%, >30 to 40%, >40 to 50%, >50 to 60%, >60 to 70%, >70 to 80%, >80 to 90%, and >90% to 100%.
  - Only subjects with BSA affected by psoriasis ≥3% at PA0008 Baseline will be included.
- MDA at each visit in PA0009.
- Change from PA0008 Baseline in DAS28(CRP) at each visit in PA0009.
- Change from PA0008 Baseline in CRP (expressed as ratio to Baseline) at each visit in PA0009.
  - For CRP the rules for handling values that are lower than the LLOQ identified in PA0008 will be followed as per Section 8.1.7
- Change from PA0008 Baseline in MASES at each visit in PA0009.
  - Only subjects with MASES >0 at PA0008 Baseline will be included.
- Change from PA0008 Baseline in LDI at each visit in PA0009.
  - Only subjects with LDI >0 at PA0008 Baseline will be included.
- Change from PA0008 Baseline in PsAID-9 score at each visit in PA0009.
- Change from PA0008 Baseline in SF-36 PCS and MCS scores at each visit in PA0009.
- Change from PA0008 Baseline in HADS-A and HADS-D scores at each visit in PA0009.
- Incidence of depression and anxiety status “normal” as defined by both HADS-D<8 and HADS-A<8 at each visit in PA0009.
- Change from PA0008 Baseline in TJC at each visit in PA0009.
- Change from PA0008 Baseline in SJC at each visit in PA0009.
- Change from PA0008 Baseline in HAQ-DI score at each visit in PA0009.

- Change from PA0008 Baseline in PtAAP at each visit in PA0009.
- Change from PA0008 Baseline in PhGADA at each visit in PA0009.
- Change from PA0008 Baseline in PGADA at each visit in PA0009.

One set of summaries will be produced for all of the above parameters using data following NRI (for binary endpoints) or MI (for continuous endpoints) as appropriate, as described in Section 4.2.1. For BSA the summary will be based on OC data only.

For each of the following variables, an additional set of summaries will be produced using OC data:

- ACR
- PASI
- MDA
- MASES
- LDI

For each of the following variables, an additional set of summaries will be produced after the response variables have been derived following MI of components:

- ACR
- PASI

Finally, for PASI, supplementary summary tables will be presented for the following based on the imputation rules described in Section 4.2.2:

- PASI response derived using LOCF
- PASI response derived based on the BSA observed at the corresponding visit

The summary tables for CRP will display the absolute value and ratio to PA0008 Baseline and will contain n, geometric mean (and 95% CI), median, first and third quartiles (Q1 and Q3), minimum and maximum. Any values for the ratio to PA0008 Baseline below 0.01 will be presented as <0.01 in the listing and summary table.

8.3.1 Maintenance of response

ACR20, ACR50, ACR70, PASI75, PASI90 and PASI100 response relative to PA0008 Baseline will, in addition, be summarized at each post-Baseline visit in PA0008 through to PA0009 Week 104, by treatment sequence, as defined in Section 3.7. These summaries will be restricted to subjects in the FAS and who were responders for the relevant endpoint at PA0008 Week 12, and data will be reported following NRI.

8.4 Subgroup analysis

Subgroup summaries will be performed for the efficacy variables of ACR and PASI response at PA0009 Week 48 for the FAS. Subgroups are defined in Section 4.8.

Subgroup summaries will be based on data following NRI only.

8.5 Impact of COVID-19

Additional sensitivity analyses as a result of the global COVID-19 pandemic are not anticipated as the onset of the pandemic was subsequent to all subjects completing Week 48; therefore, there is no impact on the analysis of the secondary efficacy endpoint.

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

Bimekizumab plasma concentrations will be summarized at each scheduled visit in PA0009 by treatment at completion of PA0008 and overall, using the SS.

If bimekizumab plasma concentration measurements are deemed to be below the level of quantification (BLQ), then for calculation of the derived statistics this sample result will be set to half the LLOQ. Descriptive statistics will be calculated only if at least 2/3 of the values are above the LLOQ at a given visit. If this is not the case, only median, minimum, and maximum will be presented.

In addition, geometric mean bimekizumab plasma concentration (with 95% CI) time curves will be plotted versus time on linear and semi-logarithmic scales by treatment group at completion of PA0008.

The summary tables for bimekizumab plasma concentrations will display n, geometric mean (and 95% CI), geometric CV%, arithmetic mean, SD, median, minimum, and maximum, where the geometric CV% is calculated using the following formula:

$$CV\% = \sqrt{e^{SD_{ln}^2} - 1} \times 100 \quad (17)$$

where SD_{ln} represents the standard deviation of the ln-transformed plasma concentration values.

Geometric mean plots will be repeated by cumulative ADAb positivity and treatment:

- The ADAb positive status will be considered in a cumulative manner at each time point (ie, if a subject has had at least 1 positive sample at any time point up to and including the given time point, that subject would be counted as positive at that time point, regardless of any subsequent negative measurements). Thus, the number of subjects included in the geometric mean for positive and negative categories will vary by time point for each treatment.
- Two plots will be presented each displaying bimekizumab plasma concentration data in PA0009 only:
  - Considering cumulative ADAb status in PA0009 only at each time point in PA0009
  - Considering cumulative ADAb status in PA0008 and PA0009 at each time point in PA0009
- Each plot (linear and semi-logarithmic) will be presented by treatment group at completion of PA0008 and ADAb positive status (4 lines per plot)

The following rules will be implemented for PK concentration summaries and corresponding figures:

- If the dosing for a visit is performed more than 14 days prior to, or more than 14 days after the scheduled dosing interval (28 days), then the plasma concentration obtained at that dosing visit will be excluded from the PK summaries and figures. Thus, if the dosing interval is less than 14 days or greater than 42 days, this rule will apply. This will also apply to doses administered at an unscheduled visit.
- If a PK sample is collected >14 days after the preceding dose and up to 1 hour after the dose at the current visit, the PK concentration for that sample will be associated with the current visit and summarized accordingly. This will include unscheduled assessments as described in Section 3.5 (if a dose was administered at an unscheduled visit). Samples collected outside this window will be excluded from the PK summaries and figures and will be listed only.
- Individual samples collected at a scheduled visit at which dosing was not performed (eg, due to AE) will be retained in the PK summaries and figures for the specific visit if these are collected >14 days and <42 days after the preceding dose, as these reflect the trough concentration from the preceding dose. The sample obtained at the subsequent scheduled visit will be excluded from the summaries (regardless of dosing) as this will not reflect a steady-state trough concentration (as the previous dose was not administered). Thereafter PK samples will be included in the summaries assuming dosing has resumed and the sample was obtained within the required window of >14 days after the preceding dose and up to 1 hour after the dose at the current visit.
  - Note samples collected at Week 104 will be retained in the PK summaries and figures if they are collected >14 days and <42 days after the last dose received
  - Note samples collected at the ET visit will be retained in the PK summaries and figures if they are collected >14 days and <42 days after the last dose received

These rules will not apply for the SFU visit as no dosing is planned at this visit. All concentrations obtained at the SFU visit will be included in the summary tables (but will not be included in the figures).

Bimekizumab plasma concentrations will be listed for the SS, separately for PA0009 and for data from PA0008 and PA0009 combined. All concentrations will be listed as received, prior to substitution of any BLQ values. The listing of the PA0009 data will include flags for concentrations that were excluded from the summary statistics where the reason for exclusion will be one of the following:

- Dosing performed out of window
- Sample collected out of window relative to current dose
- Sample collected out of window relative to previous dose
- Missed dose at preceding visit (in conjunction with one of the above reasons)
- More than one sample obtained at the same visit

All plasma concentration data will be reported in ug/mL in the tables, figures, and listings.

9.2 Pharmacodynamics and Immunogenicity

The immunological variable is ADAb evaluated at scheduled visits up to 104 weeks in accordance with the schedule of study assessments (Table 2-1).

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

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

The following rule will be implemented for by-visit ADAb summaries where applicable:

- If the ADAb sample is collected within ±21 days relative to the visit date at which the drug was administered (or ±21 days from a scheduled visit at which dosing was not performed), the ADAb result for that sample will be associated with the scheduled visit and summarized accordingly. This will include unscheduled assessments as described in Section 3.5 (if a dose was administered at an unscheduled visit). Samples collected outside this window will be excluded from the ADAb summaries and figures and will be listed only.

The rule above will apply to by-visit summaries only; summaries of cumulative ADAb status and time to treatment-emergent positivity will use all available data. This rule will not apply for Visit 13 (Week 104), ET visit or the SFU visit as no dosing is planned at these time points. All ADAb data obtained at these visits will be included in the by-visit summaries.

ADAb status will be derived as follows:

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

In addition, the ADAb status will be further classified on a subject level as outlined below:

- **Pre ADAb negative – treatment emergent ADAb negative (Category 1)**:
  - Considering PA0009 data only (Category 1a): includes subjects who are ADAb negative at PA0008 Baseline and ADAb negative at all sampling points in PA0009 (including SFU).
  - Considering PA0008 and PA0009 data (Category 1b): includes subjects who are negative at PA0008 Baseline and ADAb negative at all sampling points in PA0008 and PA0009 (including PA0009 SFU).
- **Pre ADAb negative – treatment emergent ADAb positive (Category 2)**:

- Considering PA0009 data only (Category 2a): Includes subjects who are negative at PA0008 Baseline and ADAb positive at any sampling point post treatment in PA0009 (up to and including SFU and including the PA0009 EV). This group also includes subjects who have a missing pre-treatment sample (either missing or insufficient volume) at PA0008 Baseline with one or more ADAb positive samples in PA0009.
- Considering PA0008 and PA0009 data (Category 2b): Includes subjects who are negative at PA0008 Baseline and ADAb positive at any sampling point post treatment in PA0008 (up to and including PA0009 SFU). This group also includes subjects who have a missing pre-treatment sample (either missing or insufficient volume) at PA0008 Baseline with one or more ADAb positive samples in PA0008 or PA0009.

- **Pre ADAb positive – treatment emergent reduced ADAb (Category 3)**:
  - Considering PA0009 data only (Category 3a): Includes subjects who are positive at PA0008 Baseline, and ADAb negative at all sampling points in PA0009 (including SFU).
  - Considering PA0008 and PA0009 data (Category 3b): Includes subjects who are positive at PA0008 Baseline, and ADAb negative at all sampling points in PA0008 and PA0009 (including SFU).
- **Pre ADAb positive – treatment emergent unaffected ADAb positive (Category 4)**:
  - Considering PA0009 data only (Category 4a): Includes subjects who are positive at PA0008 Baseline and are positive at any sampling point in PA0009 (including SFU) with titer values of the same magnitude as PA0008 Baseline (ie, less than a predefined fold increase from the PA0008 Baseline value defined within the validation of the assay).
  - Considering PA0008 and PA0009 data (Category 4b): Includes subjects who are positive at PA0008 Baseline and are positive at any sampling point in PA0008 or PA0009 (including SFU) with titer values of the same magnitude as PA0008 Baseline (ie, less than a predefined fold increase from the PA0008 Baseline value defined within the validation of the assay).

  For the purposes of this study, this is set at an increase of less than or equal to a 3-fold difference from PA0008 Baseline.
- **Pre ADAb positive – treatment emergent ADAb boosted positive (Category 5)**:
  - Considering PA0009 data only (Category 5a): Includes subjects who are positive at PA0008 Baseline and are positive at any sampling point post treatment in PA0009 (including PA0009 EV and SFU) with increased titer values compared to PA0008 Baseline.
  - Considering PA0008 and PA0009 data (Category 5b): Includes subjects who are positive at PA0008 Baseline and are positive at any sampling point post treatment in PA0008 or PA0009 (including SFU) with increased titer values compared to PA0008 Baseline.

  The increase in titer values is defined as an increase greater than a predefined fold increase from PA0008 Baseline value which is defined within the validation of the assay. For the

purposes of this study, this is set at an increase greater than a 3-fold difference (ie, a minimum of a 4-fold increase).

Note: For any subject who is positive at PA0008 Baseline and positive at a post-Baseline time point, but for whom titers are not available to determine treatment unaffected or treatment boosted status, the subject will be considered as treatment boosted (ie, Category 5), assuming no other samples are available.

- **Inconclusive (Category 6)**:
  - Considering PA0009 data only (Category 6a): Includes subjects who have a positive pre-treatment sample at PA0008 Baseline and some PA0009 samples are missing, while other PA0009 samples are ADAb negative.
  - Considering PA0008 and PA0009 data (Category 6b): Includes subjects who have a positive pre-treatment sample at PA0008 Baseline and some PA0008 or PA0009 samples are missing, while other PA0008 and PA0009 samples are all ADAb negative.
- **Total treatment-emergent (Category 7 [Categories 2 and 5 combined])**:
  - Considering PA0009 data only (Category 8a): Includes subjects who are pre ADAb negative – treatment emergent ADAb positive (Category 2a) and pre ADAb positive – treatment boosted ADAb positive (Category 5a).
  - Considering PA0008 and PA0009 data (Category 8b): Includes subjects who are pre ADAb negative – treatment emergent ADAb positive (Category 2b) and pre ADAb positive – treatment boosted ADAb positive (Category 5b).
- **Total pre ADAb positive (Category 8 [Categories 3, 4, 5 and 6 combined])**: Subjects that are tested ADAb positive at PA0008 Baseline.
- **Missing (Category 9)**:
  - Considering PA0009 data only (Category 9a): Includes subjects who have a missing or negative pre-treatment sample at PA0008 Baseline and some PA0009 samples are missing, while other PA0009 samples are ADAb negative.
  - Considering PA0008 and PA0009 data (Category 9b): Includes subjects who have a missing or negative pre-treatment sample at PA0008 Baseline and some PA0008 or PA0009 samples are missing, while other PA0008 and PA0009 samples are all ADAb negative.

The following summaries, figures and listings will be produced:

- Summary tables displaying the number and percentage of subjects with a positive ADAb status at each PA0009 visit and at any visit by treatment group at completion of PA0008. Two tables will be presented:
  - Considering ADAb status in PA0009 only
  - Considering ADAb status in PA0008 and PA0009 (this table will include only the overall summary visits as detailed below).

For the overall summary at any visit 2 summaries will be presented as follows (all summaries exclude data obtained at PA0008 Baseline):

- PA0009 data only: Including any visit during the PA0009 treatment period (as defined in Section 3.2.2). Thus, this summary will exclude data obtained at the SFU visit and will include data obtained at the PA0009 EV.
- PA0009 data only: Including any visit during PA0009. Thus, this summary will include both data obtained at the SFU visit and at the PA0009 EV.
- PA0008 and PA0009 data: Including any visit during the PA0008 and PA0009 treatment period. Thus, this summary will exclude data obtained at the PA0009 SFU visit.
- PA0008 and PA0009 data: Including any visit during PA0008 and PA0009. Thus, this summary will include data obtained at the PA0009 SFU visit.

- Summary tables (by treatment at completion of PA0008) of the time point of the first occurrence of ADAb treatment-emergent positivity during PA0009, including the PA0009 EV and the SFU visit. This summary will include the following categories:
  - Category 2: Pre ADAb negative – treatment-emergent ADAb positive
  - Category 5: Pre ADAb positive – treatment-boosted ADAb positive

  The table will summarize the number and percentage of subjects who are either treatment-emergent ADAb positive or treatment-boosted ADAb positive for the first time at the specified time point in PA0009 and will include the cumulative number and percentage of subjects with treatment-emergent ADAb positive results at each time point.

  The table will be repeated considering ADAb status at each visit in both PA0008 and PA0009 and will therefore display all visits in both PA0008 and PA0009.

  An additional table will be presented considering ADAb status at each visit in both PA0008 and PA0009, and will be presented by treatment at randomization in PA0008.
- Summary tables displaying the number and percentage of subjects in each of the ADAb categories as defined above by treatment at completion of PA0008. Two tables will be presented:
  - Considering data from PA0009 only
  - Considering data from PA0008 and PA0009
- The time to achieving treatment-emergent ADAb positivity in PA0009, separated by treatment group at completion of PA0008, will be graphically presented. Subjects will be considered to have an event at the time point at which treatment-emergent ADAb positivity is first achieved. The plot will display the cumulative percentage of subjects with treatment-emergent positivity and will include the following categories (4 lines per plot):
  - Category 2: Pre ADAb negative – treatment-emergent ADAb positive
  - Category 5: Pre ADAb positive – treatment-boosted ADAb positive
    - Category 2 and Category 5 subjects will be combined in 1 group (2 lines per plot) if the percentage of subjects in each treatment group in Category 5 is <10%.

The figure will be repeated considering data from both PA0008 and PA0009 and will therefore display all visits in both PA0008 and PA0009.

In the event that ≥10% of subjects in either treatment group are classified as Category 5 the figure will be presented by treatment and ADAb status (4 lines per plot). This will be implemented for both plots (considering only PA0009 and considering data from both PA0008 and PA0009).

An additional figure will be presented considering data from both PA0008 and PA0009, and will be presented by treatment at randomization in PA0008 (for this figure the 160mgLD and 160mg treatments will be pooled). This figure will be presented as follows:

- If <10% of subjects in each treatment group (based on treatment at randomization) are classified as Category 5, the figure will be presented with 5 lines on 1 plot (1 for each treatment) and both categories combined
- If ≥10% of subjects in any treatment group (based on treatment at randomization) are classified as Category 5, the figure will be presented by category and treatment at randomization with separate plots (each with 5 lines) for each category

- A summary of efficacy response (ACR50 responders [based on NRI]) as a function of ADAb titer will be presented graphically. The x-axis will display the ADAb titer at the Week 48 time point (categorized as negative, Q1, Q2, Q3 and Q4 where the latter represents the quartiles for the ADAb titers at Week 48) and the y-axis will display percentage of ACR50 responders at the Week 48 time point within each titer category.

  Subjects with negative ADAb results at the Week 48 time point will be included in the 'negative' category on the x-axis; subjects with missing ADAb data at the Week 48 time point will be excluded from the plot. The figure will be based on the FAS.

- A summary of efficacy response (ACR50 responders) versus time will be presented graphically including the following ADAb groups (3 lines per plot):
  - ADAb positive
    - Defined as subjects having at least 2 ADAb positive samples during PA0009 (including PA0009 EV and SFU) regardless of other ADAb negative samples and/or missing or inconclusive samples
  - ADAb negative
    - Defined as subjects for whom either (1) all samples in PA0009 (including PA0009 EV and SFU) are ADAb negative and there are no missing or inconclusive samples or (2) only 1 sample in PA0009 is ADAb positive and all other samples in PA0009 (including PA0009 EV and SFU) are ADAb negative or missing/inconclusive or (3) only 1 sample is missing/inconclusive and the remaining samples are ADAb negative.
  - Missing
    - Defined as subjects who do not fulfil the criteria for one of the 2 groups listed above.

  The figure will be repeated considering ADAb status based PA0008 and PA0009 combined, with the following definitions:

- ADAb positive
  - Defined as subjects having at least 2 ADAb positive samples during PA0008 and PA0009 (excluding PA0008 Baseline and including PA0009 EV and SFU) regardless of other ADAb negative samples and/or missing or inconclusive samples
- ADAb negative
  - Defined as subjects for whom either (1) all samples in PA0008 and PA0009 (excluding PA0008 Baseline and including PA0009 EV and SFU) are ADAb negative and there are no missing or inconclusive samples or (2) only 1 sample in PA0008 or PA0009 is ADAb positive and all other samples in PA0008 and PA0009 (including PA0009 EV and SFU) are ADAb negative or missing/inconclusive or (3) only 1 sample is missing/inconclusive and the remaining samples in PA0008 and PA0009 are ADAb negative.
- Missing
  - Defined as subjects who do not fulfil the criteria for one of the 2 groups listed above.

Both figures described above will be based on the FAS and the data for ACR responders will be based on NRI. If the percentage of subjects in the missing category is ≤5%, this category will be omitted from the plot.

- Spaghetti plots of ADAb titer (y-axis) versus time (x-axis), separated by treatment group at completion of PA0008 for all ADAb positive subjects. This plot will include the following ADAb categories, based on data collected in PA0009:
  - Category 2: Pre ADAb negative – treatment-emergent ADAb positive
  - Category 5: Pre ADAb positive – treatment-boosted ADAb positive

  Separate plots will be presented for each treatment group with both categories on the same plot. Plots will be presented using a semi-logarithmic scale for the ADAb titers (ADAb negative samples will therefore be excluded from the plot). The x-axis will reflect time from the PA0009 EV.
- Listings of individual subject-level ADAb results will be presented for the following:
  - Including only data from PA0009.
  - Including data from both PA0008 and PA0009.

  The listing of PA0009 data will also include flags for ADAb measurements that were excluded from the by-visit summaries. The reason for exclusion will be one of the following:
  - Sample collected out of window relative to current dose or visit
  - More than one sample obtained at the same visit

  Any ADAb measurements that were outside the tolerance limit of the assay will also be flagged in the listing.

All outputs described in this section will be presented using the SS, unless otherwise stated.

10 SAFETY ANALYSES

AEs will be coded according to MedDRA.

AEs will be summarized by treatment group at completion of PA0008 and overall, by primary SOC, HLT, and PT in alphabetical order. This summary will include incidence, exposure-adjusted incidence rates (EAIRs) with associated 95% CIs, and exposure-adjusted event rates (EAERs) where the EAIR and EAER are expressed per 100 subject-years of exposure. Subject exposure at risk is defined in Section 10.1.

Change from PA0009 Laboratory Baseline values in laboratory variables (except CRP) will be summarized descriptively by visit and by treatment group at completion of PA0008 and overall.

Change from PA0008 Baseline values in ECG and vital signs variables will be summarized descriptively by visit and by treatment group at completion of PA0008 and overall.

Safety variables will be reported for the SS. Key safety analyses will be repeated for both SS Sub-populations (see Section 3.6.2) and/or will include data from PA0008 for subjects who continued in to PA0009, as described below.

10.1 Extent of exposure

Study medication duration will be calculated for each of the following using the imputation rules in Section 4.2.5 for partial treatment end dates:

- Total bimekizumab duration: Between the first dose of bimekizumab in PA0008 and last dose of bimekizumab in PA0009.
- Total duration on bimekizumab 160mg and 160mgLD combined (required for AE summaries only): Between the first dose of bimekizumab 160mgLD or 160mg and last dose of bimekizumab 160mg (in PA0008 or PA0009).
- Duration on bimekizumab 320mg: Between the first dose of bimekizumab 320mg in PA0008 and first dose of bimekizumab 160mg in PA0009 (calculated only for subjects who took bimekizumab 320mg in PA0008).
- Duration on bimekizumab 160mg in PA0009: Between the first and last dose of bimekizumab 160mg in PA0009.

The duration of exposure will be calculated as outlined in Table 10-1.

Table 10-1: Study medication duration

Duration Category	Start Date	End Date	Study Medication Duration
Total BKZ duration	First dose of BKZ in PA0008	Last dose of BKZ in PA0009	End date – start date + 28[a]
Total duration on BKZ 160mgLD and BKZ 160mg	First dose of BKZ 160mgLD or 160mg in PA0008 or PA0009	Last dose of BKZ 160mg in PA0009	End date – start date + 28[a]

Table 10-1: Study medication duration

Duration Category	Start Date	End Date	Study Medication Duration
Duration on BKZ 320mg	First dose of BKZ 320mg in PA0008	First dose of BKZ 160mg in PA0009	End date – start date + 1
Duration on BKZ 160mg in PA0009	First dose of BKZ 160mg in PA0009	Last dose of BKZ 160mg in PA0009	End date – start date + 28[a]
Subjects who died[b]	Start date for each option as above	Date of death	End date – start date + 1

BKZ=bimekizumab; LD=loading dose.
[a] 28 days refer to one half-life of BKZ.
[b] For subjects who died, the date of death will be used to replace the end date in the calculation of study medication duration only if the subject died within the dosing interval (ie, within 28 days following the last dose [not applicable for duration on BKZ 320mg]) or if the subject died before dosing in PA0009 (for duration on BKZ 320mg). If the subject died more than 28 days after the last dose of BKZ in PA0009 the study medication duration will be calculated using the dosing interval of 28 days.

The exposure time at risk will be calculated as outlined in Table 10-2.

Table 10-2: Exposure time at risk

Exposure Category	Start Date	End Date	Duration of Exposure
Total BKZ exposure	First dose of BKZ in PA0008	Last dose of BKZ in PA0009	Minimum of (End date – start date + 140[a]) and (Date of last clinical contact[b] – start date + 1)
Total exposure to BKZ 160mgLD and 160mg	First dose of BKZ 160mgLD or 160mg in PA0008 or PA0009	Last dose of BKZ 160mg in PA0009	Minimum of (End date – start date + 140[a]) and (Date of last clinical contact[b] – start date + 1)
Exposure to BKZ 320mg	First dose of BKZ 320mg in PA0008	First dose of BKZ 160mg in PA0009 for subjects who were dosed in PA0009[c]. Last dose of BKZ 320mg in PA0008 for subjects who were not dosed in PA0009	(End date – start date + 1) for subjects who were dosed in PA0009. Minimum of (End date – start date + 140[a]) and (Date of last clinical contact[b] – start date + 1) for subjects who were not dosed in PA0009.
Exposure to BKZ 160mg in PA0009	First dose of BKZ 160mg in PA0009	Last dose of BKZ 160mg in PA0009	Minimum of (End date – start date + 140[a]) and (Date of last clinical contact[b] – start date + 1)

Table 10-2: Exposure time at risk

Exposure Category	Start Date	End Date	Duration of Exposure
Subjects who died[d]	Start date for each option as above	Date of death	End date – start date + 1

BKZ=bimekizumab; LD=loading dose.

[a] 140 days refer to 5 half-lives of BKZ.

[b] Date of last clinical contact for each subject is defined as the maximum of [last visit date including SFU visit, last AE start date (including imputed AE start dates), date of study termination or completion, last date of study drug administration following rules for partial treatment end dates as per Section 4.2.5].

[c] In the event that the first dose in PA0009 was more than 140 days after the last dose in PA0008, the exposure time at risk for 320mg will be calculated using PA0008 end date – PA0008 start date + 140 days.

[d] For subjects who died, the date of death will be used to replace the end date in the calculation of exposure time at risk only if the subject died within the 'at risk' interval (ie, within 140 days following the last dose [not applicable for duration on BKZ 320mg]) or if the subject died before dosing in PA0009 (for time at risk on BKZ 320mg). If the subject died more than 140 days after the last dose of BKZ in PA0009 the exposure time at risk will be calculated using the 'at risk' interval of 140 days. Note that date of death should be equivalent to date of last clinical contact.

In the event that a subject received an incorrect (unplanned) treatment sequence the calculations for study medication duration and exposure time at risk will be adjusted accordingly following the principles outlined above and this will be documented in the relevant dataset specifications.

Three summaries of exposure will be provided: 2 for exposure in PA0009 and 1 for exposure in PA0008 and PA0009 combined:

- For the PA0009 summary, durations of exposure and times at risk will be summarized by treatment group at completion of PA0008 and overall. This summary will be repeated by SS Sub-population.
- For the PA0008 and PA0009 combined table, the duration of exposure and time at risk for 'BKZ 160mg/BKZ 160mgLD combined', 'BKZ 320mg' and 'BKZ Total' will be summarized. Subjects who took bimekizumab 320mg during PA0008 will contribute to all three columns. Subjects who did not take 320mg in PA0008 will contribute to the 'BKZ 160mg/BKZ 160mgLD' and 'BKZ Total' columns.

The total time at risk in years will be included in the exposure tables. This will be calculated by summing the time at risk across all subjects (per treatment group) and will be expressed in years and presented to 1 decimal place.

Start date of study medication in PA0008, start and end dates of study medication in PA0009, the durations of exposure and the times at risk will be listed.

10.2 Adverse events

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

AEs that occurred during the PA0008 study and are ongoing at the time of enrolment (signed informed consent) in PA0009 will be captured in the PA0009 database and followed up until the AEs have resolved, have stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up.

This follow-up requirement applies to AEs, SAEs, AEs of special interest (AESI), and AEs defined as Safety Topics of Interest; further details regarding follow-up of Potential Drug-induced Liver Injury (PDILI) events are provided in the protocol Section 9.5.1. Information on SAEs obtained after clinical database lock will be captured through the Patient Safety database without limitation of time.

If an AE is ongoing at the end of the PA0009 study, follow-up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is clinically significant, or until the subject is lost to follow-up. If no follow-up is provided, the Investigator must provide a justification. The follow-up will usually be continued for 20 weeks after the subject has discontinued his/her IMP.

All AEs occurring during the PA0009 study (ie, after signature of the informed consent document) will be recorded in the eCRF. For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was classified as a SAE, as an AESI, intensity, relationship to study medication, action taken with study medication, other action taken, outcome, date of outcome, and whether the AE led to study drug discontinuation or to study discontinuation.

The following code lists will be used for AE recording:

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

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

- Non-treatment emergent AEs are those with onset date after a 140-day period after the end date of study medication.
  - Any AE occurring more than 140 days after the last administration of study medication in PA0008 and prior to the first administration of study medication in PA0009 will also be considered as non-treatment emergent, and will therefore be excluded from the summary tables. Such events will be included in the listings.
- TEAEs are those with onset date on or after the start date of study medication in PA0009.
- Events that were ongoing at the end of PA0008 will have their treatment-emergent status taken from the PA0008 database.

For all AEs the following variables will be calculated (see Section 10.2.1):

- Duration.
- Time since first bimekizumab dose.
- Time since last/latest bimekizumab dose.

AE summaries will, in general, include only events with onset on or after the start date of study treatment in PA0009. Certain displays will be repeated including all AEs in PA0008 (with the exception of those with onset during placebo treatment) and PA0009 as outlined below. These displays will include only subjects from PA0008 who were enrolled in PA0009.

In general, the attributes of these events (for AEs that started and were resolved in PA0008) will be taken from the PA0008 database. However, the identification of Safety Topics of Interest will be made across all events in PA0008 and PA0009 using the criteria defined in this SAP.

For events which were ongoing at the end of PA0008, the following rules will be implemented:

- Onset date (and derived variables) will be taken from the PA0008 database
- End date, outcome, actions taken and seriousness will be taken from the PA0009 database.
- In order to ensure that AEs are not duplicated in the outputs these will be merged across the studies by Subject ID, verbatim term (AETERM), dictionary-derived term (AEDECOD), start date (AESTDTC), relationship (AEREL) and severity (AESEV) to create one record for the specific event.

Summaries of AEs in PA0008 and PA0009 combined will include AEs with onset on the first dose of bimekizumab in PA0008 up to 140 days after the last dose of bimekizumab in PA0009. AEs which occur on the day of a treatment switch will be considered to have begun on the previous treatment, with the exception of the following AEs which will be considered to have begun on the new treatment:

- Events that fulfill the anaphylaxis criteria for acute events (see Section 10.2.3).
- Events that fulfill the hypersensitivity reaction criteria for (see Section 10.2.3).
- Events with a HLT of "Administration site reactions NEC".
- Events with an HLT of "Injection site reactions".

AEs that occur on the first day of bimekizumab treatment in PA0008 following initial treatment with placebo will not be included in the summaries, unless they fulfill 1 of the 4 exception criteria above. AEs that occur after the last dose of bimekizumab in PA0009 and up to 140 days after the last dose of bimekizumab in PA0009 will be assigned to bimekizumab 160mg.

AEs will be presented as "number of subjects (percentage of subjects) [number of events]". "[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.

An overview of TEAE (number and percentage of subjects with any TEAE, serious TEAE, TEAE leading to study discontinuation, TEAE leading to permanent withdrawal of study medication, drug-related TEAE, severe TEAE, fatal AE [see note below], fatal TEAE and TEAE

with missing seriousness) will be provided by treatment group at completion of PA0008 and overall. This summary will be repeated by SS Sub-population.

This table will be repeated including all TEAEs in PA0008 and PA0009 reported for subjects in the PA0009 SS (with the exception of those with onset during placebo treatment) combined. The 'BKZ 160mg' treatment column in this table will include subjects in both the BKZ 160mgLD and BKZ 160mg treatment groups.

The category for fatal AEs will be based on all subjects enrolled in PA0009 in all the above summaries.

The following categories of TEAE will be summarized by MedDRA SOC, HLT and PT, including EAIR and EAER (calculated as described in Section 10.2.2), where all summaries refer to AEs reported in PA0009 only except where stated:

- All TEAEs by treatment group at completion of PA0008 and overall.
- All TEAEs by treatment group at completion of PA0008 and overall, by SS Sub-population.
- Serious TEAEs by treatment group at completion of PA0008 and overall.
- Serious TEAEs by treatment group at completion of PA0008 and overall, by SS Sub-population.
- All TEAEs in PA0008 and PA0009 by treatment at time of AE onset (BKZ 160mg, BKZ 320mg and BKZ Total).
  - The 'BKZ 160mg' treatment column in this table will include subjects in both the BKZ 160mgLD and BKZ 160mg treatment groups.
- Serious TEAEs in PA0008 and PA0009 by treatment at time of AE onset (BKZ 160mg, BKZ 320mg and BKZ Total).
  - The 'BKZ 160mg' treatment column in this table will include subjects in both the BKZ 160mgLD and BKZ 160mg treatment groups.
- All TEAEs by timing of onset relative to ADAb status in PA0009. This will include columns for the following (regardless of PA0008 Baseline ADAb status):
  - TEAEs starting before the first ADAb positive result in PA0009 including the PA0009 EV (includes ADAb Categories 2a, 4a and 5a).
  - TEAEs starting on the same date or after the first ADAb positive result in PA0009 including the PA0009 EV (includes ADAb Categories 2a, 4a and 5a).
  - TEAEs for subjects who are ADAb negative at all time points in PA0009 including the PA0009 EV (includes ADAb Categories 1a and 3a).

The following categories of TEAE will be summarized by MedDRA SOC, HLT, and PT, by treatment group at completion of PA0008 and overall:

- TEAEs leading to study discontinuation and/or permanent withdrawal of study medication.
- TEAEs leading to permanent withdrawal of study medication.
- TEAEs with a fatal outcome.

- All TEAEs by maximum relationship.
- Serious TEAEs by maximum relationship.
- TEAEs with a fatal outcome by maximum relationship.
- All TEAEs by maximum intensity.
- Non-serious TEAEs reported by more than the reporting threshold of 5% of subjects. The cut-off will be applied before rounding on each treatment group and overall.

A further summary will be presented by treatment group at completion of PA0008 and overall displaying the frequency of TEAEs by descending frequency of PT.

An additional table will be presented by MedDRA SOC, HLT and PT, by treatment at time of AE onset (BKZ 160mg, BKZ 320mg and BKZ Total) for all TEAEs in PA0009 and all TEAEs that were ongoing from PA0008 at the time of the PA0009 EV. Ongoing TEAEs are defined as TEAEs that started prior to the PA0009 EV and continued after the first dose of study medication in PA0009. The 'BKZ 160mg' treatment column in this table will include subjects in both the BKZ 160mgLD and BKZ 160mg treatment groups.

TEAEs classified as Safety Topics of Interest and associated tables are defined in Section 10.2.3.

The following AE listings will be provided based on the ES:

- Glossary table for all AEs (this listing will include all events in PA0008 and PA0009 for subjects that were enrolled in PA0009 [with the exception of AEs with onset during placebo treatment]).
- All AEs (this listing will include all events in PA0008 and PA0009 for subjects that were enrolled in PA0009 [with the exception of AEs with onset during placebo treatment]).
- All SAEs (this listing will include all events in PA0008 and PA0009 for subjects that were enrolled in PA0009 [with the exception of AEs with onset during placebo treatment]).
- All AEs leading to study discontinuation.
- All deaths.

The following listings will be provided based on the SS:

- Serious infections TEAEs.
- Fungal infectious disorder TEAEs.
- Opportunistic infection (including tuberculosis) TEAEs.
- Malignant or unspecified tumor TEAEs.
- Malignant tumor TEAEs.
- Adjudicated cardiovascular TEAEs by event type.
- Adjudicated cardiovascular TEAEs by event type for major adverse cardiac events (MACE)
- Adjudicated cardiovascular TEAEs by event type for extended MACE
- TEAEs identified for potential review by the Cardiovascular Event Adjudication Committee.

- Neutropenia TEAEs.
- Suicidal ideation and behavior TEAEs.
- TEAEs identified for potential review by the Neuropsychiatric Adjudication Committee.
- TEAEs adjudicated by the Neuropsychiatric Adjudication Committee.
- Inflammatory bowel disease TEAEs.
- Hypersensitivity reaction TEAEs.
- Anaphylactic reaction TEAEs.
- Hepatic events TEAEs.
- Hospitalization/Emergency Room Visits.

10.2.1 Adverse event duration and time since first/last dose

Missing start or end dates will be imputed as described in Section 4.2.3 prior to any calculation described in this section.

The duration of each AE will be calculated as:

$$Duration\ (days) = date\ of\ outcome - date\ of\ onset + 1 \quad (18)$$

The time since first bimekizumab dose for each TEAE will be calculated three times:

- Relative to the date of first administration of bimekizumab in PA0008.
- Relative to the date of the first dose of bimekizumab 160mg or 160mgLD, only for AEs with onset during treatment with bimekizumab 160mg or 160mg LD OR
- Relative to the date of the first dose of bimekizumab 320mg, only for AEs with onset during treatment with bimekizumab 320mg.
  - For these criteria during treatment refers to TEAEs with onset up to 140 days after the last dose on that treatment.
- Relative to the start date of study medication in PA0009.

Time since first dose will be calculated as follows for AEs occurring on or after the reference date (as defined above):

$$Time\ since\ first\ BKZ\ dose\ (days) = Date\ of\ onset - Reference\ date + 1 \quad (19)$$

The time since most recent bimekizumab dose for each TEAE will be calculated as follows for AEs occurring on or after the reference date (as defined above):

$$Time\ since\ most\ recent\ BKZ\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (20)$$

For any AE occurring on the same day as a given dosing occasion the most recent dose will be considered to be the dose given on the same day ie, time since most recent dose would be equal to 1 for all such AEs.

For AEs occurring prior to the reference date (as defined above) the time since dosing will be calculated as follows for first/most recent BKZ dose:

$$Time\ since\ BKZ\ dose\ (days) = Date\ of\ AE\ onset - Reference\ date \quad (21)$$

Days on treatment at AE onset will be calculated three times using the same three reference dates as for time since first dose. Days on treatment at AE onset will be calculated as:

$$\begin{aligned} &Days\ on\ treatment\ at\ AE\ onset \\ &\quad = Date\ of\ last\ or\ latest\ dose\ prior\ to\ AE\ onset \\ &\quad - Reference\ date + 1 \end{aligned} \quad (22)$$

As above, for any AE occurring on the same day as a given dosing occasion the last or latest dose prior to AE onset will be considered to be the dose given on the same day as the event.

For AEs occurring prior to the reference date, the days on treatment will be 0.

10.2.2 Exposure-adjusted incidence rate and exposure-adjusted event rate

The time at risk (in days) at AE onset is the same as the time since first bimekizumab dose as described in Section 10.2.1 .

Total time at risk (as defined in Section 10.1) and time at risk at AE onset will be divided by 365.25 to give years at risk.

EAIR and EAER will be calculated separately for tables including all events in PA0008 and PA009 combined, and for tables including events with onset in PA0009 only. The former tables will use time at risk relative to the start date of bimekizumab 160mg/160mgLD or 320mg (for the 'BKZ 160mg' [this includes both BKZ 160mg and BKZ 160mgLD] and 'BKZ 320mg' columns) and time at risk relative to the date of the first dose of bimekizumab (for the 'BKZ Total' column). The latter table will use time at risk relative to the start date of study medication in PA0009.

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

$$EAIR = 100 * \frac{n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (23)$$

where n_{AE} is the number of subjects with the AE, $T_{Exp,i}$ is a subject's time at risk at AE onset in years (equation [16] in years) and $T_{Risk,j}$ is the total time at risk in years for subjects who did not experience the AE of interest.

If a subject has multiple events at the level of coding evaluated, the time at risk at AE onset is calculated from the first occurrence of the AE.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (24)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (25)$$

$$CI_{Lower} = 100 * \frac{LCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (26)$$

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (27)$$

where n_{AE} is the number of subjects with the AE and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's time at risk at AE onset in years, n_{noAE} is the number of subjects without the AE and $T_{Risk,j}$ the total time at risk for subjects who did not experience the AE.

The EAER is defined as the number of AEs reported up to 140 days after last dose, including repeat occurrences in individual subjects, and adjusted for exposure, and will be scaled to 100 subject-years:

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (28)$$

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

No CI will be computed for EAER.

10.2.3 Adverse events of special interest and safety topics of interest

AESI (in the opinion of the investigator) will be flagged in the study database. In addition, an AESI is considered to have occurred if any TEAE which meets the Hy's Law criteria, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality. Hy's law criteria will be summarized as described in Section 10.3.

TEAEs are defined as Safety Topics of Interest and reported as follows:

1. Infections (serious, opportunistic, fungal and TB)

- Serious infections will be identified based on MedDRA classification (SOC "Infections and infestations"). (Although not required by the 'Safety Topics of Interest for the Bimekizumab Program' document, a separate table will be created for these events.)
- 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 "Fungal infectious disorders".
- Opportunistic infections (including TB) 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 process for identifying opportunistic infections is outlined in Section 12.4.

2. Malignancies

- One table will be based on the criteria standardized MedDRA query (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 "Malignancies" table will be a subset of the events included in the "Malignancies (including unspecified)" table. While the "Malignant tumours (SMQ)" is most relevant, "Malignant or unspecified tumours (SMQ)" must be reviewed for potential malignancies.

The output tables will include 2 different overall incidence rows:

- The first overall incidence row will summarize "Any Malignancy" 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 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)".

3. MACE

Major adverse cardiac events will be presented in a table. The classification of an event as MACE is determined by an external cardiovascular event adjudication committee.

A separate table and listing will present adjudicated cardiovascular events by type. For each cardiovascular event type (24 in total), the individual PTs which fall within each event type will be summarized.

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 event types in Table 10-3 will be considered an extended MACE event.

Table 10-3: Extended MACE types

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 (ie, cause of death unknown)

CV=cardiovascular; ER=emergency room; MI=myocardial infarction.

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.

4. Neutropenia

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

- Autoimmune neutropenia
- Band neutrophil count decreased
- Cyclic neutropenia
- Febrile neutropenia
- Idiopathic neutropenia
- Neutropenia

- Neutropenic infection
- Neutropenic sepsis
- Neutrophil count decreased

5. Suicidal Ideation and Behavior

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). A table and listing for SIB events as determined by the adjudication committee will be produced.

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. A separate listing will also be produced to summarize the adjudicated results of all events escalated to the full committee.

6. Inflammatory bowel disease

An external IBD adjudication committee will evaluate potential IBD events and will classify these according to the event type in Table 10-4.

Table 10-4: Inflammatory bowel disease types

Event Type Code	Event Type
1	Possible IBD – Crohn's Disease
2	Probable IBD – Crohn's Disease
3	Definite IBD – Crohn's Disease
4	Possible IBD – Ulcerative Colitis
5	Probable IBD – Ulcerative Colitis
6	Definite IBD - Ulcerative Colitis
7	Possible IBD - Unclassified
8	Probable IBD - Unclassified
9	Definite IBD - Unclassified
10	Symptoms not consistent with IBD
11	Possible IBD – Microscopic Colitis
12	Probable IBD – Microscopic Colitis
13	Definite IBD - Microscopic Colitis
14	Possible IBD – no further differentiation possible
15	Probable IBD – no further differentiation possible

Table 10-4: Inflammatory bowel disease types

Event Type Code	Event Type
16	Definite IBD - no further differentiation possible
99	Not enough information to adjudicate

IBD=inflammatory bowel disease.

A table for adjudicated definite IBD events (including event type codes 3, 6, 9, 13 and 16), as determined by the adjudication committee, will be presented for all subjects and stratified by previous medical history of IBD. Previous medical history of IBD will be determined using the information recorded on the Extra-Articular Assessment form at Screening in PA0008 ("Does subject have a history of IBD?").

Similar tables will be presented for adjudicated probable IBD events (including event type codes 2, 5, 8, 12 and 15) and adjudicated possible IBD events (including event type codes 1, 4, 7, 11 and 14). These tables will be produced for all subjects and stratified by previous medical history of IBD as defined above.

A listing of all events identified for potential review by the IBD adjudication committee will be presented. This listing will indicate whether each event was escalated to the committee for formal review and adjudication.

A separate table and listing will present the adjudicated IBD events by type. For each of the 17 IBD event types (event type codes 1 through 16 and 99), the individual PTs which fall within each event type will be summarized.

Finally, a separate listing will be presented showing individual diagnostic criteria met for each adjudicated IBD event.

7. Hypersensitivity (including Anaphylaxis)

A separate table will be prepared based on the MedDRA anaphylaxis algorithm (Section 12.5) 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. 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.

Injection site reactions will be evaluated based on the "any TEAE" table by looking under the following HLTs: "Administration site reactions NEC" and "Injection site reactions".

8. Hepatic events and DILI

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, all TEAEs will be included which code to a PT included in the Scope=Broad and/or Scope=Narrow.

Note that all AEs meeting the above criteria will be included and will not be limited to events that the Investigator determined to be related to study drug.

The incidence of AEs defined as Safety Topics of Interest will be summarized by MedDRA SOC, HLT, and PT (apart from the summary of each cardiovascular event type which will use PT only). The EAIR with associated 95% CI and the EAER will be included in the summary tables.

10.2.4 Impact of COVID-19

In order to assess the impact of the COVID-19 global pandemic on the primary safety endpoint of incidence of TEAEs and serious TEAEs, additional listings and summaries will be presented.

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

- If the date of AE onset (based on imputed start date) is prior to 11 March 2020 the AE will be assigned as 'Prior to COVID-19 pandemic'
- If the date of AE onset (based on imputed start date) on or after 11 March 2020 the AE will be assigned as 'During the COVID-19 pandemic'
  - The date of 11 March 2020 is chosen as the date the World Health Organization declared COVID-19 as a pandemic.

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

The following categories of TEAE will be summarized by MedDRA SOC, HLT and PT, including EAIR and EAER:

- All TEAEs by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic' and 'During the COVID-19 pandemic')
- All TEAEs by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic' and 'During the COVID-19 pandemic') and by region
- All serious TEAEs by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic' and 'During the COVID-19 pandemic')
- All serious TEAEs by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic' and 'During the COVID-19 pandemic') and by region
- All COVID-19 related TEAEs by treatment at completion of PA0008 and overall
  - COVID-19 related TEAEs will be identified based on the verbatim term including the text string 'COVID'. These will include confirmed or suspected COVID-19 infections.

- All COVID-19 related TEAEs by treatment at completion of PA0008 and overall, and by region

The following categories of TEAE will be summarized by MedDRA SOC, HLT and PT:

- TEAEs leading to study discontinuation and/or permanent withdrawal of study medication by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic' and 'During the COVID-19 pandemic')
- TEAEs leading to study discontinuation and/or permanent withdrawal of study medication by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic' and 'During the COVID-19 pandemic') and by region

A separate listing of all COVID-19 related AEs will be presented, where COVID-related AEs are identified as described above. In addition, the time of onset of each AE relative to the COVID-19 pandemic will be flagged in all AE listings.

For the purpose of calculating EAIR and EAER prior to and during the COVID-19 pandemic the rules in Table 10-5 will be applied in the calculation of exposure time at risk. An individual subject may therefore be counted in the denominator for both periods ('Prior to COVID-19 pandemic' and 'During the COVID-19 pandemic') dependent on whether the subject is still considered at risk on 11 March 2020. In this case time at risk will be calculated separately for each period. Subjects who have discontinued study medication prior to 11 March 2020 may be included in the denominator for the 'During the COVID-19 pandemic' period if they are still considered to be at risk following the last dose of study medication in the 'Prior to COVID-19 pandemic' period.

Subjects who are no longer in the exposure time at risk period (Table 10-2) on 11 March 2020, will not be counted in the denominator for the 'During the COVID-19 pandemic' period.

Table 10-5: Calculation of exposure time at risk in relation to COVID-19

Study Period	Start Date	End Date	Duration of Exposure
Prior to COVID-19 pandemic	First dose of BKZ 160mg in PA0009	10MAR2020	For subjects who did not discontinue medication in the 'Prior to COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is on or after 11MAR2020): (End date – start date + 1) For subjects who discontinued medication in the 'Prior to COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is prior to 11MAR2020): If the following is true: Minimum of (Last dose date in PA0009 + 140[a]) and (Date of last clinical contact[b]) is ≥11MAR2020 Then the duration of exposure will be calculated as follows: (End date – start date + 1) Else duration of exposure will be calculated as follows: Minimum of (Last dose date in PA0009 – First dose date in PA0009 + 140[a]) and (Date of last clinical contact[b] – First dose date in PA0009 + 1) For subjects that died on or before 10MAR2020: Date of death – Start date + 1 Note: If the date of death is later than 140 days following the last dose of BKZ, this rule does not apply.

Table 10-5: Calculation of exposure time at risk in relation to COVID-19

Study Period	Start Date	End Date	Duration of Exposure
During the COVID-19 pandemic	11MAR2020	Last dose of BKZ 160mg in PA0009	For subjects who did not discontinue medication in the 'Prior to COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is on or after 11MAR2020): Minimum of (Last dose date in PA0009 – 11MAR2020 + 140[a]) and (Date of last clinical contact[b] – 11MAR2020 + 1) For subjects that died: Date of death – 11MAR2020 + 1. Note: If the date of death is later than 140 days following the last dose of BKZ, this rule does not apply. For subjects who discontinued medication in the 'Prior to COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is prior to 11MAR2020): If the following is true: Minimum of (Last dose date in PA0009 + 140[a]) and (Date of last clinical contact[b]) is ≥11MAR2020 Then the duration of exposure will be calculated as follows: [Minimum of (Last dose date in PA0009 – 11MAR2020 + 140[a]) and (Date of last clinical contact[b] – 11MAR2020 +1)] For subjects that died within 140 days following the last dose of BKZ this rule be adjusted to: Date of death – 11MAR2020 + 1

AE=adverse event; BKZ=bimekizumab; SFU=Safety Follow-Up.
[a] 140 days refer to 5 half-lives of BKZ.
[b] Date of last clinical contact for each subject is defined as the maximum of [last visit date including SFU visit, last AE start date (including imputed AE start dates), date of study termination or completion, last date of study drug administration following rules for partial treatment end dates as per Section 4.2.5].

10.3 Clinical laboratory evaluations

The routine clinical laboratory evaluations specified in Table 10–6 will be summarized. If any

additional analytes are recorded, they will be listed only.

Table 10–6: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	Urine dipstick for pregnancy testing[a]
Eosinophils	Chloride	Urinalysis[b]
Lymphocytes	Magnesium	
Atypical lymphocytes	Potassium	
Monocytes	Sodium	
Neutrophils	Glucose (random)	
Hematocrit	BUN	
Hemoglobin	Creatinine	
MCH	AST	
MCHC	ALT	
MCV	ALP	
Platelet count	GGT	
RBC count	Total bilirubin	
WBC count	LDH	
	Total cholesterol	
	Uric acid	
	CRP	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=high sensitivity C-reactive protein; GGT=gamma glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume

[a] A urine pregnancy test will be performed for women of childbearing potential if there is a suspicion of pregnancy. A positive urine pregnancy test should always be confirmed with a serum pregnancy test.

[b] These measurements will be performed only if a urinalysis is required for safety reasons.

Separate summary tables for hematology and biochemistry variables will be provided, based on data from scheduled visits. Observed values and changes from PA0009 Laboratory Baseline will be summarized, by treatment group at completion of PA0008 and overall. CRP will be summarized separately as described in Section 8.3.

Any laboratory values (with the exception of CRP) reported as <xx or >xx in the database will be imputed as the value of 'xx' for the purpose of calculating changes from baseline and for summary statistics. The original value will be reported in any listings.

Summary tables of the number and percentage of subjects experiencing at least 1 on-treatment markedly abnormal value during the Treatment Period (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication) for each hematology and biochemistry variable will be presented by treatment group at completion of PA0008 and overall. Markedly abnormal values for hematology and biochemistry are defined in Table 10–7 and Table 10–8.

Tables of markedly abnormal laboratory data subject numbers will be provided including all values classified as markedly abnormal at scheduled and unscheduled visits.

Table 10–7: Definitions of markedly abnormal hematology values

Variable (SI Units)	Markedly Abnormal Definition	
	Low	High
Hemoglobin (g/L)	<80	>40 above ULN
Lymphocytes (10^9/L)	<0.5	>20.0
Neutrophils (10^9/L)	<1.0 [a]	N/A
Platelets (10^9/L)	<50	N/A
Leukocytes (10^9/L)	<2.0	>100

N/A=not applicable; ULN=upper limit of normal

Data source: modified from Appendix Rheumatology Common Toxicity Criteria v.2.0 presented in Woodworth et al, 2007

[a] Withdrawal criteria for neutrophils is <0.5.

Table 10–8: Definitions of markedly abnormal biochemistry values

Variable (SI Units)	Markedly Abnormal Definition	
	Low	High
ALP	N/A	>5.0 x ULN

Table 10–8: Definitions of markedly abnormal biochemistry values

Variable (SI Units)	Markedly Abnormal Definition	
	Low	High
ALT	N/A	>5.0 x ULN
AST	N/A	>5.0 x ULN
Total bilirubin	N/A	>3.0 x ULN
GGT	N/A	>5.0 x ULN
Creatinine	N/A	>3.0 x ULN
Glucose (mmol/L)	<1.7	>13.9
Calcium (mmol/L)	<1.75	>3.1
Magnesium (mmo/L)	<0.4	>1.23
Potassium (mmol/L)	<3.0	>6.0
Sodium (mmol/L)	<130	>155
Total cholesterol (mmol/L)	N/A	>10.34

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma glutamyl transferase; N/A=Not applicable; ULN=upper limit of normal.

A summary of the number and percentage of subjects with a given Common Terminology Criteria for Adverse Events (CTCAE) grade (0, 1, 2, 3 or 4) based on minimum/maximum on-treatment value in PA0009 (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication), will be presented by laboratory variable and treatment group at completion of PA0008. This summary will be provided only for selected laboratory variables. Definitions of CTCAE grades are given in Table 10–9 and Table 10–10.

A shift table of the number and percentage of subjects experiencing CTCAE grade 0, 1, 2, 3 or 4 values (as applicable) at PA0009 Laboratory Baseline to minimum/maximum post-PA0009 Laboratory Baseline CTCAE grade will be presented by laboratory variable and treatment group at completion of PA0008. The minimum/maximum post-PA0009 Laboratory Baseline CTCAE grade will include all on-treatment scheduled and unscheduled assessments (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication).

Table 10–9: Definitions of CTCAE grade 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

LLN=lower limit of normal, N/A=not applicable; ULN=upper limit of normal; WBC=white blood cell

Table 10–10: Definitions of CTCAE grade by biochemistry parameter

Parameter (unit)	Definition	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine	High	umol/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

LLN=lower limit of normal, N/A=not applicable; ULN=upper limit of normal.
Note that subjects who meet the decreased potassium criterion of 3.0-<LLN, which is specified as the decreased potassium lab criterion for both CTCAE Grade 1 and Grade 2, will be counted as Grade 2.

The number and percentage of subjects with elevated liver function tests will be presented by treatment group at completion of PA0008 and overall, using on-treatment assessments from all visits in PA0009 (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication) from all visits in PA0009 including those at PA0009 Laboratory Baseline, unscheduled, ET and SFU visits. Each subject will be counted once only. The number and percentage of subjects in the following categories at any time during the study will be presented:

- AST: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN.
- ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN.
- AST or ALT: >3xULN, >5xULN, >8xULN, >10xULN, >20xULN.
- Total bilirubin: >1.5xULN, >2xULN.

The number and percentage of subjects who meet Hy's Law criteria (Section 10.2.3) will be presented by treatment group at completion of PA0008 and overall, using on-treatment assessments (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication) from all visits including PA0009 Laboratory Baseline, unscheduled, ET and SFU visits. Hy's Law criteria are displayed below:

- (AST ≥3xULN or ALT ≥3xULN) and Total Bilirubin ≥2xULN in the absence of ALP ≥2xULN.

To meet the above criterion, a subject must experience the elevation in total bilirubin and ALT or AST and the absence of ALP elevation at the same visit.

All hematology and biochemistry laboratory data (except CRP) will be listed, including age, sex, race, weight, changes from PA0009 Laboratory Baseline for numeric variables, flags for measurements outside the normal ranges, flags for measurements meeting the criteria for each CTCAE grade (Table 10–9 and Table 10–10), the relative study day, a flag for whether the test was not done and a flag for whether the subject was fasting.

CRP will be listed separately as described in Section 8.

Values that are below the lower limit of the reference range will be flagged as 'L' (low) and values that are above the upper limit of the reference range will be flagged as 'H' (high) in listings. Values that meet the criteria for each CTCAE grade will be flagged as 'LGrx' or 'HGrx' accordingly.

The markedly abnormal laboratory results will be listed separately.

Any additional laboratory assessments performed during the study will be listed separately.

10.4 Potential drug-induced liver injury assessment

All PDILI events require immediate action, testing, and monitoring. The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the study medication are included but not limited to those listed in Table 10–11 and Table 10–12.

PDILI laboratory results and additional PDILI information will be listed by treatment group at completion of PA0008 and subject. Where appropriate data will be included in the standard listings as indicated below:

- Family medical history, including any DILI-relevant medical conditions or inheritable disorders, start year and end year (or ongoing if applicable) (presented in the demographics section only for subjects with PDILI events)
- Study medication administration, including the date and time of most recent study medication administration, whether the subject discontinued study medication and the reason

for discontinuation (presented in the compliance and drug concentration data section with a separate listing for PDILI events).

- Blood sample collection for PK including the variable, unit, date and time the sample was taken, and the result (presented in the compliance and drug concentration data section as part of the standard listing).
- Laboratory tests as detailed in Table 10–6 (presented in the laboratory measurements section with a separate listing of PDILI events).
- Vital signs (presented in the safety analysis section as part of the standard listing)
- Lifestyle, including whether the subject has used alcohol in the past 6 months and whether the subject has used illicit drugs in the past 6 months (presented in the demographics section only for subjects with PDILI events).
- Hepatic event medical history, including any medical conditions which could have contributed to the suspected hepatic event prior to study entry will be listed together with all medical history data (presented in the demographics section).
- Symptoms of hepatitis and hypersensitivity, including whether the subject has taken any potentially hepatotoxic medications, whether the subject is experiencing symptoms of hepatitis, and whether the subject is experiencing symptoms of hypersensitivity (presented in the safety analysis section only for subjects with PDILI events).

Table 10–11: Additional potential drug-induced liver injury information

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
Pertinent medical history, including the following: • History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other “fatty liver disease”) • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (eg, Gilbert’s syndrome, alpha-1 antitrypsin deficiency) • Recent travel • Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)

Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
Alcohol and illicit drug use
Results of liver imaging or liver biopsy, if done
Results of any specialist or hepatology consult, if done
Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Table 10–12: Potential drug-induced liver injury laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophil antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen[a]
Chemistry	Amylase
	ALT, AST
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[b]
	Serum pregnancy test
	PK sample

Table 10–12: Potential drug-induced liver injury laboratory measurements

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

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

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

10.5 Vital signs and other observations related to safety

10.5.1 Vital signs

The following vital signs measurements will be assessed:

- Systolic blood pressure (mmHg).
- Diastolic blood pressure (mmHg).
- Pulse rate (bpm).
- Temperature (°C).
- Body weight (kg)

The following summaries will be provided:

- A summary of the absolute and change from PA0008 Baseline for each vital sign variable at each visit, by treatment group at the completion of PA0008 and overall.
  - This summary will include the derived BMI at each time point.
- A summary of the number and percentage of subjects experiencing at least 1 on-treatment markedly abnormal value, as defined in Table 10–13, for a vital sign variable during the Treatment Period (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication) by treatment group at the completion of PA0008 and overall (based on change from PA0008 Baseline).

Table 10–13: Definitions of markedly abnormal blood pressure values

Variable (Unit)	Markedly abnormal low	Markedly abnormal high
Systolic blood pressure (mmHg)	<90 and a decrease from PA0008 Baseline of ≥20	>180 and an increase from PA0008 Baseline of ≥20
Diastolic blood pressure (mmHg)	<50 and a decrease from PA0008 Baseline of ≥15	>105 and an increase from PA0008 Baseline of ≥15

Vital signs measurements, including age, sex, race, weight, and flags to identify markedly abnormal values, will be listed. The listing will include the derived BMI at each time point.

10.5.2 Electrocardiograms

A summary of the number and percentage of subjects with normal, abnormal not clinically significant, and abnormal clinically significant ECG results by visit will be presented by treatment group at completion of PA0008 and overall.

The following ECG variables will be summarized by visit (absolute values and change from PA0008 Baseline), by treatment group at completion of PA0008 and overall:

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

Outliers in QTcF and QTcB are defined as values meeting the following criteria at any time in PA0009:

- QTcF or QTcB >450 ms OR
- QTcF or QTcB change from PA0008 Baseline >30 ms

Outliers will be summarized using the following categories:

- Values >450 ms, >480 ms and >500 ms
- Increase from PA0008 Baseline of >30 ms, >60 ms and >90 ms
- Value >450 ms AND increase from PA0008 Baseline of >30 ms
- Value >500 ms AND increase from PA0008 Baseline of >60 ms

The summary will include the number and percentage of subjects who meet the criteria above at any on-treatment (scheduled or unscheduled) assessment (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication).

All ECG variables will be listed. A separate listing of ECG findings will be presented together with the interpretation (normal, abnormal not clinically significant, or abnormal clinically significant).

10.5.3 Other safety variables

Assessment of Tuberculosis

Scheduled TB laboratory test results will be included in the laboratory data listings. Results of unscheduled TB testing at local laboratories will be listed separately. The response to the first question of the 'Evaluation of signs and symptoms of tuberculosis' questionnaire data will be listed.

Electronic Columbia Suicide Severity Rating Scale

The electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Posner et al, 2011; Mundt et al, 2010).

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

[redacted]

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

[redacted]

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

Self-injurious behavior without suicidal intent will also be reported.

The eC-SSRS can be administered to assess suicidal ideation and behavior over a lifetime, or since the last time it was assessed. The intent in this OLE study was to assess suicidal ideation and behavior since the last time it was assessed and refer back to the lifetime assessment conducted at the start of PA0008. However, some subjects completed the 'lifetime' assessment (in error) at one or more visits in PA0009 and recorded positive responses to some questions. Based on a review of their original lifetime assessment in PA0008, these positive responses are not considered to represent a change in suicidal ideation and behavior during the study. The summary tables will include only the 'since last assessment' responses; all responses will be listed.

The incidence of subjects with suicidal ideation, suicidal behavior, suicidal ideation or behavior and self-injurious behavior at any on-treatment assessment (excluding any measurements that occurred prior to the first administration of study medication in PA0009 or more than 140 days after the last administration of study medication), will be summarized by treatment group at completion of PA0008.

eC-SSRS data will be listed.

Health Care Provider Consultations

Out-patient non-protocol health care provider consultations will be listed.

Extra-articular assessments

Extra-articular assessments performed after the PA0009 EV will be listed separately for the SS.

10.5.4 Comments

A listing of comments will be presented, based on the ES. This listing will include comments received from the laboratory vendors (including safety laboratory data, PK data, and ADAb data).

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12 APPENDIX

12.1 American College of Rheumatology Response Criteria

The rules for handling missing data in relation to defining the achievement of ACR20 response are provided in Table 12-1. Similar rules will apply for the definition of ACR50 and ACR70. This table also indicates, where appropriate, the imputation as a nonresponder (DTYPE = WC) in the analysis datasets for the NRI analyses. For tables presented on OC data, the data selected will include all instances where DTYPE is not populated in the analysis datasets.

Table 12-1: Handling Missing Data for American College of Rheumatology Response Criteria Derivation

Components – Joint Counts	Other Components	Other Component Status	ACR	DTYPE
TJC and SJC both missing, or one is missing and the other improved ≥20%	3 or more components present	3 or more components ≥20% improvement	N	WC
TJC and SJC both missing, or one is missing and the other improved ≥20%	5 components present	2 or fewer components ≥20% improvement	N	
TJC and SJC both missing, or one is missing and the other improved ≥20%	4 components present	2 or more components ≥20% improvement	N	WC
TJC and SJC both missing, or one is missing and the other improved ≥20%	4 components present	1 or no components ≥20% improvement	N	
TJC and SJC both missing, or one is missing and the other improved ≥20%	3 components present	2 or 1 components ≥20% improvement	N	WC
TJC and SJC both missing, or one is missing and the other improved ≥20%	3 components present	No components with improvement ≥20%	N	

Table 12-1: Handling Missing Data for American College of Rheumatology Response Criteria Derivation

Components – Joint Counts	Other Components	Other Component Status	ACR	DTYPE
TJC and SJC both missing, or one is missing and the other improved ≥20%	0, 1 or 2 components present	Any	N	WC
TJC or SJC missing and the component present did not improve ≥20%	Any or none	Any	N	
TJC and SJC present but one or fewer ≥20% improvement	Any or none	Any	N	
TJC and SJC present and both ≥20% improvement	All 5 components present	3 or more components ≥20% improvement	Y	
		Fewer than 3 components ≥20% improvement	N	
	4 components present	3 or more components ≥20% improvement	Y	
		2 components ≥20% improvement	N	WC
		1 or fewer components ≥20% improvement	N	
	3 components present	3 components ≥20% improvement	Y	
		2 or 1 components ≥20% improvement	N	WC
		No components ≥20% improvement	N	
	0, 1 or 2 components present	Any	N	WC

12.2 Minimal Disease Activity

The rules for handling missing data in relation to defining the achievement of MDA are provided in Table 12-2. This table also indicates, where appropriate, the imputation as a nonresponder (DTYPE = WC [worst case]) in the analysis datasets for the NRI analyses. For tables presented on OC data, the data selected will include all instances where DTYPE is not populated in the analysis datasets.

Table 12-2: Handling Missing Data for MDA Derivation

Components	Component Status	MDA	DTYPE
All 7 components present	5 or more meet criteria for MDA	Y	
	Less than 5 meet criteria for MDA	N	
6 components present	5 or more meet criteria for MDA	Y	
	4 meet criteria for MDA	N	WC
	3 or fewer meet criteria for MDA	N	
5 components present	All meet criteria for MDA	Y	
	3 or 4 meet criteria for MDA	N	WC
	2 or fewer meet criteria for MDA	N	
4 components present	4, 3 or 2 meet criteria for MDA	N	WC
	1 or fewer meet criteria for MDA	N	
3 components present	Any meet criteria for MDA	N	WC
	None meet criteria for MDA	N	
0, 1 or 2 components present	Any	N	WC

12.3 Classification of the SF-36 questionnaire

The 8 different scores calculated from the SF-36 questionnaire are presented in Table 12–3.

Table 12–3: Classification of the SF-36 questionnaire

	Scales
[redacted]	Physical Functioning
	Role-Physical
	Bodily Pain
	General Health
[redacted]	Vitality
	Social Functioning
	Role-Emotional
	Mental Health

12.4 Identification of Opportunistic infections

Opportunistic infections are identified based on a reference spreadsheet (OI - MedDRA V 19.0.xlsx)

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 PTs to be classified as opportunistic infections using either a single 'x' or a double 'xx'.

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

Step 2: Refer to column C of the spreadsheet which identifies the PTs that need to be evaluated on a case-by-case basis by the study physician in order to determine whether 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. The IDC will then agree on the final adjudication for each potential opportunistic infection.

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.

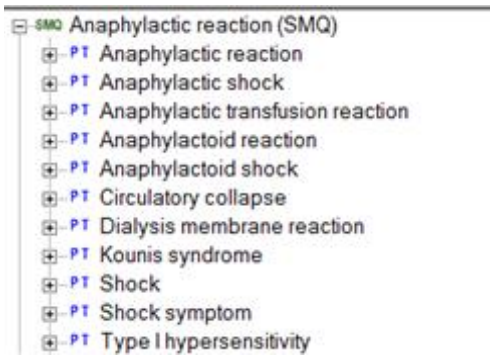
Opportunistic Infection – Final Adjudication – For new events, this is always left blank by the programmers. It should be completed by the study physician/IDC for every event that appears in the listing. For events adjudicated as opportunistic, the field should be populated with a "Y".

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.

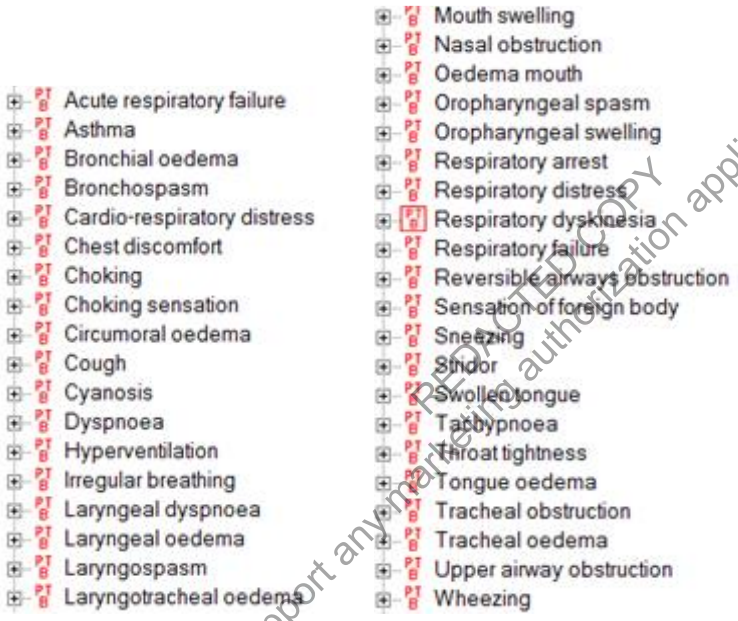
12.5 MedDRA algorithmic approach to anaphylaxis

The SMQ Anaphylactic reaction consists of three parts:

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

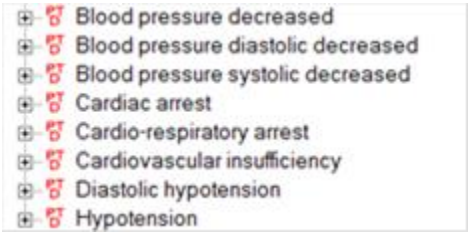


- A **broad search** that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction and categorized in B, C or D
  - Cat B



  - Cat C

– Cat D



- 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 events 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.

12.6 COVID-19 data collection

For study visits impacted by COVID-19, additional data will be collected on a separate dedicated eCRF page.

The following information will be reported:

- Specification of the impacted visit (eg, Visit 5)
- Date of the impacted visit
- Category of the impact (multiple categories may apply to the same visit)
  - 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
  - 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
- Relationship to COVID-19
  - Confirmed COVID-19 infection
  - Suspected COVID-19 infection
  - General circumstances around COVID-19 without infection
  - Other

A narrative of the event will also be collected.

13 AMENDMENT TO THE STATISTICAL ANALYSIS PLAN

13.1 Amendment 1

13.1.1 Rationale for the amendment

The main objective of this SAP amendment is to incorporate relevant updates based on Protocol Amendment 2, dated 09 Mar 2018 and Protocol Amendment 3, dated 11 Dec 2019. Additional details and modifications have been made throughout the document in order to align with the most recent bimekizumab program conventions.

13.1.2 Modifications and changes

The SAP has been amended to:

- Amend the study procedures and assessments to be performed at the SFU visit. Efficacy assessments were removed since they are not required at the SFU visit.
- Key inclusion criteria have been removed from the SAP as these are available in the final protocol and not relevant to the analyses described within the SAP.
- Change from PA0009 EV for safety and efficacy variables will no longer be presented, since the EV assessment is made after 36 or 48 weeks of bimekizumab treatment and there is unlikely to be any further important change.
- Change from PA0008 Baseline and from PA0009 EV for laboratory parameters (apart from CRP) will not be presented, due to a change in laboratory vendor between PA0008 and PA0009. Laboratory Baseline is defined as the earliest value in PA0009 at or prior to PA0009 Week 12.
- Summaries of ACR20, ACR50, ACR70, PASI75, PASI90 and PASI100 response at each post-PA0008 Baseline visit through to PA0009 Week 104, for subjects who were responders at PA0008 Week 12 have been added. These summaries will be used to assess maintenance of response.
- A summary of BSA at each visit in PA0009 has been added
- The relative day will now be calculated twice, once relative to the start of study medication in PA0008 and once relative to the start of study medication in PA0009.
- A definition of the dosing period has been added.
- Baseline values (with the exception of PA0009-Laboratory Baseline values) will now be taken directly from PA0008 database, and not re-derived.
- The previous version of the SAP stated that ET visits would be mapped to a scheduled site visit if they fell on the scheduled date for that visit. This has been updated to say that they will be mapped to a scheduled visit if they fall within the protocol-defined visit window for that visit, unless there is an existing scheduled site visit in that window, in which case they will be mapped to the next scheduled site visit. Unscheduled visits will now also mapped to scheduled visits if they fall within the protocol-defined window for that visit, unless there is already a scheduled site visit or ET visit in that window. The wording has been clarified regarding unscheduled assessments performed at specific time points.

- The definition of the sub-populations for the SS has been clarified to be based on concomitant rescue medications only.
- Sub-populations of the SS are used to report only TEAEs, serious TEAEs, AE Overview and Exposure rather than all primary and secondary safety variables.
- Summaries based on sub-populations of the SS will only be reported in the event that the number of subjects receiving rescue medication is ≥10% of the total number of subjects in the SS.
- The previous definition of the FAS included all enrolled subjects who received at least 1 dose of IMP and have a valid measurement for at least 1 efficacy variable at PA0009 study entry. This has been updated to include all subjects in the ES who received at least one dose of study medication in PA0009 and have a valid measurement for at least one efficacy variable after PA0009 EV in order to identify subjects who have had assessments during PA0009.
- Summaries by randomized treatment in PA0008 will not be produced, as subjects will have been on a constant dose of bimekizumab 160mg or 320mg for at least 36 weeks prior to PA0009 entry. Maintenance of response displays will be split by treatment sequence across PA0008 and PA0009. Safety displays using PA0008 information will incorporate exposure in PA0008.
- For summaries of AEs including data from both PA0008 and PA0009, the 160mgLD and 160mg treatments have been combined.
- The subgroup definition of 'Concomitant disease-modifying anti-rheumatic drug (DMARD) status at PA0009 entry' has been updated to 'Concomitant DMARD status at start of PA0008'.
- The rules for NRI and MI for missing efficacy data have been clarified to state that imputations will only be performed for subjects in the FAS for PA0009. In addition the SAP has been updated to state that for NRI, the imputation will be re-derived at the PA0009 EV instead of using the PA0008 Week 48 imputed value; this is due to slight differences in the derivation rules for some endpoints between the PA0008 and PA0009 SAPs.
- The MI procedures have been updated for all endpoints to use OC data from both PA0008 and PA0009 studies such that missing data across both studies will be imputed. Thus, the procedure will estimate an imputation model at each post-PA0008 Baseline visit where efficacy variables are collected. The covariate for PA0009 EV has therefore been deleted from the model.
- Additional imputation rules have been added for PASI responder data
- The endpoints/components for which MI will be performed have been clarified in the section on handling missing data for the efficacy analyses.
- The presentation of CRP data following MI has been updated to use the geometric mean and 95% CI for the geometric mean.
- The handling of missing data for AEs and concomitant medications has been updated to clarify the rules in the presence of a partial start date and a known end date.

- For summaries based on MI of missing data, the covariates in the MI model will no longer include disease duration and concomitant DMARD status.
- The seed used for all MI procedures has been updated to 2017.
- A summary of study medication discontinuation and a listing of subjects excluded from at least one analysis set have been added.
- Methods for calculating total days on study medication have been added to the SAP
- Tables and listings presenting the impact of COVID-19 on the study data collection have been added
- The listing of lifestyle data has been removed, as this data is not generally collected in PA0009. Lifestyle data may be collected for PDILI cases, and this data will be listed.
- The categories and rules for identifying rescue medications have been updated.
- Efficacy data collected after a subject has used a prohibited medication will no longer be treated as missing since the primary purpose of this study is to assess safety.
- Compliance categories have been updated from ≤80% and >80% to ≤75% and > 75% to match the overall program conventions for bimekizumab.
- Sensitivity analyses based on OC data were restricted to ACR, PASI, MDA, LDI and MASES. Additional sensitivity analyses based on MI of component scores were added for ACR and PASI response variables.
- Summaries of MASES were restricted to subjects with enthesitis (MASES > 0) at PA0008 Baseline. Summaries of LDI were restricted to subjects with dactylitis (LDI > 0) at PA0008 Baseline.
- Summaries of ACR component scores (TJC, SJC, HAQ-DI, PtAAP, PhGADA and PGADA) were added.
- CRP values below the LLOQ will now be set to half LLOQ (0.08mg/L) prior to reporting
- Plots of geometric mean bimekizumab plasma concentration versus time by treatment group and cumulative ADAb status have been added based on ADAb status in PA0008 and PA0009.
- ADAb status categories have been redefined and appropriate plots and summaries have been added based on the most recent bimekizumab program conventions.
- Summaries of all TEAEs and serious TEAEs in PA0008 and PA0009 combined, a corresponding AE overview table and a table of exposure across PA0008 and PA0009 have been added.
- Summaries have been added for fatal TEAEs; TEAEs leading to permanent withdrawal of study medication; serious TEAEs by maximum relationship and fatal TEAEs by maximum relationship. The Adverse Drug Reaction summary has been removed. A listing of Hospital/ER visits has been added.
- A summary of TEAEs by descending frequency of PT has been added

- A summary of TEAEs in PA0009 and ongoing TEAEs from PA0008 has been added
- Tables and listings have been added to evaluate the effect of COVID-19 on reporting of TEAEs
- The summaries and listings for AEs of special interest have been updated to match more recent guidelines.
- Further clarification has been added to the definitions of EAIR and EAER.
- Summaries and shift tables of subjects experiencing a given CTCAE grade for selected laboratory parameters have been added.
- Summaries presenting outliers for QTcB and QTcB have been added.
- A listing of ECG findings has been added.
- Body weight and BMI have been added to the listing and summary table for vital signs variables
- Physical examination data will no longer be listed as this data is not collected.
- A listing of healthcare provider consultations listing has been added.
- A listing of comments has been added.
- A listing of procedure history has been added.
- The appendices containing the copies of the individual questionnaires have been removed

13.2 Amendment 2

Not applicable.

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

This document has been reviewed and approved per the Review and Approval of Clinical Documents Standard Operating Procedures. Signatures indicate that the final version of the Statistical Analysis Plan (SAP) or amended SAP is released for execution.

Approval Signatures

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