STATISTICAL ANALYSIS PLAN

Study: AS0009

Product: Bimekizumab

A MULTICENTER, PHASE 2B, OPEN-LABEL EXTENSION STUDY TO EVALUATE THE LONG-TERM SAFETY AND EFFICACY OF BIMEKIZUMAB IN SUBJECTS WITH ANKYLOSING SPONDYLITIS

SAP/Amendment Number	Date
Final SAP 1.0	09 Feb 2018
Final SAP 2.0	26 Mar 2018
SAP Amendment 1	04 Aug 2020
SAP Amendment 2	13 Jun 2022
SAP Amendment 3	10 Jan 2023

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LIST OF ABBREVIATIONS

ACP	above the cut point
ADAb	anti-bimekizumab antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AS	ankylosing spondylitis
ASAS20,40,5/6	Assessment in SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria
ASAS-PR	Assessment in SpondyloArthritis International Society Partial Remission response
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score-C-reactive protein
ASQoL	Ankylosing Spondylitis Quality of Life
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BCP	below the cut point
BKZ	bimekizumab
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
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
DMARD	disease-modifying antirheumatic 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
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
IXRS	interactive voice or web response system
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MASES	Maastricht Ankylosing Spondylitis Enthesitis Index
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov-Chain Monte Carlo
MCS	Mental Component Summary
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MRD	minimum required dilution
MTX	methotrexate
n	number of observations
NCP	not confirmed positive
NRI	non-responder imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
OC	observed case
OLE	open-label extension
PCS	Physical Component Summary
PDILI	potential drug-induced liver injury
PGADA	Patient's Global Assessment of Disease Activity
PT	preferred term
Q4W	every 4 weeks
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
SOC	system organ class
SMQ	standardized MedDRA query

SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TNF	tumor necrosis factor
TNSP	Total Nocturnal and Spinal Pain
ULN	upper limit of normal
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 AS0009. 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, 17 July 2017.
- Protocol Amendment 2, 21 Mar 2018.
- Protocol Amendment 3, 06 Feb 2020.

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

2 PROTOCOL SUMMARY

This is a Phase 2b, multicenter, 208-week, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of bimekizumab (also known as UCB4940), in up to 285 subjects with ankylosing spondylitis (AS). Only subjects who complete AS0008, a Phase 2b study, are eligible for enrollment into AS0009. At Week 48 of AS0008, all subjects continuing into AS0009 will undergo the final AS0008 study assessments and any non-overlapping AS0009 study entry assessments, and will then receive their first open-label dose (160mg every 4 weeks [Q4W] subcutaneously [sc]) of bimekizumab.

The study duration for each subject is up to a maximum of 224 weeks: an Open-Label Treatment Period of up to 204 weeks, followed by a Safety Follow-up (SFU) Visit 20 weeks after the last dose of bimekizumab.

2.1 Study objectives

2.1.1 Primary objective

The primary objective is to assess the long-term safety and tolerability of bimekizumab administered sc Q4W at a dose of 160mg over a period of up to 204 weeks.

2.1.2 Secondary objectives

The secondary objective is to assess the long-term efficacy of bimekizumab.

2.1.3 Other objectives

- To assess the impact on patient-reported quality of life
- To assess the impact on enthesitis
- To assess the plasma concentration 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 from the study 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:

- Change from AS0009 Laboratory Baseline (as defined in Section 3.3) in clinical laboratory variables (hematology and biochemistry, with the exception of high-sensitivity C-reactive protein [CRP]) at each visit (AS0009 Week 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208, SFU).
- Change from AS0008 Baseline in vital signs (pulse, temperature and blood pressure) (AS0009 Entry Visit [EV], Week 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208, Completion/ET, SFU) and body weight (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208, SFU).

Note that the change from AS0009 EV variables specified in the protocol will not be reported, since the EV assessment is made after 36 or 48 weeks of bimekizumab treatment and there is unlikely to be any further important change.

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 of this study is to assess long-term safety and tolerability.

2.2.2.2 Secondary efficacy variables

The secondary efficacy variables are:

- Assessment in Spondyloarthritis International Society (ASAS) 40% response criterion (ASAS40) at AS0009 Week 48, relative to AS0008 Baseline.
- ASAS 20% response criterion (ASAS20) at AS0009 Week 48, relative to AS0008 Baseline.
- Change from AS0008 Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at AS0009 Week 48.

2.2.2.3 Other efficacy variables

The other efficacy variables are:

- ASAS40 and ASAS20 response at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208), relative to AS0008 Baseline.
  - ASAS40 and ASAS20 response will also be reported at each post-AS0008 Baseline visit in AS0008 through to AS0009 Week 208 (AS0008 Week 1, 2, 4, 8, 12, 16, 24 and 36 and AS0009 EV [AS0008 Week 48], Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208), for subjects who were responders at AS0008 Week 12. These are additional variables to those specified in the protocol and will be used to assess maintenance of response.
- ASAS 5/6 response criterion (ASAS5/6) response at each visit (AS0009 EV, Week 48, 96, 156 and 204), relative to AS0008 Baseline.
  - ASAS5/6 response will also be reported at each post-AS0008 Baseline visit in AS0008 through to AS0009 Week 204 (AS0008 Week 4, 8, 12, 16, 24 and 36 and AS0009 EV [AS0008 Week 48], Week 48, 96, 156 and 204), for subjects who were responders at AS0008 Week 12. These are additional variables to those specified in the protocol and will be used to assess maintenance of response.
- ASAS partial remission (ASAS-PR) response at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208), relative to AS0008 Baseline.
- Change from AS0008 Baseline in Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).
- Ankylosing Spondylitis Disease Activity Score Inactive Disease (ASDAS-ID) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).
- Change from AS0008 Baseline in BASDAI at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).
- Change from AS0008 Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).
- Change from AS0008 Baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI) at each visit (AS0009 EV, Week 48, 96, 156, 204).
- Change from AS0008 Baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) Index at each visit (AS0009 EV, Week 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 208).
- Change from AS0008 Baseline in Patient's Global Assessment of Disease Activity (PGADA) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).
- Change from AS0008 Baseline in total and nocturnal spinal pain (TNSP) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).

- Change from AS0008 Baseline in Short-Form 36-Item Health Survey (SF-36) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 208).
- Change from AS0008 Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 208).
- Change from AS0008 Baseline in Hospital Anxiety and Depression Scale (HADS) - Anxiety (HADS-A) and HADS - Depression (HADS-D) scores at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).
- Incidence of "normal" depression and anxiety status (HADS-D<8 and HADS-A<8) at each visit (AS0009 EV, Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, 208).

2.2.3 Pharmacokinetic/pharmacodynamic variables

2.2.3.1 Other pharmacokinetic variable

The pharmacokinetic variable is the plasma concentration of bimekizumab at each visit (AS0009 EV, Week 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 208, 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 variables

The immunological variable is the anti-bimekizumab antibody (ADAb) level at each visit (AS0009 EV, Week 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 208, SFU).

2.3 Study design and conduct

AS0009 is a multicenter OLE study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult subjects with AS who completed the Phase 2b study AS0008. At Week 48 of AS0008, all eligible subjects continuing into AS0009 will undergo their final AS0008 study assessments and any non-overlapping AS0009 entry assessments, and will then receive their first open-label dose of bimekizumab.

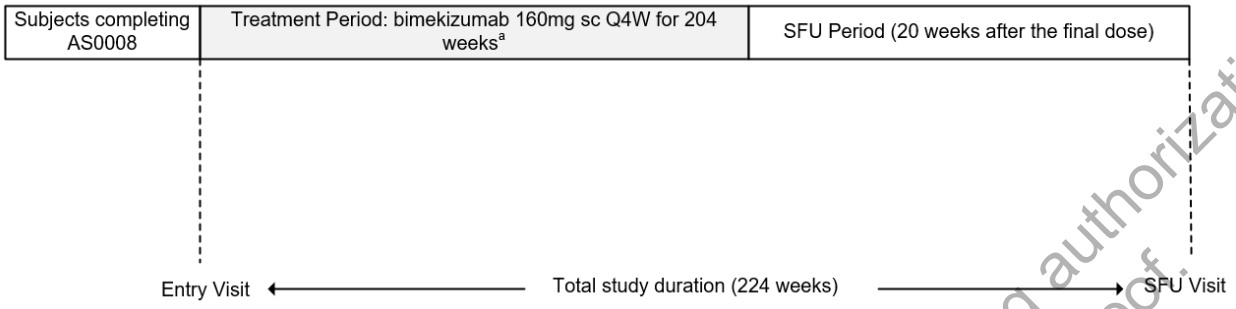
Up to 285 subjects could be enrolled into this OLE study. The study duration for each subject is up to a maximum of 224 weeks. No randomization will be performed and all subjects will receive open-label treatment with bimekizumab 160mg Q4W sc for a maximum of 204 weeks (~4 years) followed by a SFU visit 20 weeks after the last dose of bimekizumab.

Subjects may require additional treatment in addition to medications received during AS0008 to control their AS symptoms. Such rescue therapies are defined in Section 6.5. The decision to implement such therapy will be at the discretion of the Investigator.

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

A study schematic diagram of AS0009 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 Week 16 onwards) as described in Table 2–1.
[a] Subjects will receive their final dose of study drug on Week 204 and the SFU Visit will be conducted 20 weeks after the last dose of investigational medicinal product (IMP).

Schedules of study assessments for Week 1 to Week 104 and for Week 108 to Week 208 are provided in Table 2–1 and Table 2–2.

Table 2–1: Schedule of study assessments (Week 1 through Week 104)

Protocol activity	Treatment Period																	
Weeks[a]	**EV[b]**	**4**	**12**	**16**	**24**	**28**	**36**	**40**	**48**	**52**	**60**	**64**	**72**	**76**	**84**	**88**	**96**	**100**
		8		**20**		**32**		**44**		**56**		**68**		**80**		**92**		**104**
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**	**H[c]**
Informed consent	X[d]																	
Inclusion/exclusion	X[e]																	
Concomitant medications	X[f]	X	X		X		X		X		X		X		X		X	
Adverse events	X[f]	X	X		X		X		X		X		X		X		X	
eC-SSRS	X[e,f]	X	X		X		X		X		X		X		X		X	
HADS	X[f]		X		X		X		X		X		X		X		X	
ASQoL	X[f]		X		X		X		X		X		X		X		X	
BASDAI	X[f]		X		X		X		X		X		X		X		X	
BASFI	X[f]		X		X		X		X		X		X		X		X	
SF-36	X[f]		X		X		X		X		X		X		X		X	
PGADA	X[f]		X		X		X		X		X		X		X		X	
Total and nocturnal spinal pain	X[f]		X		X		X		X		X		X		X		X	
TB questionnaire	X[f]		X		X		X		X		X		X		X		X	
Vital signs (pulse, temperature, BP)[g]	X[e,f]	X	X		X		X		X		X		X		X		X	
Body weight	X[f]		X		X		X		X		X		X		X		X	
Physical examination[h]	X[f]								X								X	
MASES	X[f]		X		X		X		X				X				X	
BASMI	X[f]								X								X	
ECG	X[f]								X								X	

Table 2–1: Schedule of study assessments (Week 1 through Week 104)

Protocol activity	Treatment Period																	
Weeks[a]	EV[b]	4	12	16	24	28	36	40	48	52	60	64	72	76	84	88	96	100
		8		20		32		44		56		68		80		92		104
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	H[c]
Hematology/biochemistry/urine pregnancy[i, j]	X[f]		X		X		X		X		X		X		X		X	
Blood Sample for CRP[j]	X[f]		X		X		X		X		X		X		X		X	
Blood sample for bimekizumab plasma concentrations[j]	X[f]		X		X		X		X				X				X	
Blood sample for anti-bimekizumab antibodies[j]	X[f]		X		X		X		X				X				X	
IGRA TB test[k]	X								X								X	
IXRS	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

ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; BASFI=Bath Ankylosing Spondylitis Metrology Index; BP=blood pressure; CRP=C-reactive protein; ECG=electrocardiogram; eC SSRS=electronic Columbia-Suicide Severity Rating Scale; EV=Entry Visit; H=home; HADS=Hospital Anxiety and Depression Scale; IGRA=interferon gamma release assay; IMP: investigational medicinal product; IXRS=interactive voice or web response system; MASES= Maastricht Ankylosing Spondylitis Enthesitis Index; PGADA=Patient's Global Assessment of Disease Activity; SF 36=36 item short form health survey; SFU=Safety Follow Up; TB=tuberculosis;
Note: The SFU Visit will occur 20 weeks after the last dose of IMP.

[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 which should occur no more than 3 days prior the scheduled visit date and within 7 days after the scheduled visit date (-3 days /+7 days).

[b] AS0009 entry will occur at the end of the lead-studies. At Week 48 of AS0008, all subjects continuing into AS0009 will undergo the final AS0008 study assessments and any nonoverlapping AS0009 entry assessments and will then receive 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 AS0009 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 AS0008 and will be used as the AS0009 entry value.

Table 2–1: Schedule of study assessments (Week 1 through Week 104)

Protocol activity	Treatment Period																	
Weeks[a]	EV[b]	4	12	16	24	28	36	40	48	52	60	64	72	76	84	88	96	100
		8		20		32		44		56		68		80		92		104
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	H[c]

[g] At AS0009 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 (any time). All other procedures will only be done prior to dosing.
[h] Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.
[i] If there has been a delay in menses, perform a urine pregnancy test.
[j] All blood samples are to be taken prior to dosing.
[k] 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.

Table 2–2: Schedule of study assessments (Week 108 through Week 208)

Protocol activity	Treatment Period																		
Weeks[a]	**108**	**112**	**120**	**124**	**132**	**136**	**144**	**148**	**156**	**160**	**168**	**172**	**180**	**184**	**192**	**196**	**204**	**208/ET**	**SFU**
		116		**128**		**140**		**152**		**164**		**176**		**188**		**200**			
Visit[a]	**12**	**H[b]**	**13**	**H[b]**	**14**	**H[b]**	**15**	**H[b]**	**16**	**H[b]**	**17**	**H[b]**	**18**	**H[b]**	**19**	**H[b]**	**20**	**21**	
Concomitant medications	X		X		X		X		X		X		X		X		X	X	X
Adverse events	X		X		X		X		X		X		X		X		X	X	X
eC-SSRS	X		X		X		X		X		X		X		X		X	X	X
HADS	X		X		X		X		X		X		X		X		X	X	
ASQoL			X				X				X				X			X	X
BASDAI	X		X		X		X		X		X		X		X		X	X	X
BASFI	X		X		X		X		X		X		X		X		X	X	X
SF-36			X				X				X				X			X	
PGADA	X		X		X		X		X		X		X		X		X	X	
Total and nocturnal spinal pain	X		X		X		X		X		X		X		X		X	X	X
TB questionnaire	X		X		X		X		X		X		X		X		X	X	X
Vital signs (pulse, temperature, BP)[c]	X		X		X		X		X		X		X		X		X	X	X
Body weight	X		X		X		X		X		X		X		X		X	X	X
Physical examination[d]									X									X	X
MASES			X				X				X				X			X	
BASMI									X								X		
ECG									X									X	
Hematology/biochemistry/urine pregnancy[e,f]	X		X		X		X		X		X		X		X		X	X	X
Blood Sample for CRP[f]	X		X		X		X		X		X		X		X		X	X	X

Table 2–2: Schedule of study assessments (Week 108 through Week 208)

Protocol activity	Treatment Period																		
Weeks[a]	**108**	**112**	**120**	**124**	**132**	**136**	**144**	**148**	**156**	**160**	**168**	**172**	**180**	**184**	**192**	**196**	**204**	**208/ET**	**SFU**
		116		**128**		**140**		**152**		**164**		**176**		**188**		**200**			
Visit[a]	**12**	**H[b]**	**13**	**H[b]**	**14**	**H[b]**	**15**	**H[b]**	**16**	**H[b]**	**17**	**H[b]**	**18**	**H[b]**	**19**	**H[b]**	**20**	**21**	
Blood sample for bimekizumab plasma concentrations[f]			X				X				X				X			X	X
Blood sample for anti-bimekizumab antibodies[f]			X				X				X				X			X	X
IGRA TB test[g]							X								X				X
IXRS	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		

ASQoL=Ankylosing Spondylitis Quality of Life; BASMI=Bath Ankylosing Spondylitis Metrology Index; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BP=blood pressure; CRP=C-reactive protein; ECG=electrocardiogram; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; H=home; HADS=Hospital Anxiety and Depression Scale; IGRA=interferon gamma release assay; IMP: investigational medicinal product; IXRS=interactive voice or web response system; MASES=Maastricht Ankylosing Spondylitis Enthesitis Index; PGADA=Patient's Global Assessment of Disease Activity; SF-36=36-item short form health survey; SFU=Safety Follow-Up; TB=tuberculosis;
Note: The SFU Visit will occur 20 weeks after the last dose of IMP.

[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 which should occur no more than 3 days prior the scheduled visit date and within 7 days after the scheduled visit date (-3 days /+7 days).

[b] Self-administration by the subject/caregivers/appropriate designee will be possible.

[c] At all visits except AS0009 study entry, collect pulse and BP prior to drug administration and once after dosing (any time). All other procedures will only be done prior to dosing.

[d] Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.

[e] If there has been a delay in menses, perform a urine pregnancy test.

[f] All blood samples are to be taken prior to dosing.

[g] 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 for this study. The sample size is determined by the number of subjects in AS0008 who are eligible for AS0009. Up to 285 subjects from AS0008 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 non-responder (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 displayed to 1 decimal place. No percentage will be displayed for zero counts, and no decimal will be presented when the percentage is 100%. 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 always 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
ASDAS-CRP	1	2
BASDAI	1	2
BASFI	1	2
BASMI	1	2
MASES	1	2
TNSP	1	2
SF-36 MCS	2	3
SF-36 PCS	2	3
ASQoL	0	1
HADS-A	0	1
HADS-D	0	1

The abbreviation BKZ will be used in tables and listings headers.

All data will be presented in by-subject data listings sorted by planned (randomized) treatment group at completion of AS0008 (for efficacy listings) or actual treatment group at completion of AS0008 (for all other listings), site, subject number, variables (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 24h clock format as "hh:mm".

In all listings (where applicable) the subject level demographic information (i.e., gender, age, race, weight) will be based on the data reported at AS0008 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 AS0008 and the second relative to the start date of study medication in AS0009. 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:

$$Current\ date - end\ date\ of\ study\ medication\ in\ AS0009 \quad (5)$$

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 (204 weeks), starts with the first dose of open-label bimekizumab in AS0009 and ends with the last dose of study medication.
- Dosing period: The dosing period starts at the start date of study medication in AS0009 and ends at 1 dosing interval (28 days) after the end date of study medication.
- Safety follow-up (SFU): The SFU is the period after the last dose of bimekizumab administration with the SFU visit scheduled for 20 weeks after the last dose of bimekizumab.

3.3 Definition of Baseline values

The Baseline value defined in the AS0008 database will be used as a Baseline for AS0009, without additional derivation. The change from AS0008 Baseline will be calculated.

Due to a change in laboratory vendor between AS0008 and AS0009, laboratory values (with the exception of CRP) will use the AS0009 Laboratory Baseline, defined as the earliest post-EV value recorded in AS0009 at or prior to AS0009 Week 12 (excluding any local laboratory measurements). Change from AS0009 Laboratory Baseline will be calculated for these parameters. Change from Baseline will not be calculated for local laboratory measurements as there is no Baseline defined for these values.

The CRP values from the two laboratory vendors have been calibrated, so change from AS0008 Baseline will be calculated for CRP.

3.4 Protocol deviations

Important protocol deviations are defined as those deviations from the protocol likely to have a meaningful impact on study conduct, or on the safety or efficacy outcomes for an individual

subject. The criteria for identifying important protocol deviations 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 Coronavirus Disease 2019 (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 12.5. All data reported on this eCRF page will be reviewed during ongoing data cleaning meetings in order to determine if these should be considered as important protocol deviations.

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 AS0009 (planned at the AS0009 EV), but if the dose was missed at that visit, the date of the AS0009 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 site 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 mapping are provided in Section 8.1.5 for BASMI and Section 9.1 and Section 9.2 for PK and ADAb summaries respectively.

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 AS0009. But if the dose was missed at that visit, the date of the AS0009 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 AS0009 EV if the first dose was missed) will be left as unscheduled.
- Unscheduled assessments obtained at specific time points (e.g., 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 (e.g., 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 208". Data obtained at scheduled visits will be reported as per the database (i.e., these will not be remapped as described above).

Assessments mapped to visits at which the assessment was not planned, unscheduled visits and unscheduled assessments which are not mapped to 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 AS0009.

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 AS0009.

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: Sub-population 1 will consist of all subjects in the SS who took no concomitant rescue medication in AS0009, and Sub-population 2 will consist of all subjects in the SS who took concomitant rescue medication in AS0009, 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 one dose of study medication in AS0009 and have a valid measurement for at least one efficacy variable at any scheduled visit (excluding SFU visits) after AS0009 EV where efficacy is planned to be collected. This will include any data collected at an unscheduled or ET visit, and which has been remapped to a scheduled visit where efficacy data are planned. The protocol definition suggested that a valid measurement for at least one efficacy variable at AS0009 EV was required, but in order to identify subjects who have had assessments during AS0009, the requirement has been changed to 'after'. This has been further clarified to include scheduled visits in AS0009 (where efficacy data is planned), excluding SFU visits, in order to ensure that all subjects in the FAS have data available to contribute to any of the efficacy analyses.

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 AS0008 (presented as 'BKZ 160mg' or 'BKZ 320mg') and an overall 'BKZ Total' column will be used to summarize data in AS0009.

The endpoints assessing maintenance of ASAS response over time will be summarized by treatment sequence across AS0008 and AS0009, and overall. Treatment sequences take the form 'A/ B/ C', where A is the treatment in the first 12 weeks of AS0008, B is the treatment from Week 12 to Week 48 of AS0008, and C is the treatment in AS0009. The eight 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 64mg/BKZ 160mg/BKZ 160mg.
- BKZ 64mg/BKZ 320mg/BKZ 160mg.
- BKZ 160mg/BKZ 160mg/BKZ 160mg.
- BKZ 320mg/BKZ 320mg/BKZ 160mg.

Safety summaries including AS0009 data only will be presented by treatment group at the completion of AS0008 and overall. Safety summaries including data from both AS0008 and AS0009 combined will be presented for 'BKZ 160mg', 'BKZ 320mg', and 'BKZ Total', based on the SS for AS0009. Subjects who took bimekizumab 320mg during AS0008 will contribute to all three columns. Subjects who did not take 320mg in AS0008 will contribute to the 'BKZ 160mg' and 'BKZ Total' columns. The combined summaries will present data from AS0008 and AS0009 for the subjects who were enrolled in AS0009. The AS0009 only summaries will include only data collected in AS0009 (unless otherwise stated).

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

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

For actual and planned treatments in AS0008, the data will be used directly from the AS0008 analysis database without any rederivation of treatment assignments in each period.

In AS0009 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 AS0008 Week 48, they will also be considered to have received the planned treatment. Thus for all subjects in AS0009 the actual treatment will be the same as the planned treatment.

3.8 Center pooling strategy

Centers will be grouped in the geographic regions North America (country codes USA, CAN), Western Europe (country codes DEU, ESP) and Eastern Europe (country codes BGR, CZE, HUN, POL, RUS and UKR) for use as a covariate in statistical analyses and for sub-group analyses (see Section 4.1 and Section 8.4). An additional region grouping of North America (country codes USA, CAN) and Europe (country codes BGR, CZE, DEU, ESP, HUN, POL, RUS and UKR) 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 AEs 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 MAR2021 of the World Health Organization Drug Dictionary and will be classified by Anatomical Therapeutic Chemical (ATC) 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:

- Change from AS0009 EV for safety 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 AS0008 Baseline and AS0009 EV for laboratory variables will not be presented, due to a change in laboratory vendor between AS0008 and AS0009. Laboratory Baseline has been defined as the earliest value in AS0009 at or prior to AS0009 Week 12.
- Summaries of ASAS40, ASAS20 and ASAS5/6 response at each post-AS0008 Baseline visit have been added for subjects who were responders at AS0008 Week 12. These summaries include all post-AS0008 Baseline visits through to AS0009 Week 208, for subjects in the FAS for AS0009, and will be used to assess maintenance of response.
- The protocol describes the FAS as consisting of all enrolled subjects who receive at least 1 dose of IMP and have a valid measurement for at least 1 efficacy variable at AS0009 study entry. This has been updated to include all subjects in the ES who received at least one dose of study medication in AS0009 and have a valid measurement for at least one efficacy variable at a scheduled visit (excluding SFU visits) after AS0009 EV. This was updated in order to identify subjects who have had assessments during AS0009 and which contribute to any of the efficacy analyses.
- Summaries by randomized treatment in AS0008 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 AS0009 entry. Maintenance of response displays will be split by treatment sequence across AS0008 and AS0009. Safety displays using AS0008 information will incorporate exposure in AS0008.
- The protocol defines subgroups based on ‘Concomitant non-steroidal anti-inflammatory drug (NSAID) status at AS0009 entry. This has been updated to ‘Concomitant NSAID status at start of AS0008’.
- The protocol stated that all safety analysis would be performed for both Sub-populations; instead only key safety analyses will be repeated by 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.

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 AS0008 Baseline (North America, Western Europe, Eastern Europe), as defined in Section 3.8.
- Previous (past) tumor necrosis factor (TNF) inhibitor agent exposure in AS0008. The value in the AS0008 database for past anti-TNF therapy (as collected on the eCRF) will be used for AS0009, 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 4.2.2 and Section 4.2.3.

4.2 Handling of dropouts or 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 sub-sections 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 non-responder imputation (NRI) and multiple imputation (MI) as described below will be performed only for subjects in the FAS for AS0009.

For assessments missing during AS0008 which are used in AS0009 for reporting maintenance of response, the imputed value (based on NRI) from the AS0008 database will be used.

For all visits in AS0009 (including AS0009 EV), missing values or values which cannot be constructed due to missing components for binary secondary/other efficacy variables (ASAS40, ASAS20, ASAS5/6) will be imputed using NRI. For each visit, subjects with missing data or who have dropped out of the study will be counted as non-responders. This includes any subjects with missing baseline values.

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

- ASAS components:
  - Total Spinal Pain, Question 1 from TNSP
  - Inflammation, derived as the mean of Question 5 and 6 from the BASDAI
- ASDAS-CRP components:

  - Total Back Pain, Question 2 from the BASDAI
  - Duration of Morning Stiffness, Question 6 from the BASDAI
  - PGADA (this is already included below as this is required as a standalone endpoint)
  - Peripheral Pain/Swelling, Question 3 from the BASDAI
  - CRP

    ASDAS-CRP and ASDAS-ID will be determined after MI of the individual components of the ASDAS-CRP (ie, MI will not be applied to the overall ASDAS-CRP score). Note that for CRP the rules for handling measurements that are below the limit of quantification (BLQ) should be followed as per Section 8.1.2. Thus, if any imputed values are <2mg/L these will be replaced with a constant value of 2mg/L for subsequent derivation of ASDAS-CRP. For the ASDAS-ID, the number of subjects within each disease activity category will be derived for each imputation and the mean number of subjects within each category across imputations will be presented.

- BASDAI
- BASFI
- BASMI
- MASES
  - For MASES the MI model will be restricted to subjects with a MASES score > 0 at AS0008 Baseline. Subjects with a MASES score of zero at AS0008 Baseline will be excluded prior to performing the procedure outlined below.
- PGADA
- TNSP
- SF-36
  - For SF-36 this will be performed for the Physical Component Summary score (PCS) and Mental Component Summary score (MCS) and for each of the 8 domain scores (Physical Functioning, Role Physical, General Health, Bodily Pain, Vitality, Social Functioning, Role Emotional and Mental Health).
- ASQoL
- 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
- CRP
  - Note that for CRP as a standalone endpoint the rules for handling measurements that are below the limit of quantification should be followed as per Section 8.1.12. Thus, if any

imputed values are <0.16mg/L these will be replaced with 0.08mg/L prior to any subsequent reporting.

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, e.g. the missing data are missing at random.

All MI procedures will be performed using data from both AS0008 and AS0009 such that missing data across both studies will be imputed. Any previous MI or last observation carried forward (LOCF) (or other e.g., next observation carried backward) imputation performed in AS0008 will not be considered for AS0009 such that the procedure will use OC data only across both studies.

As the AS0008 Week 48 time point is synonymous with the AS0009 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 AS0008, 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-AS0008 Baseline visit where efficacy variables are collected, with AS0008 Baseline, geographic region, and past TNF inhibitor exposure (as collected on the eCRF in AS0008 for past anti-TNF exposure) as covariates, separately for each treatment group at the completion of AS0008.
- 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-AS0008 Baseline values will be specified in chronological order in the imputation model so that the SAS® PROC MI imputes variables from left to right. In case an AS0008 Baseline raw value is missing, the study participant will be excluded. The imputation model based on the MCMC method will only allow multivariate normal continuous variables as predictors. Therefore, past TNF inhibitor exposure and geographic region will be re-coded as indicator variables. For past TNF inhibitor exposure, this will be 0 for no past exposure and 1 for past TNF exposure. For region, there will be 2 indicator variables, the first of which will

be 1 for subjects from Western Europe and 0 for all other subjects and the second of which will be 1 for subjects from Eastern Europe and 0 for all other subjects. The order of the covariates in the model will be as follows: region indicator variables (Western Europe =1, Other =0; Eastern Europe=1, Other=0), past TNF inhibitor exposure (Yes=1, No=0), Baseline and then the 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 one 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 AS0008 Baseline variable when appropriate.

Table 4–1: Allowable ranges for continuous efficacy variables

Variable	Minimum	Maximum
BASDAI	0	10
BASFI	0	10
BASMI	0	10
MASES	0	13
PGADA	0	10
TNSP	0	10
SF-36 MCS[a]	-3.33	80.09
SF-36 PCS	5.02	79.78
SF-36 Bodily Pain	21.68	62
SF-36 General Health	18.95	66.5
SF-36 Mental Health	11.63	63.95
SF-36 Physical Functioning	19.26	57.54
SF-36 Role Emotional	14.39	56.17
SF-36 Role Physical	21.23	57.16
SF-36 Social Functioning	17.23	57.34
SF-36 Vitality	22.89	70.42
ASQoL	0	18

Table 4–1: Allowable ranges for continuous efficacy variables

HADS-A	0	21
HADS-D	0	21
ASAS component score (Total Spinal Pain [Question 1 from TNSP])	0	10
ASAS component score (Morning stiffness [the mean of BASDAI Questions 5 and 6])	0	10
ASDAS-CRP component score (Total Back Pain [Question 2 from the BASDAI])	0	10
ASDAS-CRP component score (Duration of Morning Stiffness [Question 6 from the BASDAI])	0	10
ASDAS-CRP (Peripheral Pain/Swelling [Question 3 from the BASDAI])	0	10
ASDAS-CRP component score (CRP[b])	2	NA
CRP[c]	0.08	NA

ASAS=Assessment in SpondyloArthritis International Society; ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score-C-reactive protein; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI= Bath Ankylosing Spondylitis Metrology Index; CRP=high sensitivity C-reactive protein; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; MASES=Maastricht Ankylosing Spondylitis Enthesitis Index; PGADA=Patient's Global Assessment of Disease Activity; SF-36 MCS=Short Form 36-Item – Mental Component Summary; SF-36 PCS=Short Form 36-Item – Physical Component Summary; TNSP=Total Nocturnal and Spinal Pain.

[a] SF-36 ranges are used for imputation purposes only. Any observed values outside the ranges based on norm-based scores will be reported as calculated in all tables and listings.

[b] For the purposes of the MI any numerical CRP values obtained in AS0009 that were <0.16mg/L will be substituted with half the lower limit of quantification (LLOQ) from AS0008 (ie, 0.08mg/L) prior to performing the MI. Subsequently any observed or imputed values of <2mg/L will be replaced by the value of 2mg/L for the purposes of deriving the ASDAS-CRP. Any CRP values of >=500mg/L will be set to missing prior to performing the MI procedure.

[c] For the purposes of the MI any numerical CRP values obtained in AS0009 that were <0.16mg/L will be substituted with half the LLOQ from AS0008 (ie, 0.08mg/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. 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, Q1, Q3, 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, Q1, Q3, 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 ASAS40 and ASAS20 responses, the response variables will be derived following MI of the individual components. The ASAS responses will then be derived for each subject and each imputation (where each imputation is performed across all individual components) and the number and percentage of subjects with each ASAS response in each imputation will be calculated. The mean value (across imputations) for the percentage of subjects with each ASAS response will be reported. Further details regarding data handling for the derivation of the ASAS response are provided in Section 8.1.1.1 and will be implemented accordingly.

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<8 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 AS0009 EV onwards (although the MI procedure will incorporate data from both AS0008 and AS0009).

Table 4–2: Missing data handling

Variable	Type	Missing data handling approach		
		NRI	MI/MCMC (monotone regression)	OC
ASAS40, 20	Responder	P	S[a]	S
ASAS component score (Total Spinal Pain [Question 1 from TNSP])	Continuous		P	
ASAS component score (Morning stiffness [the mean of BASDAI Questions 5 and 6])	Continuous		P	
ASAS5/6	Responder	P		S
BASDAI	Continuous		P	S
ASAS-PR	Responder	P		S
ASDAS-CRP	Continuous		P[b]	
ASDAS-CRP component score (Total Back Pain [Question 2 from the BASDAI])	Continuous		P	
ASDAS-CRP component score (Duration of Morning Stiffness [Question 6 from the BASDAI])	Continuous		P	
ASDAS-CRP (Peripheral Pain/Swelling [Question 3 from the BASDAI])	Continuous		P	
ASDAS-CRP (CRP[c])	Continuous		P	
ASDAS-ID (including Moderate, High and Very High Disease Activity Categories)	Responder		P[a]	
BASFI	Continuous		P	
BASMI	Continuous		P	
MASES	Continuous		P	
PGADA	Continuous		P	
TNSP	Continuous		P	
SF-36 PCS, MCS and domain scores	Continuous		P	

Table 4–2: Missing data handling

ASQoL	Continuous		P	
HADS-A, HADS-D	Continuous		P	
Incidence of normal depression/anxiety status (using HADS)	Responder		P[a]	
CRP[d]	Continuous		P	

ASAS=Assessment in SpondyloArthritis International Society; ASAS-PR= Assessment in SpondyloArthritis International Society Partial Remission; ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score-C-reactive protein; ASDAS-ID=Ankylosing Spondylitis Disease Activity Score-Inactive Disease; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI= Bath Ankylosing Spondylitis Metrology Index; CRP=high sensitivity C-reactive protein; HADS-A=Hospital Anxiety and Depression Scale – Anxiety; HADS-D=Hospital Anxiety and Depression Scale – Depression; MASES=Maastricht Ankylosing Spondylitis Enthesitis Index; P=primary method;PGADA=Patient's Global Assessment of Disease Activity; S=sensitivity method; SF-36 MCS=Short Form 36-Item – Mental Component Summary; SF-36 PCS=Short Form 36-Item – Physical Component Summary; TNSP=Total Nocturnal and Spinal Pain.

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

[b] Imputation for ASDAS-CRP overall score is based on the MI of the individual components of the ASDAS-CRP with subsequent recalculation of the overall ASDAS-CRP based on each imputation in turn; for each subject the mean of the ASDAS-CRP scores will be used in the summaries. Direct MI of the ASDAS-CRP overall score is not performed.

[c] Refers to imputation of CRP for the purposes of calculating the ASDAS-CRP.

[d] Refers to imputation of CRP for the summaries of CRP as a standalone endpoint.

4.2.2 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 AS0008 (including those which were ongoing at the start of AS0009) will be imputed using the imputed start date from the AS0008 database.

Imputation of partial AE start dates for events reported in AS0009 only will follow the rules below (treatment switching rules refer to AS0008 only and data were used directly from the AS0008 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 AS0009 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 AS0009 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 AS0009 are the same as the month and year of the AE start date, then use the start date of study medication in AS0009 (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 AS0009 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 AS0009 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 AS0009 is the same as the year of the AE start date, then use the start date of study medication in AS0009 (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 AS0009 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 AS0009 is the same as the year of the AE start date, then use the start month of study medication in AS0009 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 AS0009 (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 AS0009, then use the start date of study medication in AS0009.

Imputation of partial AE stop date:

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

In the event of ambiguity or incomplete data which makes it impossible to determine whether the AE was treatment-emergent, the AE will be considered treatment-emergent. 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. If the seriousness of an AE is unknown, every attempt should be made to resolve this prior to database lock.

4.2.3 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 (i.e. no imputed values will be displayed in data listings).

Partial start dates for medications which started during AS0008 and were ongoing at the start of AS0009 will be taken from the AS0008 database based on the dedicated eCRF page for imported medications in AS0009

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 AS0008 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 AS0009 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 AS0009 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 AS0009 are the same as the month and year of the medication start date, then use the start date of study medication in AS0009 (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 AS0009 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 AS0009 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 AS0009 is the same as the year of the medication start date, then use the start date of study medication in AS0009 (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 AS0009 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 AS0009 is the same as the year of the medication start date, then use the start month of study medication in AS0009 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 AS0009 (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 AS0009, then use the start date of study medication in AS0009.

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.

4.2.4 Handling of partial treatment end dates

The date of last study drug administration in AS0009 may be completely unknown (e.g., 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 (i.e., YYY-MMM-XX) on the study termination page of the CRF.

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 AS0009 will be the date/time of the last known dose as reported on the study medication administration page of the CRF.

  - For any subjects who terminated the study in AS0009 without receiving a dose of study medication, the treatment end date will be the last date of last study drug administration in AS0008.

- For subjects for whom the treatment end date is partially missing (i.e., 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 (i.e., 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 i.e., 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 e.g., 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 i.e., without imputation.

4.3 Interim analyses and data monitoring

An interim analysis will be performed after the final subject has reached AS0009 Week 108, based on two years' exposure in the study. All outputs described in this SAP will be presented with the exception of COVID-19 related tables and listings. The datasets for the interim analysis will include all data collected up to this point; the 'by-visit' summaries will present data only up to the Week 108 time point; summaries of AEs and exposure will present all data collected up to the time of the database cut-off date (ie, when the final subject has reached AS0009 Week 108).

Additional data cuts may also be performed for regulatory and publication purposes.

4.4 Multicenter studies

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

Centers will be grouped into the geographic regions of North America, Western Europe and Eastern Europe as described in Section 3.8 for use as a covariate in statistical analyses and for sub-group 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 analyses will be performed for the following secondary efficacy variables:

- ASAS20, ASAS40 and ASAS5/6 response at AS0009 Week 48.
- Change from Baseline in BASDAI at AS0009 Week 48.

The following variables for subgroup analyses will be used:

- Geographic region at AS0008 Baseline (North America, Western Europe and Eastern Europe)
- Previous (past) TNF inhibitor exposure at AS0008 Baseline (yes, no). The value in the AS0008 database for past anti-TNF therapy (as collected on the eCRF) will be used for AS0009, without additional derivation.
- Concomitant NSAID status at start of AS0008 (yes, no). The value in the AS0008 database for past NSAID therapy (as collected on the eCRF) will be used for AS0009, 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 by treatment group at completion of AS0008 and overall for the ES.

The number and percentage of subjects in each analysis set (ES, SS and Sub-populations, and FAS) will be presented by treatment group at completion of AS0008 and overall.

The number and percentage of subjects who started, completed and discontinued the study, along with the primary reason for discontinuation will be summarized by treatment group at completion of AS0008 and overall for the SS (a subject will be considered to have completed the study if they attended Visit 21 [Week 208]). 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 summarized by treatment group at completion of AS0008 and overall for the SS (a subject will be considered to have completed study treatment if they received a dose at Visit 20 [Week 204]). 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 i.e., 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 also be summarized by treatment group at completion of AS0008 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 AS0009, treatment sequence across AS0008 and AS0009, treatment received at completion of AS0008, start and end date/time and relative days of study medication in AS0009, 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 AS0008 and to the start of study medication in AS0009 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 one 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 AS0009', 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 AS0009 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 AS0008 and from the start date in AS0009 will be included.

These will be calculated as described below:

$$Total\ days\ on\ study\ medication\ from\ start\ date\ in\ AS0009 = (Date\ of\ last\ dose\ in\ AS0009 - Date\ of\ first\ dose\ in\ AS0009) + 1 \quad (6)$$

$$Total\ days\ on\ study\ medication\ from\ start\ date\ in\ AS0008 = (Date\ of\ last\ dose\ in\ AS0009 - Date\ of\ first\ dose\ in\ AS0008) + 1 \quad (7)$$

For the total days on study medication in AS0008 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 AS0008 and in AS0009, 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 impacted visit (if applicable), date of visit (if applicable), relationship to COVID-19, impact category and a narrative (short description) of the event. These data will also be summarized by treatment group at completion of AS0008, 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 table 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
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- TNSP

For visits conducted remotely (as reported on the dedicated eCRF page) it is not possible to assess MASES or BASMI 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 as missing due to COVID-19. For these visits it will therefore not be possible to assess ASAS 5/6 response or ASDAS-CRP.

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 AS0008 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 AS0008 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 AS0008 and overall for the SS.

One summary table will be produced for AS0008 Baseline values. Age, sex, weight and BMI collected at AS0009 EV will be listed only.

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

Age will be categorized as:

- ≤18, 19-<65, ≥65 years (clinicaltrials.gov requirement).
- 18-<65, 65-<85, ≥85 years (EudraCT requirement).
- 18-<45, ≥45-<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-<30, ≥30 kg/m^2.

Demographic data, including AS0008 Baseline and AS0009 EV values for the repeated variables, will be listed for the ES.

6.2 Other baseline characteristics

AS history including the time since first diagnosis of AS (at time of enrolment in AS0008 and at time of enrolment in AS0009), time since first symptoms of AS (at time of enrolment in AS0008 and at time of enrolment in AS0009), age at first diagnosis date, and AS subtype (clinical criterion a, b, c or radiologic criterion) will be summarized by treatment group at completion of AS0008 and overall for the SS.

Time since first diagnosis will be summarized as a continuous variable and as categorical variable. Time since first diagnosis of AS at time of enrolment in AS0008 will be taken from the AS0008 database. Time since first diagnosis of AS at time of enrolment in AS0009 will be calculated as below, where date of diagnosis will be taken from the AS0008 database:

$$\begin{aligned} &Time\ since\ first\ diagnosis \\ &= Date\ of\ informed\ consent\ in\ AS0009 \\ &- Date\ of\ first\ diagnosis\ in\ AS0008 \end{aligned} \quad (9)$$

Time since first diagnosis for each study will be categorized as: <5, ≥5 years.

Time since first symptoms of AS at time of enrolment in AS0008 will be taken from the AS0008 database. Time since first symptoms at time of enrolment in AS0009 will be calculated as:

$$\begin{aligned} &Time\ since\ first\ symptom \\ &= Date\ of\ informed\ consent\ in\ AS0009 \\ &- Date\ of\ first\ symptom\ in\ AS0008 \end{aligned} \quad (10)$$

Age at first diagnosis will be taken from the AS0008 database. AS history will be listed for the ES.

The following baseline characteristics will be summarized by treatment group at the completion of AS0008 and overall for SS:

- BASDAI total score.
- BASDAI spinal pain (Question 2).
- PGADA.
- Total spinal pain (Question 1 of the TNSP questionnaire).
- BASFI.
- ASDAS-CRP.
- CRP.
- HLA-B27 (positive, negative).
- Anti-TNF therapy prior to first dose in AS0008 (yes, no). The value in the AS0008 database for past anti-TNF therapy (as collected on the eCRF) will be used for AS0009, without additional derivation.
- NSAID therapy prior to first dose to first dose in AS0008 (yes, no). The value in the AS0008 database for past NSAID therapy (as collected on the eCRF) will be used for AS0009, without additional derivation.
- Current number of NSAID therapies (0, 1, 2, ≥3).
- Current synthetic disease modifying anti-rheumatic drugs (DMARDs) (methotrexate [MTX], sulfasalazine, hydroxychloroquine) (yes, no).
- Current corticosteroid use (yes, no)

One summary table will be produced for AS0008 Baseline values and another for AS0009 EV values. NSAID, HLA-B27 and anti-TNF therapy prior to first dose will be based on data collected in AS0008 and will be included in the AS0008 Baseline table only.

BASDAI, BASDAI spinal pain (Q2), PGADA, total spinal pain (Q1 of the TNSP questionnaire), BASFI, ASDAS-CRP, CRP, current NSAID, current synthetic DMARDs and current corticosteroids will be included in both tables. CRP values at AS0009 EV will be taken from the Week 48 record in the AS0008 database. For the summary of AS0009 EV data, current NSAID, current synthetic DMARD and current corticosteroid therapy are defined as medications that are

ongoing at the AS0009 EV, or that started on the date of the AS0009 EV. This does not include medications that were stopped on the date of the AS0009 EV. In addition, for AS0009, current corticosteroid therapy will include oral medications only.

Baseline characteristics, including AS0008 Baseline and AS0009 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 first study medication administration in AS0008 and any additional conditions collected prior to first dose of study medication in AS0009 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 the completion of AS0008 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 AS0009.

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 AS0008 and overall, for the SS, based on data collected at the AS0009 EV. The number and percentage of subjects with an occurrence of extra-articular manifestations (uveitis, IBD, psoriasis) post-EV will be summarized by treatment group at completion of AS0008 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 AS0008 or were started during AS0009 will be reported.

Concomitant medications are medications taken at least 1 day in common with the study medication dosing period in AS0009 (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 AS0009 + 28 days, and the stop date is either missing or on or after the start date of study medication in AS0009. This includes medications that started prior to dosing in AS0009 and continued after.

For the purposes of the analysis, past medications are medications that started and stopped prior to dosing in AS0008. These include past TNF therapy (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 of missing data 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 ATC class, presenting Anatomical Main Group (ATC Level 1), Pharmacological Subgroup (ATC level 3), and PT, by treatment group at completion of AS0008 and overall for the SS.

All medications reported in AS0009, including flags to identify concomitant and rescue medications, and start and stop days relative to the start date of study medication in AS0008 and start and stop days relative to the start of study medication in AS0009, 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 AS0009' will be considered SS Sub-population 2 and other subjects will be considered SS Sub-population 1. Rescue medications will be identified using the flag collected in the eCRF.
- NSAIDs to identify subgroups/covariates.
- Prohibited medications.

Rescue medications and NSAIDs will be classified into subcategories for reporting purposes. The identification and classification of concomitant medications will be performed by merging an external physician-reviewed spreadsheet (which includes relevant flags for selecting medications in each category) with the data entered into the study database in order to categorize the medications correctly for the tables.

The number and percentage of subjects who receive the following categories of rescue medication will be summarized by treatment group at completion of AS0008 and overall for the SS.

- Any rescue medication in AS0009 that is classified as a concomitant medication as defined in Section 6.4.
- NSAID at AS0009 EV
- No NSAID at AS0009 EV
  - No NSAID at AS0009 EV and initiate NSAID [but not Cox-2 inhibitors] in AS0009 (only the initiation of NSAIDs that are classified as concomitant medications as defined in Section 6.4 will be included).
  - No NSAID at AS0009 EV and initiate Cox-2 inhibitors in AS0009 (only the initiation of Cox-2 inhibitors that are classified as concomitant medications as defined in Section 6.4 will be included).
- Use of any DMARDs in AS0009 alone or in combination (includes MTX, sulfasalazine, leflunomide and hydroxychloroquine). Only concomitant medications will be included as defined in Section 6.4.
- Intra-articular corticosteroid in AS0009 that is classified as concomitant as defined in Section 6.4.
- Oral corticosteroid in AS0009 that is classified as concomitant as defined in Section 6.4.

- Analgesics in AS0009 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 AS0008 and AS0009 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 as the number of doses received relative to the number of doses expected:

$$Percent\ treatment\ compliance = \frac{100 * (\text{Number of doses received})}{\text{Number of doses expected}} \quad (11)$$

where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes OLE treatment 52 doses are expected (EV and every 4th week afterwards until AS0009 Week 204). 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 AS0008 (see Section 3.7) and overall for the SS.

Treatment compliance will be listed for the SS.

A summary of the injection setting (study site/home) and person performing the injection (site personnel/subject/caregiver) will be presented by dosing visit (excluding unscheduled dosing visits) and treatment at completion of AS0008 and overall for the SS. The summary will include the total number of subjects injected at each visit and the number and percentage of subjects in each category for injection setting and person performing the injection. Percentages will be based on the number of subjects injected at each visit.

An additional summary, by treatment at completion of AS0008 and overall, will present the number and percentage of subjects in each of the following categories:

- One or more self-administrations during the study
- One or more home administrations during the study
- One or more self-administrations also performed at home during the study

Percentages will be based on the number of subjects in the SS for each treatment group or overall, as applicable.

A 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:

- ASAS40 response relative to AS0008 Baseline at each visit in AS0009.
- ASAS20 response relative to AS0008 Baseline at each visit in AS0009.
- ASAS 5/6 response relative to AS0008 Baseline at each visit in AS0009.
- Change from AS0008 Baseline in BASDAI at each visit in AS0009.

A further sensitivity analysis will be performed for ASAS40 and ASAS20 response relative to AS0008 Baseline. The response endpoint will be re-derived and summarized based on the mean value (across multiple imputations) of the individual component scores after imputation for missing data.

Efficacy variables will be summarized and listed for the FAS. Summaries of MASES will be restricted to subjects with a MASES >0 at AS0008 Baseline. Maintenance of response summaries will be restricted to subjects who achieved a response at AS0008 Week 12 for the specific endpoint (where the response at AS0008 Week 12 is taken directly from the AS0008 datasets).

Responder variables (e.g. ASAS40 response) will be derived relative to the AS0008 Baseline and summarized using n and percentage at each visit, by treatment group at completion of AS0008 and overall.

Maintenance of response will be assessed for ASAS40, ASAS20 and ASAS5/6. The responses will be derived relative to AS0008 Baseline and summarized using n and percentage at each post-AS0008 Baseline visit, by treatment sequence across AS0008 and AS0009. These summaries will therefore include AS0008 Week 1, 2, 4, 8 12, 16, 24, and 36 and AS0009 EV (AS0008 Week 48), Week 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132, 144, 156, 168, 180, 192, 204, and Week 208. AS0008 Week 1 and 2 are not applicable for ASAS5/6 response.

Absolute and change from AS0008 Baseline for all continuous efficacy variables will be summarized descriptively by visit, by treatment group at completion of AS0008 and overall.

Any data collected at the SFU visit will be excluded from all efficacy summaries; this data will be included in the listings only.

8.1 Derivation of efficacy variables

Derived efficacy variables at AS0008 Baseline will be taken from the AS0008 database. Derivations described below will only be performed for data in the AS0009 database (which includes AS0008 Week 48 re-labelled as AS0009 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 Assessment in Axial Spondyloarthritis International Society Response Criteria

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

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

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

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

The comparison of changes to the specified cut-offs (i.e., >=1 or >=2 units) will be based on non-rounded data.

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, which includes, in addition to the 4 domains above, spinal mobility (lateral spinal flexion as recorded for BASMI) and CRP as more objective measures (Brandt et al, 2004). In the calculation of the ASAS 5/6 response the actual assessment value for the lateral spinal flexion will be used and not the transformed value used in the calculation of the BASMI score.

If the CRP value is below the lower limit of quantification (LLOQ) defined in AS0008 then it will be set to half of the LLOQ (as described in Section 8.1.12).

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

8.1.1.1 Data Handling Rules for ASAS40 and ASAS20

The ASAS40 and ASAS20 will be derived based on the data handling rules below. These rules will be implemented prior to performing any NRI or MI procedures, and will therefore be integrated as part of any OC summaries i.e., they are considered as OC data.

The rules will apply for all visits in AS0009 where at least one component is present at the specific visit. For summaries of maintenance of response, the ASAS responses at visits in AS0008 will not be re-derived and will be taken directly from the AS0008 database.

- If 3 components are present (and the other component is missing), and all 3 components meet the criteria for improvement, the remaining component will be assumed not to have deteriorated and the subject will be considered a responder for ASAS40 (or ASAS20).
- If at least 1 component is present (and 1 or more other components are missing) and meets the criteria for a deterioration, the subject is a non-responder for ASAS40 (or ASAS20)
- If a single component value is missing at Baseline (and the other 3 components are not missing), the percent and absolute improvement from Baseline for all visits for that component will be set to 0 for purposes of ASAS response calculations. Thus, the subject may still be considered a responder for ASAS40 (or ASAS20) if the other 3 components all meet the criteria for improvement.
  - Note that for MI any component with a missing Baseline will be excluded from the MI modelling as Baseline is included as a covariate in the model.
  - Thus, for the MI this will mean that a maximum of 3 components only will be available at each visit and all 3 components must therefore demonstrate an improvement based on the imputed values in order for the subject to be defined as a responder at that visit. In all other cases the subject will be regarded as a non-responder when the response is re-derived based on the imputed components.
- If more than 1 component value is missing at Baseline, the percent and absolute improvement from Baseline for all visits for those components will be set to 0 for purposes of ASAS response calculations. Thus, the subject would be considered a non-responder for ASAS40 (and ASAS20) at all visits.
  - Any subject with more than 1 component missing at Baseline will therefore be excluded from any summaries based on MI as there would be insufficient data available to derive a response.
- If the Baseline value for a given component is 0 the percent improvement from Baseline is not calculable. In this case the following rules will apply:
  - If the post-Baseline value is also 0, the percent and absolute improvement at that visit will be treated as 0 for purposes of ASAS response calculations.
  - If the post-Baseline value is greater than 0 and the arithmetic change from Baseline is >=1.0, then that component will be treated as having a 20% worsening and a 1-unit absolute worsening from Baseline for purposes of ASAS response calculations (i.e., the component has deteriorated).
  - If the post-Baseline value is greater than 0 and the arithmetic change from Baseline is <1.0, then that component will be treated as having neither improved nor worsened for purposes of ASAS response calculations.

  - If the post-Baseline value is missing, it will be regarded as 0 and the percent and absolute improvement at that visit will be treated as 0 for purposes of ASAS response calculations (NB: For the MI procedure the observed data will be included in the model as received without imputation with 0, and the percent and absolute improvement will be assumed to be 0 after performing the MI, regardless of the imputed absolute values)

- For component scores with a Baseline value >0 and a post-Baseline value of 0, percentage improvement will be calculated as for any other non-missing data.

With regards to the BASFI component see Section 8.1.3 for calculation in case of missing values of single questionnaire items.

With regards to the BASDAI component see Section 8.1.4 for calculation in case of missing values of single questionnaire items.

Further details regarding the assumptions and assignment of worst-case imputations for NRI are provided in Section 12.1.

8.1.1.2 Data Handling Rules for ASAS5/6

The ASAS5/6 will be derived based on the data handling rules below. These rules will be implemented prior to performing any NRI procedures and will therefore be integrated as part of any OC summaries.

The rules will apply for all visits in AS0009 where at least one component is present at the specific visit. For summaries of maintenance of response, the ASAS responses at visits in AS0008 will not be re-derived and will be taken directly from the AS0008 database.

- If 5 components are present (and the other component is missing), and all 5 components meet the criteria for improvement, the subject will be considered a responder for ASAS5/6.
- If all components are present and 5 components meet the criteria for improvement, the subject will be considered a responder for ASAS5/6 regardless of whether the remaining component has stayed the same or deteriorated.
- If a single component value is missing at Baseline (and the other 5 components are not missing), the percent and absolute improvement from Baseline for all visits will be treated as 0 for purposes of ASAS response calculations. Thus, the subject may still be considered a responder for ASAS5/6 if the other 5 components all meet the criteria for improvement.
- If more than 1 component value is missing at Baseline, the percent and absolute improvement from Baseline for all visits for those components will be set to 0 for purposes of ASAS response calculations. Thus, the subject would be considered a non-responder for ASAS5/6 at all visits.
- If the Baseline value for a given component is 0 the percent improvement from Baseline is not calculable. In this case the following rules will apply:
  - If the post-Baseline value is also 0, the percent and absolute improvement at that visit will be treated as 0 for purposes of ASAS response calculations.
  - If the post-Baseline value is greater than 0 and the arithmetic change from Baseline is >=1.0, then that component will be treated as having a 20% worsening and a 1-unit

absolute worsening from Baseline for purposes of ASAS response calculations (i.e., the component has deteriorated). This will not affect the ASAS5/6 response as this is based on improvement only.

  - If the post-Baseline value is greater than 0 and the arithmetic change from Baseline is <1.0, then that component will be treated as having neither improved nor worsened for purposes of ASAS response calculations. This will not affect the ASAS5/6 response as this is based on improvement only.
  - If the post-Baseline value is missing, it will be regarded as 0 and the percent and absolute improvement at that visit will be treated as 0 for purposes of ASAS response calculations

- For component scores with a Baseline value >0 and a post-Baseline value of 0, percentage improvement will be calculated as for any other non-missing data

With regards to the BASFI component see Section 8.1.3 for calculation in case of missing values of single questionnaire items.

With regards to the BASDAI component see Section 8.1.4 for calculation in case of missing values of single questionnaire items.

Further details regarding the assumptions and assignment of worst case for NRI are provided in Section 12.1.

8.1.2 Ankylosing Spondylitis Disease Activity Score – C-reactive Protein

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

- 0.121 x Total Back pain (BASDAI Question 2 result)
- 0.058 x Duration of morning stiffness (BASDAI Question 6 result)
- 0.110 x PGADA
- 0.073 x Peripheral pain/swelling (BASDAI Question 3 result)
- 0.579 x (natural logarithm of the (CRP [mg/L] + 1))

Back pain, PGADA, duration of morning stiffness and peripheral pain/swelling are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009). If the CRP value is <2mg/L, the constant value of 2mg/L should be used in the calculation. The sum of these weighted components gives the ASDAS-CRP.

If any individual components of the ASDAS-CRP are missing then the ASDAS-CRP will be regarded as missing. The imputed value for ASDAS-CRP will then be based on the imputed values for the individual components.

Disease activity categories based on ASDAS-CRP are as follows:

- ASDAS-ID: ASDAS-CRP <1.3
- ASDAS-Low Disease Activity: ASDAS-CRP >=1.3 to <2.1
- ASDAS-High Disease Activity: ASDAS-CRP >=2.1 to <=3.5

- ASDAS-Very High Disease Activity: ASDAS-CRP >3.5

For classification of the above, MI methods will be used to impute the individual components of the ASDAS-CRP, the ASDAS-CRP will be re-derived and this will subsequently be used to derive the appropriate disease activity category.

8.1.3 Bath Ankylosing Spondylitis Functional Index

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

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

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

8.1.4 Bath Ankylosing Spondylitis Disease Activity Index

The BASDAI is the most commonly used instrument to measure the disease activity of AS. The BASDAI is a validated self-reported instrument which consists of 6 NRSs, each with 10 units to measure the severity of the 5 major symptoms: fatigue, spinal pain, peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. To give each symptom equal weighting, the average of the 2 scores relating to morning stiffness is taken. The resulting 0 to 50 sum score is divided by 5 to give a final BASDAI score between 0 and 10, with lower scores indicating lower disease activity.

The BASDAI is calculated as follows:

$$BASDAI = \frac{\left(Q1 + Q2 + Q3 + Q4 + \left(\frac{Q5 + Q6}{2}\right)\right)}{5} \quad (12)$$

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

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

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

8.1.5 Bath Ankylosing Spondylitis Metrology Index

The BASMI characterizes the spinal mobility of a subject with AS and consists of 5 clinical measures to reflect axial status: cervical rotation; tragus-to-wall distance; lateral spinal flexion; lumbar flexion (modified Schober); intermalleolar distance. Each of the 5 movements is scored according the linear BASMI definition (van der Heijde et al, 2008) (Table 8-1). The mean of the 5 scores provides the BASMI score. The BASMI score ranges from 0 to 10. The higher the BASMI score, the more severe the subject's limitation of movement due to their AS.

Table 8-1: BASMI linear definition

Clinical Movement (Unit)	S=0 If:	S Between 0 and 10:	S=10 If:
Lateral spinal flexion[a] (cm)	A≥21.1	S = (21.1cm – A) / 2.1cm	A≤0.1
Tragus-to-wall distance[a] (cm)	A≤8	S = (A – 8cm) / 3cm	A≥38
Lumbar flexion[a] (modified Schober) (cm)	A≥7.4	S = (7.4cm – A) / 0.7cm	A≤0.4
Intermalleolar distance (cm)	A≥124.5	S = (124.5cm – A) / 10cm	A≤24.5
Cervical rotation angle[a] (°)	A≥89.3	S = (89.3° – A) / 8.5°	A≤4.3

S=BASMI Score; A=assessment.

[a] For cervical rotation and lateral spinal flexion, the mean of the left and right measurements will be calculated, if both are available. Otherwise, the available measurement will be used. If multiple attempted measurements are obtained, calculate the mean of the attempts. The mean of the attempts should be calculated after averaging the left and right measurements, where applicable.

For all clinical measures, values outside the ranges presented in Table 8-2 (Maksymowych, 2006) will be regarded as invalid and set to missing in the calculation of the component scores. For clinical movement parameters with repeated attempts at the same visit (ie, lateral spinal flexion, tragus-to-wall distance, cervical rotation and lumbar flexion), if only 1 attempt is considered valid per the ranges below, then this attempt will be used to calculate the BASMI score. If both attempts are considered invalid, the specific movement clinical movement parameter will be regarded as missing.

Table 8-2: BASMI linear definition permitted ranges

Clinical Movement	Range
Lateral spinal flexion (mean right/left)	0.75 to 25.00cm
Tragus-to-wall distance (mean right/left)	9.00 to 37.50cm
Lumbar flexion (modified Schober)	0.00 to 9.00cm
Intermalleolar distance	13.00 to 160.00cm
Cervical rotation (mean right/left)	0.00 to 94.00 °

For calculation of the overall BASMI score the following imputation rules will be applied:

- If 1 or 2 clinical measures for the BASMI are missing at one visit, the missing measure will be imputed by carrying the last observation forward, and the BASMI will be calculated

accordingly. This will include using AS0008 values as the last observation if applicable. In this case missing values will be carried forward from the relevant AS0008 visit until the next valid, non-missing value is present.

- If more than 2 clinical measures are missing, the BASMI score will be regarded as missing.
- Missing AS0008 Baseline values will not be imputed.

The following sequential steps will be followed when calculating the BASMI score:

- Individual assessment values (A) that are considered invalid (Table 8-2) will be discarded (ie, set to missing).
- The mean of the (valid) left and right assessment (A) values will be calculated per subject, analysis visit, parameter, and attempt (for those parameters where more than 1 attempt has been performed and there is more than 1 valid value available).
- The mean of the assessment (A) values will be calculated across attempts per subject, analysis visit and parameter (only for visits having more than 1 attempt with a valid value).
- The BASMI component score (S) will be calculated from the averaged assessment (A) values per subject, analysis visit and parameter.
- Values obtained at the ET visit and values obtained at unscheduled visits will be re-mapped as described in Section 3.5. Re-mapping will be performed on a per-parameter basis prior to the calculation of the BASMI score (this method is adopted in the event that not all parameters are assessed at each visit).
- If 1 or 2 BASMI component scores (S) are missing for a given subject and analysis visit, the most recent non-missing value will be carried forward and used at the current analysis visit.
- The final BASMI score will be calculated for a given subject and analysis visit if 1 value is available for each component score (including values that have been carried forward); in this case the BASMI score is the mean of the 5 component scores (S). If 1 value is not available for each component score the BASMI score will be set to missing for that subject and analysis visit.

8.1.6 Maastricht Ankylosing Spondylitis Enthesitis Index

The MASES Index comprises 13 items (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest and proximal insertion of the achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each scored as 0 = yes or 1 = no and then summed for a possible score of 0 to 13, with higher scores indicating worse enthesitis.

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

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

Summaries of MASES will be restricted to subjects with a MASES >0 at AS0008 Baseline.

8.1.7 Patient's Global Assessment of Disease Activity

Subjects will complete the PGADA using a NRS. The range covers 0 (not active) to 10 (very active).

8.1.8 Total and Nocturnal Spinal Pain

The pain experienced by AS subjects is measured by 2 separate questions: 1) total pain in the spine due to AS (i.e. "How much pain of your spine due to spondylitis do you have?"); and 2) pain in the spine at night due to AS (i.e. "How much pain of your spine due to spondylitis do you have at night?") (Sieper et al, 2009; van der Heijde et al, 2005; Committee for Proprietary Medicinal Product/EWP/556/95, 2002).

The arithmetic mean of both questions describes the TNSP. If the response to one question is missing the TNSP will be taken as the response to the non-missing question. If both responses are missing, the TNSP will be regarded as missing.

8.1.9 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 health domains 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). The concepts represented by these scales contribute to physical, mental, and social aspects of HRQoL One additional item (Question 2) asks respondents about perceived stability or change in health (Health Transition) over the past year. The classification of the questionnaire items to the health scales is shown in Section 12.2.

In addition to the domain scores, the Physical Component Score (PCS) and Mental Component Score (MCS) are calculated from the 8 domains (excluding the Health Transition item). Component scores appreciate the impact of each domain on physical and mental health status.

The 2 SF-36 component summaries (PCS and MCS) and the 8 domain scores are standardized with a mean of 50 and a SD of 10 in the general US population. An individual respondent's score that falls outside the T-score range of 45 to 55 should be considered outside the average range for the general US population. When considering group-level data, a score below 47 should be considered indicative of impaired functioning within that health domain or dimension. Similar to individual respondent data, group mean scores 47 or greater should be considered average or above average as compared to the general US population. Higher scores indicate a better health status.

For the calculation of the SF-36 domain scores and the component summaries PCS and MCS, the scoring software Quality Metric's PRO CoRE will be used). The software uses updated 2009 US population norms and applies a Full Missing Score Estimation method as follows:

- A health domain score (except the Physical Functioning domain) will be estimated provided that at least 1 non-missing response is available within that domain.
- For the Physical Functioning domain item response theory will be used to develop a model for estimates of the missing score.

- Regression methods are then applied to estimate the PCS and the MCS on the basis of the scores for each domain.

8.1.10 Ankylosing Spondylitis Quality of Life

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

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

Note that in the raw data the results are coded as 1 = yes and 2 = no; these will be re-coded as above prior to calculation of the ASQoL score.

8.1.11 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 Zigmond, 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 and HADS-A <8 at the same visit) will be derived.

8.1.12 High-sensitivity C-reactive protein levels

Note that high sensitivity C-reactive protein will be referred to as CRP throughout this SAP. CRP levels will be analyzed by the central laboratory. Any CRP assessments performed at local laboratories will not be considered for efficacy analyses (including ASDAS-CRP).

Due to a change in laboratory vendor between AS0008 and AS0009, CRP values from the AS0009 laboratory have been calibrated to match those from the AS0008 laboratory, and these values will be used for all CRP summaries and listings.

In AS0008 the LLOQ was 0.16mg/L, however in AS0009 it was possible to measure concentrations below this value and report these as a numeric result. The LLOQ in AS0008 will therefore be applied to the AS0009 data in order to retain consistency in reporting across the studies. Thus, numeric values of less than 0.16mg/L (<0.16mg/L) in AS0009 will be imputed with half the LLOQ from AS0008 (ie, 0.08mg/L) prior to summary reporting or any derivation of composite parameters (NB different criteria apply for the derivation of ASDAS-CRP as described in Section 8.1.2). The original values will be included in the listing.

CRP values at AS0008 Baseline and AS0009 EV will be taken from the AS0008 database (Baseline and Week 48 records respectively).

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.

8.2 Statistical analyses of secondary efficacy variables

The following secondary efficacy variables will be summarized for the FAS by treatment group at the completion of AS0008 and overall:

- ASAS40 response relative to AS0008 Baseline at AS0009 Week 48
- ASAS20 response relative to AS0008 Baseline at AS0009 Week 48
- Change from AS0008 Baseline in BASDAI at AS0009 Week 48

One set of summaries will be produced using data following NRI (ASAS responses) or MI (BASDAI) and another set using OC data. For ASAS responses, a further set of tables will be produced after the response variables have been derived following MI of the individual components. Summaries will not be presented for individual components of the ASAS (with the exception of PGADA which is a standalone endpoint).

8.3 Statistical analyses 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 completion of AS0008 and overall:

- ASAS40, ASAS20 and ASAS5/6 response at each visit in AS0009, relative to AS0008 Baseline.
  - Summaries will not be presented for individual components of the ASAS with the exception of PGADA which is a standalone endpoint.
- ASAS-PR response at each visit in AS0009, relative to AS0008 Baseline.
- Change from AS0008 Baseline in ASDAS-CRP at each visit in AS0009.
  - Summaries will not be presented for the individual components of the ASDAS-CRP with the exception of PGADA which is a standalone endpoint.
- ASDAS-ID at each visit in AS0009 (including Low Disease Activity, High Disease Activity and Very High Disease Activity categories).
- Change from AS0008 Baseline in BASDAI at each visit in AS0009.
- Change from AS0008 Baseline in BASFI at each visit in AS0009.
- Change from AS0008 Baseline in BASMI at each visit in AS0009.
- Change from AS0008 Baseline in MASES at each visit in AS0009.
  - Only subjects with MASES >0 at AS0008 Baseline will be included.
- Change from AS0008 Baseline in PGADA at each visit in AS0009.
- Change from AS0008 Baseline in TNSP at each visit in AS0009.
- Change from AS0008 Baseline in SF-36 PCS and MCS at each visit in AS0009.

- Change from AS0008 Baseline in SF-36 domain scores (Physical Functioning, Role Physical, General Health, Bodily Pain, Vitality, Social Functioning, Role Emotional and Mental Health) at each visit in AS0009.
- Change from AS0008 Baseline in ASQoL at each visit in AS0009.
- Change from AS0008 Baseline in HADS-A and HADS-D scores at each visit in AS0009.
- Incidence of depression and anxiety status "normal" as defined by HADS-A and HADS-D scores below 8 at each visit in AS0009
- Change from AS0008 Baseline (expressed as ratio to Baseline) in CRP at each visit in AS0009
  - For CRP the rules for handling values that are lower than the LLOQ identified in AS0008 will be followed as per Section 8.1.12.

One set of summaries will be produced for all the above parameters using data following NRI or MI as appropriate, as described in Section 4.2.1.

For ASAS40, ASAS20, ASAS5/6 and BASDAI, an additional set of summaries will be produced using OC data.

Finally, for ASAS40 and ASAS20 responses only, a further set of tables will be produced after the response variables have been derived following MI of components.

The summary tables for CRP will display the absolute value and ratio to AS0008 Baseline and will contain n, geometric mean (and 95% CI), median, first and third quartile (Q1 and Q3), minimum. Any values for the ratio to AS0008 Baseline below 0.01 will be presented as <0.01 in the listing and summary table.

8.3.1 Maintenance of response

ASAS20, ASAS40 and ASAS5/6 response relative to AS0008 Baseline will, in addition, be summarized at each post-Baseline visit in AS0008 through to AS0009 Week 208 (or to AS0009 Week 204 for ASAS5/6 response), by treatment sequence as defined in Section 3.7. These summaries will be restricted to subjects with a response at AS0008 Week 12, and data will be reported following NRI. Summaries will be based on the FAS for AS0009.

8.4 Subgroup analysis

Subgroup summaries will be performed on the following efficacy variables for the FAS:

- ASAS20 response at AS0009 Week 48, relative to AS0008 Baseline.
- ASAS40 response at AS0009 Week 48, relative to AS0008 Baseline.
- ASAS5/6 response at AS0009 Week 48, relative to AS0008 Baseline.
- BASDAI change from AS0008 Baseline at AS0009 Week 48.

Subgroups are defined in Section 4.8.

All subgroup analyses are based on imputed data using either NRI (ASAS endpoints) or MI (BASDAI).

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 and 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 AS0009 by treatment at completion of AS0008 and overall, using the SS.

If bimekizumab plasma concentration measurements are deemed to be 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 and n≥3. 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 AS0008.

The summary table 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:

$$CV\% = \sqrt{e^{SD_{ln}^2} - 1} \times 100 \quad (13)$$

here 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:
  - A subject will be counted positive from the first time point at which the subject had a positive ADAb sample resultregardless of any subsequent missing or negative ADAb sample results.
  - If a subject has only negative ADAb samples or only one missing sample with all negative ADAb samples up to a specific time point, the subject will be classified as negative at that time point. If the AS0008 Baseline sample is missing, then the sample will be classified as being negative for the cumulative ADAb status.
  - 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 AS0009 only:
  - Considering cumulative ADAb in status in AS0009 only at each time point in AS0009
  - Considering cumulative ADAb status in AS0008 and AS0009 at each time point in AS0009

- Each plot (linear and semi-logarithmic) will be presented by treatment group at completion of AS0008 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 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 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 208 or 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 AS0009 and for data from AS0008 and AS0009 combined. All concentrations will be listed as received, prior to substitution of any BLQ values. The listing of the AS0009 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

- 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 the ADAb evaluated at scheduled visits up to 208 weeks in accordance with the schedule of assessments in Table 2–1 and Table 2–2.

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 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 21 (Week 208), ET visit or the SFU visit as no dosing is planned at these time points. Thus, all ADAb data obtained at these visits will be included in the by-visit summaries.

ADAb status will be derived as follows:

- Sample 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 AS0009 data only (Category 1a): includes subjects who are negative at AS0008 Baseline and ADAb negative at all sampling points in AS0009 (including SFU).
  - Considering AS0008 and AS0009 data (Category 1b): includes subjects who are negative at AS0008 Baseline and ADAb negative at all sampling points in AS0008 and AS0009 (including AS0009 SFU).

- **Pre ADAb negative – treatment emergent ADAb positive (Category 2)**:
  - Considering AS0009 data only (Category 2a): Includes subjects who are negative at AS0008 Baseline and ADAb positive at any sampling point in AS0009 (up to and including SFU and including the AS0009 EV). This group also includes subjects who have a missing pre-treatment sample (either missing or insufficient volume) at AS0008 Baseline with one or more ADAb positive samples in AS0009.
  - Considering AS0008 and AS0009 data (Category 2b): Includes subjects who are negative at AS0008 Baseline and ADAb positive at any sampling point post treatment in AS0008 and/or AS0009 (up to and including AS0009 SFU). This group also includes subjects who have a missing pre-treatment sample (either missing or insufficient volume) at AS0008 Baseline with one or more ADAb positive samples in AS0008 or AS0009.
- **Pre ADAb positive – treatment emergent reduced ADAb (Category 3)**:
  - Considering AS0009 data only (Category 3a): Includes subjects who are positive at AS0008 Baseline, and ADAb negative at all sampling points in AS0009 (including SFU).
  - Considering AS0008 and AS0009 data (Category 3b): Includes subjects who are positive at AS0008 Baseline, and ADAb negative at all sampling points in AS0008 and AS0009 (including SFU).
- **Pre ADAb positive – treatment emergent unaffected ADAb positive (Category 4)**:
  - Considering AS0009 data only (Category 4a): Includes subjects who are positive at AS0008 Baseline and are positive at any sampling point in AS0009 (including SFU) with titer values of the same magnitude as AS0008 Baseline (i.e. less than a predefined fold increase from the AS0008 Baseline value defined within the validation of the assay).
  - Considering AS0008 and AS0009 data (Category 4b): Includes subjects who are positive at AS0008 Baseline and are positive at any sampling point in AS0008 or AS0009 (including SFU) with titer values of the same magnitude as AS0008 Baseline (i.e. less than a predefined fold increase from the AS0008 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 AS0008 Baseline.
- **Pre ADAb positive – treatment emergent ADAb boosted positive (Category 5)**:
  - Considering AS0009 data only (Category 5a): Includes subjects who are positive at AS0008 Baseline and are positive at any sampling point in AS0009 (including AS0009 EV and SFU) with increased titer values compared to AS0008 Baseline.
  - Considering AS0008 and AS0009 data (Category 5b): Includes subjects who are positive at AS0008 Baseline and are positive at any sampling point post treatment in AS0008 and/or AS0009 (including SFU) with increased titer values compared to AS0008 Baseline.

The increase in titer values is defined as an increase greater than a predefined fold increase from AS0008 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).

The fold increase in ADAb is calculated as follows:

$$Fold\ increase = \left\lceil \frac{ADAb\ titer\ at\ time\ point - ADAb\ titer\ at\ AS0008\ Baseline}{ADAb\ titer\ at\ AS0008\ Baseline} \right\rceil \quad (14)$$

Note: For any subject who is positive at AS0008 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 (i.e., Category 5), assuming no other samples are available.

- **Inconclusive (Category 6)**:
  - Considering AS0009 data only (Category 6a): Includes subjects who have a positive pre-treatment sample at AS0008 Baseline and some AS0009 samples are missing, while other AS0009 samples are ADAb negative.
  - Considering AS0008 and AS0009 data (Category 6b): Includes subjects who have a positive pre-treatment sample at AS0008 Baseline and some AS0008 or AS0009 samples are missing, while other AS0008 and AS0009 samples are all ADAb negative.
- **Total treatment-emergent (Category 7 [Categories 2 and 5 combined])**:
  - Considering AS0009 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 AS0008 and AS0009 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 AS0008 Baseline.
- **Missing (Category 9)**:
  - Considering AS0009 data only (Category 9a): Includes subjects who have a missing or negative pre-treatment sample at AS0008 Baseline and all AS0009 samples are either missing or ADAb negative.
  - Considering AS0008 and AS0009 data (Category 9b): Includes subjects who have a missing or negative pre-treatment sample at AS0008 Baseline and all AS0008 or AS0009 samples are either missing or 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 AS0009 visit and at any visit by treatment group at completion of AS0008 and overall. Two tables will be presented:
  - Considering ADAb status in AS0009 only
  - Considering ADAb status in AS0008 and AS0009 (this table will include only the overall summary visits as detailed below).

  For the overall summary at any visit two summaries will be presented as follows (all summaries exclude data obtained at AS0008 Baseline):
  - AS0009 data only: Including any visit during the AS0009 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 AS0009 EV.
  - AS0009 data only: Including any visit during AS0009. Thus, this summary will include both data obtained at the SFU visit and at the AS0009 EV.
  - AS0008 and AS0009 data: Including any visit during the AS0008 and AS0009 treatment period. Thus, this summary will exclude data obtained at the AS0009 SFU visit.
  - AS0008 and AS0009 data: Including any visit during AS0008 and AS0009. Thus, this summary will include data obtained at the AS0009 SFU visit.
- Summary tables (by treatment at completion of AS0008 and overall) of the time point of the first occurrence of ADAb treatment-emergent positivity during AS0009, including the AS0009 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 AS0009 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 AS0008 and AS0009 and will therefore display all visits in both AS0008 and AS0009.

  An additional table will be presented considering ADAb status at each visit in both AS0008 and AS0009, and will be presented by actual treatment at randomization in AS0008 only.
- Summary tables displaying the number and percentage of subjects in each of the ADAb categories as defined above by treatment at completion of AS0008. Two tables will be presented:
  - Considering data from AS0009 only
  - Considering data from AS0008 and AS0009
- The time to achieving treatment-emergent ADAb positivity, by treatment group at completion of AS0008 and overall (3 lines per plot), 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. This plot will display the cumulative percentage of subjects with treatment-emergent positivity and will include the following categories:

- 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 (3 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 AS0008 and AS0009 and will therefore display all visits in both AS0008 and AS0009.

In the event that >=10% of subjects in either treatment group are classified as Category 5 the figure will be repeated by treatment at completion of AS0008 and overall and by ADAb status (6 lines per plot). This will be implemented for both plots (considering only AS0009 and considering data from both AS0008 and AS0009).

An additional figure will be presented considering data from both AS0008 and AS0009, and will be presented by actual treatment at randomization in AS0008 only. 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 (ASAS40 responders [based on NRI]) as a function of ADAb titer will be presented graphically. The x-axis will display the ADAb titer at the AS0009 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 ASAS40 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 (ASAS40 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 AS0009 (including AS0009 EV and excluding 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 AS0009 (including AS0009 EV and excluding SFU) are ADAb negative and there are no missing or inconclusive samples or (2) only 1 sample in AS0009 is ADAb positive and all other samples in AS0009 (including AS0009 EV and excluding SFU) are ADAb negative or missing/inconclusive or (3) only 1 sample is missing/inconclusive and the remaining samples are ADAb negative (excluding SFU).

– 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 on AS0008 and AS0009 combined, with the following definitions:

– ADAb positive

- Defined as subjects having at least 2 ADAb positive samples during AS0008 and AS0009 (excluding AS0008 Baseline and AS0009 SFU and including AS0009 EV) regardless of other ADAb negative samples and/or missing or inconclusive samples

– ADAb negative

- Defined as subjects for whom either (1) all samples in AS0008 and AS0009 are ADAb negative and there are no missing or inconclusive samples or (2) only 1 sample in AS0008 or AS0009 is ADAb positive and all other samples in AS0008 and AS0009 are ADAb negative or missing/inconclusive or (3) only 1 sample is missing/inconclusive and the remaining samples in AS0008 and AS0009 are ADAb negative. All 3 definitions exclude AS0008 Baseline and AS0009 SFU and include AS0009 EV.

– 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 ASAS 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) by visit (x-axis), separated by treatment group at completion of AS0008 for all ADAb positive subjects. This plot will include the following ADAb categories, based on data collected in AS0009:

  – 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 AS0009 EV.

- Listings of individual subject-level ADAb results will be presented for the following:

  – Including only data from AS0009.

– Including data from both AS0008 and AS0009.

The listing of AS0009 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:

– Dosing performed out of window

– Sample collected out of window relative to current or previous dose

– Sample collected out of window relative to previous dose (missed or no dose at current visit)

– More than one sample obtained at the same visit

– Sample collected out of window relative to current dose or visit date (applicable to ADAb data only)

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 AS0008 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 AS0009 Laboratory Baseline in laboratory variables (except CRP) will be summarized descriptively by visit and by treatment group at completion of AS0008 and overall.

Change from AS0008 Baseline in ECG and vital signs variables will be summarized descriptively by visit and by treatment group at completion of AS0008 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 AS0008 for subjects who continued in to AS0009, 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 4.2.4 for partial treatment end dates:

- Total bimekizumab duration: Between the first dose of bimekizumab in AS0008 and last dose of bimekizumab in AS0009.
- Total duration on bimekizumab 160mg: Between the first and last dose of bimekizumab 160mg (in AS0008 or AS0009).

- Duration on bimekizumab 320mg: Between the first dose of bimekizumab 320mg in AS0008 and first dose of bimekizumab 160mg in AS0009 (calculated only for subjects who took bimekizumab 320mg in AS0008).
- Duration on bimekizumab 160mg in AS0009: Between the first and last dose of bimekizumab 160mg in AS0009.

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 AS0008	Last dose of BKZ in AS0009	End date – start date + 28[a]
Total duration on BKZ 160mg	First dose of BKZ 160mg in AS0008 or AS0009	Last dose of BKZ 160mg in AS0009	End date – start date + 28[a]
Duration on BKZ 320mg	First dose of BKZ 320mg in AS0008	First dose of BKZ 160mg in AS0009	End date – start date + 1
Duration on BKZ 160mg in AS0009	First dose of BKZ 160mg in AS0009	Last dose of BKZ 160mg in AS0009	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.

[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 (i.e., within 28 days following the last dose [not applicable for duration on BKZ 320mg]) or if the subject died before dosing in AS0009 (for duration on BKZ 320mg). If the subject died more than 28 days after the last dose of BKZ in AS0009 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 AS0008	Last dose of BKZ in AS0009	Minimum of [(End date – start date + 140[a]) +1] 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
Total exposure to BKZ 160mg	First dose of BKZ 160mg in AS0008 or AS0009	Last dose of BKZ 160mg in AS0009	Minimum of [(End date – start date + 140[a]) +1] and (Date of last clinical contact[b] – start date + 1)
Exposure to BKZ 320mg	First dose of BKZ 320mg in AS0008	First dose of BKZ 160mg in AS0009 for subjects who were dosed in AS0009[c].	(End date – start date + 1) for subjects who were dosed in AS0009.
		Last dose of BKZ 320mg in AS0008 for subjects who were not dosed in AS0009	Minimum of [(End date – start date + 140[a]) +1] and (Date of last clinical contactb – start date + 1) for subjects who were not dosed in AS0009
Exposure to BKZ 160mg in AS0009	First dose of BKZ 160mg in AS0009	Last dose of BKZ 160mg in AS0009	Minimum of [(End date – start date + 140[a])+1] and (Date of last clinical contact[b] – start date + 1)
Subjects who died[d]	Start date for each option as above	Date of death	End date – start date + 1

BKZ=bimekizumab.

[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 (including unscheduled SFU visits), 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 4.2.4].

[c] In the event that the first dose in AS0009 was more than 140 days after the last dose in AS0008, the exposure time at risk for 320mg will be calculated using AS0008 end date – AS0008 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 (i.e., within 140 days following the last dose [not applicable for duration on BKZ 320mg]) or if the subject died before dosing in AS0009 (for time at risk on BKZ 320mg). If the subject died more than 140 days after the last dose of BKZ in AS0009 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: two for exposure in AS0009 and one for exposure in AS0008 and AS0009 combined.

- For the AS0009 summary, durations of exposure and times at risk will be summarized by treatment group at completion of AS0008 and overall. This summary will be repeated by SS Sub-population.
- For the AS0008 and AS0009 combined table, the duration of exposure and time at risk for 'BKZ 160mg', 'BKZ 320mg' and 'BKZ Total' will be summarized. Subjects who took bimekizumab 320mg during AS0008 will contribute to all three columns. Subjects who did not take bimekizumab 320mg in AS0008 will contribute to the 'BKZ 160mg' and 'BKZ Total' columns.

The total study medication duration and total time at risk will be included in the exposure tables. These will be calculated by summing the study medication duration (or 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 AS0008, start and end dates of study medication in AS0009, 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 AS0008 study and are ongoing at the time of enrolment (signed informed consent) in AS0009 will be captured in the AS0009 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 (AESIs), and AEs defined as Safety Topics of Interest; further details regarding follow-up of Potential Drug-induced Liver Injury (PDILI) events are provided in Section 9.4.1 of the protocol. 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 AS0009 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 AS0009 study (i.e. after signature of the informed consent document) will be recorded in the eCRF. For each AE the following information will be recorded in the eCRF: AE term (verbatim term), date of onset, whether or not the AE was classified as a SAE, as an 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 AS0008 and prior to the first administration of study medication in AS0009 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 AS0009.
- Events that were ongoing at the end of AS0008 will have their treatment-emergent status taken from the AS0008 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 bimekzumab dose.

AE summaries will, in general, include only events with onset on or after the start date of study treatment in AS0009. Certain displays will be repeated including all AEs in AS0008 (with the exception of those with onset during placebo treatment) and AS0009 as outlined below. These displays will include only subjects from AS0008 who were enrolled in AS0009.

In general, the attributes of these events (for AEs that started and were resolved in AS0008) will be taken from the AS0008 database. However, the identification of Safety Topics of Interest will be made across all events in AS0008 and AS0009 using the criteria defined in this SAP.

For events which were ongoing at the end of AS0008, the following rules will be implemented:

- Onset date (and derived variables) will be taken from the AS0008 database
- End date, outcome, actions taken and seriousness will be taken from the AS0009 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 AS0008 and AS0009 will include AEs with onset on the first dose of bimekizumab in AS0008 up to 140 days after the last dose of bimekizumab in AS0009. 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 which occur on the first day of bimekizumab treatment in AS0008 following initial treatment with placebo will not be included in the summaries, unless they fulfill 1 of the 4 exception criteria above. AEs which occur after the last dose of bimekizumab in AS0009 and up to 140 days after the last dose of bimekizumab in AS0009 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 AS0008 and overall. This summary will be repeated by SS Sub-population. It will also be repeated including all TEAEs in AS0008 and AS0009 reported for subjects in the AS0009 SS (with the exception of those with onset during placebo treatment) combined.

The category for fatal AEs will be based on all subjects enrolled in AS0009 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 AS0009 only except where stated:

- All TEAEs by treatment group at completion of AS0008 and overall.
- All TEAEs by treatment group at completion of AS0008 and overall, by SS Sub-population.
- Serious TEAEs by treatment group at completion of AS0008 and overall.
- Serious TEAEs by treatment group at completion of AS0008 and overall, by SS Sub-population.
- All TEAEs in AS0008 and AS0009 by treatment at time of AE onset (BKZ 160mg, BKZ 320mg and BKZ Total).
- Serious TEAEs in AS0008 and AS0009 by treatment at time of AE onset (BKZ 160mg, BKZ 320mg and BKZ Total).

- All TEAEs AS0008 and AS0009 by timing of onset relative to ADAb status in AS0008 and AS0009. This will include columns for the following:
  - TEAEs starting before the first ADAb positive result in AS0008 and AS0009 (includes ADAb Categories 2b only)
  - TEAEs starting on the same date or after the first ADAb positive result in AS0008 and AS0009 (includes ADAb Categories 2b, 3b, 4b, 5b and 6b)
  - TEAEs for subjects who are ADAb negative at all time points in AS0008 and AS0009 (includes ADAb Categories 1b only)

  Note that any TEAEs occurring for a subject who was ADAb positive at AS0008 Baseline will therefore all occur after ADAb positivity; such subjects will be excluded from the first column in the above table. Subjects in Category 9b (missing) will not be included in the table.

The following categories of TEAE will be summarized by MedDRA SOC, HLT and PT, by treatment group at completion of AS0008 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 AS0008 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 AS0009 and all TEAEs that were ongoing from AS0008 at the time of the AS0009 EV. Ongoing TEAEs are defined as TEAEs that started prior to the AS0009 EV and continued after the first dose of study medication in AS0009.

Summaries will be based on treatment at onset and include columns for BKZ 160mg, BKZ 320mg and BKZ Total (where BKZ Total includes all other doses, if applicable, excluding placebo). Tables will include only n and %, the denominator (i.e. N) will be as for the current tables (total number of subjects receiving at least one dose for each column)

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 TEAEs (this listing will include all events in AS0008 and AS0009 for subjects that were enrolled in AS0009 [with the exception of AEs with onset during placebo treatment]).
- All AEs (this listing will include all events in AS0008 and AS0009 for subjects that were enrolled in AS0009 [with the exception of AEs with onset during placebo treatment]).
- All SAEs (this listing will include all events in AS0008 and AS0009 for subjects that were enrolled in AS0009 [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 [TB]) 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 4.2.2 prior to any calculation described in this section.

The duration of each AE will be calculated as follows:

$$Duration\ (days) = date\ of\ outcome - date\ of\ onset + 1 \quad (15)$$

The time since first bimekizumab dose for each TEAE will be calculated three times for each of the reference dates below:

- Relative to the date of first administration of bimekizumab in AS0008.
- Relative to the date of the first dose of bimekizumab 160mg, only for AEs with onset during treatment with bimekizumab 160mg 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 AS0009.

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

$$\begin{aligned} &Time\ since\ first\ BKZ\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset - Reference\ date + 1 \end{aligned} \quad (16)$$

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):

$$\begin{aligned} &Time\ since\ most\ recent\ BKZ\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset \\ &\quad - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \end{aligned} \quad (17)$$

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 i.e., 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:

$$Time\ since\ BKZ\ dose\ (days) = Date\ of\ AE\ onset - Reference\ date \quad (18)$$

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:

$$\begin{aligned} &Days\ on\ treatment\ at\ AE\ onset \\ &\quad = Date\ of last\ or\ latest\ dose\ prior\ to\ AE\ onset \\ &\quad - Reference\ date + 1 \end{aligned} \quad (19)$$

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 AS0008 and AS0009 combined, and for tables including events with onset in AS0009 only. The former tables will use time at risk relative to the start date of bimekizumab 160mg or 320mg (for the 'BKZ 160mg' 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 AS0009.

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

$$EAIR = \frac{100 * n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (20)$$

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 [15] in years) and $T_{Risk,j}$ is the 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 to 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):

$$LCL = \frac{\left(\chi^2_{2n,\frac{\alpha}{2}}\right)}{2} \quad (21)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\frac{\alpha}{2}}}{2} \quad (22)$$

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

$$\frac{CI_{Upper} = 100 * UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (24)$$

where n_{AE} is the number of subjects with 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} the number of subjects without the specific 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:

$$EAER = \frac{100 * N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (25)$$

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

No CI will be computed for EAER.

10.2.3 Adverse event 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 12.3.

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

Table 10–3: Extended MACE types

Event Type Code	Event Type
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.

A separate table will present the adjudicated neuropsychiatric events by type. For each neuropsychiatric event type (6 in total), the individual PTs which fall within each event type will be summarized. The table will include events adjudicated as SIB and events adjudicated as non-suicidal (note that the event type 'Suicidal ideation' may be classified as either SIB or non-suicidal). The neuropsychiatric event types/codes are as follows:

- Event type code 1: Suicidal events/completed suicide
- Event type code 2: Suicide attempt
- Event type code 3: Preparatory acts toward imminent suicidal behavior
- Event type code 4: Suicidal ideation
- Event type code 7: Nonsuicidal Self-injurious behavior
- Event type code 8: Nonsuicidal Other

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

Table 10–4: Inflammatory bowel disease types

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

IBD=inflammatory bowel disease.

A table for adjudicated IBD events (event type codes 1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14, 15 and 16) as determined by the adjudication committee will be produced. It will summarize events determined by the adjudication committee as definite IBD (event type codes 3, 6, 9, 13, and 16), probable IBD (event type codes 2, 5, 8, 12, and 15) and possible IBD (event type codes 1, 4, 7, 11, and 14). Definite and probable IBD events will also be aggregated and summarized in the same table. This table will be stratified by subjects with or without a previous medical history of IBD. Previous medical history of IBD will be determined using the information recorded on the Extra-Articular Assessment form at Screening in AS0008 ("Does subject have a history of IBD?").

A separate table will present the adjudicated gastrointestinal events by type. For each gastrointestinal event type (event type codes 1 through 16 and 99; 17 in total), the individual PTs which fall within each event type will be summarized. This table will include events determined by the adjudication committee as definite IBD, probable IBD, and possible IBD. It will also include events determined as ‘Symptoms not consistent with IBD’ (event type code 10) and ‘Not enough information to adjudicate’ (event type code 99). A corresponding listing by event type will also be presented.

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.

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 12.4) 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', 'During the COVID-19 pandemic' or 'Post 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) is 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.

- If the date of AE onset (based on imputed start date) is after the date on which the World Health Organization declares the end of the COVID-19 pandemic the AE will be assigned as 'Post the COVID-19 pandemic'
  - If the date of the end of the COVID-19 pandemic is on or after the date of last subject, last visit, the 'Post the COVID-19 pandemic' phase will not apply.

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', 'During the COVID-19 pandemic' and 'Post the COVID-19 pandemic')
- All serious TEAEs by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic', 'During the COVID-19 pandemic' and 'Post the COVID-19 pandemic')
- All COVID-19 related TEAEs by treatment at completion of AS0008 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.

TEAEs leading to study discontinuation and/or permanent withdrawal of study medication will be summarized by MedDRA SOC, HLT, and PT, and by time of onset relative to COVID-19 pandemic ('Prior to COVID-19 pandemic', 'During the COVID-19 pandemic' and 'Post the COVID-19 pandemic').

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 all listings and summaries described above the 'Post the COVID-19 pandemic' phase will be omitted if the date of the end of the COVID-19 pandemic is on or after the date of last subject, last visit.

For the purpose of calculating EAIR and EAER prior to, during, and post 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 all applicable periods ('Prior to COVID-19 pandemic', 'During the COVID-19 pandemic' and 'Post the COVID-19 pandemic'), dependent on whether the subject is still considered at risk at the time of the start date for each successive period. The time at risk will be calculated separately for each period in which the subject is counted. Subjects who are no longer in the exposure time at risk period (Table 10–2) on the start date of a specific COVID-19 reporting period will not be counted in the denominator for that period ie, a subject who has withdrawn from the study prior to 11 March 2020 and is no longer at risk will not be included in the denominator for the 'During the COVID-19 pandemic' or the 'Post the COVID-19' pandemic periods.

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 AS0009	10MAR2020	This period is applicable for all subjects in the SS. The following rules will be applied: 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 AS0009 + 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 AS0009 – First dose date in AS0009 + 140[a]) +1] and (Date of last clinical contact[b] – First dose date in AS0009 + 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.

During the COVID-19 pandemic	11MAR2020	Date of end of pandemic	This period is applicable for all subjects in the SS who are still considered at risk on the 11MAR2020 (ie, those for whom either dosing is continuing or for whom the 140 day SFU period after last dose has not been completed [in the case of premature treatment discontinuation]). The following rules will be applied: For subjects who did not discontinue medication in the 'During the COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is on or after the date of the end of the pandemic +1): (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 AS0009 + 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 AS0009 – 11MAR2020 + 140[a]) +1] and (Date of last clinical contact[b] – 11MAR2020 + 1) For subjects that died in the 'During the COVID-19 pandemic' phase: 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 'During the COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is on or after 11MAR2020 and on or before the date of the end of the pandemic): If the following is true: Minimum of (Last dose date in AS0009 + 140[a]) and (Date of last clinical contact[b]) is > the date of the end of the pandemic Then the duration of exposure will be calculated as follows: (Date of end of pandemic – 11MAR2020 + 1) Else duration of exposure will be calculated as follows:

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

Study Period	Start Date	End Date	Duration of Exposure
			Minimum of [(Last dose date in AS0009 – 11MAR2020 + 140[a]) +1] and (Date of last clinical contact[b] – 11MAR2020 + 1) For subjects that died in the 'During the COVID-19 pandemic' phase: 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.

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

Study Period	Start Date	End Date	Duration of Exposure
Post the COVID-19 pandemic	Date of end of pandemic + 1	Last dose of BKZ 160mg in AS0009	This period is applicable for all subjects in the SS who are still considered at risk on the day after the end date of the pandemic (ie, those for whom either dosing is continuing or for whom the 140 day SFU period after last dose has not been completed [in the case of premature treatment discontinuation]). The following rules will be applied: For subjects who did not discontinue medication in the 'During the COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is on or after the date of the end of pandemic +1): Minimum of [(Last dose date in AS0009 – (date of the end of pandemic +1) + 140[a]) + 1] and (Date of last clinical contact[b] – (date of the end of pandemic +1) + 1) For subjects that died: Date of death – (date of the end of pandemic +1) + 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 'During the COVID-19 pandemic' phase (ie, where the last dose of BKZ 160mg is on or before the date of the end of pandemic): If the following is true: Minimum of (Last dose date in AS0009 + 140[a]) and (Date of last clinical contact[b]) is ≥ the date of the end of pandemic +1 Then the duration of exposure will be calculated as follows: [Minimum of [(Last dose date in AS0009 – (date of the end of pandemic +1) + 140[a]) +1] and (Date of last clinical contact[b] – (date of the end of pandemic +1) +1)] For subjects that died within 140 days following the last dose of BKZ this rule be adjusted to: Date of death – (date of the end of pandemic +1) + 1

[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 4.2.4].

BKZ=bimekizumab.

10.3 Clinical laboratory evaluations

The routine clinical laboratory evaluations specified in Table 10–6 will be summarized. If any additional analytes are also 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 central laboratory data only, from scheduled visits (including the SFU visit). Observed values and changes from AS0009 Laboratory Baseline will be summarized, by treatment group at completion of AS0008 and overall. CRP will be summarized separately as described in Section 8.

In the case where laboratory values (with the exception of CRP) are below the LLOQ, then these will be set to the midpoint between 0 and the LLOQ for the purpose of summarizing the data and calculating changes from Baseline. 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 (including unscheduled and repeat assessments, but excluding any measurements that occurred prior to the first administration of study medication in AS0009 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 AS0008 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. For all outputs presenting markedly abnormal laboratory values, only central laboratory data will be included.

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
ALT	N/A	>5.0 x ULN

Table 10–8: Definitions of markedly abnormal biochemistry values

Variable (SI Units)	Markedly Abnormal Definition	
	Low	High
AST	N/A	>5.0 x ULN
Total bilirubin	N/A	>3.0 x ULN
GGT	N/A	>5.0 x ULN
Creatinine (umol/L)	N/A	>3.0 x ULN or >3 x Baseline value[a]
Glucose (mmol/L)	<2.2	>13.9
Calcium (mmol/L)	<1.75	>3.1
Magnesium (mmol/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] The markedly abnormal definitions for creatinine are based on the logical OR; if either criterion is met the creatinine value will be designated as abnormal high.

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 AS0009 (including unscheduled and repeat assessments, but excluding any measurements that occurred prior to the first administration of study medication in AS0009 or more than 140 days after the last administration of study medication), will be presented by laboratory variable and treatment group at completion of AS0008. This summary will be provided only for selected laboratory variables and using central laboratory data only. 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 AS0009 Laboratory Baseline to minimum/maximum post-AS0009 Laboratory Baseline CTCAE grade will be presented by laboratory variable and treatment group at completion of AS0008. The minimum/maximum post-AS0009 Laboratory Baseline CTCAE grade will include all scheduled and unscheduled on-treatment central laboratory assessments (excluding any measurements that occurred prior to the first administration of study medication in AS0009 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[a]	High	g/L	>0-20 above ULN, or >0-20 above Baseline if Baseline is above ULN	>20-40 above ULN, or >20-40 above Baseline if Baseline is above ULN	>40 above ULN, or >40 above Baseline if Baseline is 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, ULN=upper limit of normal.

[a] The CTCAE grade definitions to be applied are dependent on the Baseline hemoglobin value. If the Baseline value is >ULN then the criteria relative to Baseline are applicable; otherwise the criteria relative to ULN are applicable.

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

Parameter (unit)	Definition	Unit	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine[a]	High	umol/L	>1-1.5 x Baseline or >ULN-1.5 x ULN	>1.5-3.0 x Baseline or >1.5 – 3.0 x ULN	>3.0 x Baseline or >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[b]	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
Cholesterol	High	mmol/L	>ULN-7.75	>7.75-10.34	>10.34-12.92	>12.92

LLN=lower limit of normal, ULN=upper limit of normal.

[a] The CTCAE grade definitions for creatinine are based on the logical OR; the highest applicable CTCAE grade should be assigned to a specific creatinine value.
[b] 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 AS0008 and overall, using on-treatment assessments (excluding any measurements that occurred prior to the first administration of study medication in AS0009 or more than 140 days after the last administration of study medication) from all visits in AS0009 including those at AS0009 Laboratory Baseline, unscheduled, ET and SFU visits. Assessments performed at both central and local laboratories will be included. 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.
- ALP: >1.5xULN.

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 AS0008 and overall, using on-treatment assessments (excluding any measurements that occurred prior to the first administration of study medication in AS0009 or more than 140 days after the last administration of study medication) from all visits including those at AS0009 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 criteria, 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 AS0009 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 AS0008 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 six months and whether the subject has used illicit drugs in the past six 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 (e.g. acetaminophen, herbal remedies, vitamins); dosages and dates should be included.

Pertinent medical history, including the following: • History of liver disease (e.g. autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") • Adverse reactions to drugs • Allergies • Relevant family history or inheritable disorders (e.g. 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 (e.g. 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)

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

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

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

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

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

10.5 Vital Signs 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 AS0008 Baseline for each vital sign variable at each visit, by treatment group at the completion of AS0008 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 AS0009 or more than 140 days after the last administration of study medication) by treatment group at the completion of AS0008 and overall (based on change from AS0008 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 AS0008 Baseline of ≥20	>180 and an increase from AS0008 Baseline of ≥20
Diastolic blood pressure (mmHg)	<50 and a decrease from AS0008 Baseline of ≥15	>105 and an increase from AS0008 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 AS0008 and overall.

The following ECG variables will be summarized by visit (absolute values and change from AS0008 Baseline), by treatment group at completion of AS0008 and overall:

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

Outliers in QTcF and QTcB are defined as values meeting the following criteria at any on-treatment assessment in AS0009:

- QTcF or QTcB >450 ms OR
- QTcF or QTcB change from AS0008 Baseline >30 ms

Outliers will be summarized using the following categories:

- Values >450 ms, >480 ms and >500 ms
- Increase from AS0008 Baseline of >30 ms, >60 ms and >90 ms
- Value >450 ms AND increase from AS0008 Baseline of >30 ms

- Value >500 ms AND increase from AS0008 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 AS0009 or more than 140 days after the last administration of study medication).

All ECG variables will be listed, including unscheduled and repeat visits, if applicable. 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 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 AS0008. However, some subjects completed the 'lifetime' assessment (in error) at one or more visits in AS0009 and recorded positive responses to some questions. Based on a review of their original lifetime assessment in AS0008, 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 least once for any on-treatment assessment (including unscheduled assessments, but excluding any measurements that occurred prior to the first administration of study medication in AS0009 or more than 140 days after the last administration of study medication) during AS0009, will be summarized by treatment group at completion of AS0008.

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 AS0009 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 and ADAb data).

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12 APPENDICES

12.1 Data Handling Rules for ASAS20, ASAS40 and ASAS5/6 Response

The rules for handling missing data in relation to defining the achievement of ASAS20 and ASAS40 responses are provided in Table 12-1. This table also indicates, where appropriate, the imputation as a non-responder (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: Data Handling Rules for ASAS20 and ASAS40

Components	Component Status	ASAS[a]	DTYPE
4 components present	3 or more components improved >=40% and >=2 units AND no deterioration in remaining component	Y	
4 components present	3 components improved >=40% and >=2 units AND remaining component deteriorated >=20% and >=1 unit	N	
At least 1 component present	1 or more component(s) has deteriorated >=20% and >=1 unit	N	
3 components present	3 or more components improved >=40% and >=2 units	Y	
3 components present	2 components improved >=40% and >=2 units AND no deterioration in remaining component(s)	N	WC
3 components present	1 or 0 components improved >=40% and >=2 units AND no deterioration in remaining component(s)	N	
2 components present	2 or 1 components improved AND no deterioration in remaining component(s)	N	WC
2 components present	0 components improved	N	
1 or 0 components present	1 or 0 components improved >=40% and >=2 units AND no deterioration in remaining component(s)	N	WC

[a] Rules are based on ASAS40, similar rules will be implemented for ASAS20 response where improvement is defined as a change >=20% and >=1 units.
WC = worst case.

Similar rules for defining the achievement of ASAS5/6 response are presented in Table 12-2.

Table 12-2: Data Handling Rules for ASAS5/6 Response

Components	Component Status	ASAS	DTYPE
6 components present	5 or more components improved >=20%	Y	
6 components present	4 or fewer components improved >=20%	N	
5 components present	5 components improved >=20%	Y	
5 components present	4 components improved >=20%	N	WC
5 components present	3 or fewer components improved >=20%	N	
4 components present	4 or 3 components improved >=20%	N	WC
4 components present	2 or fewer components improved >=20%	N	
3 components present	3 or 2 components improved >=20%	N	WC
3 components present	1 or 0 component(s) improved >=20%	N	
2 components present	2 or 1 components improved >=20%	N	WC
2 components present	0 component(s) improved >=20%	N	
1 or 0 components present	1 or 0 components improved >=20%	N	WC

WC = worst case.

12.2 Classification of the SF-36 questionnaire

Table 12–3 describes the 8 different scores calculated from the SF-36 questionnaire.

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

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

12.3 Identification of Opportunistic infections

Opportunistic infections are identified in two steps:

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

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

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

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

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

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

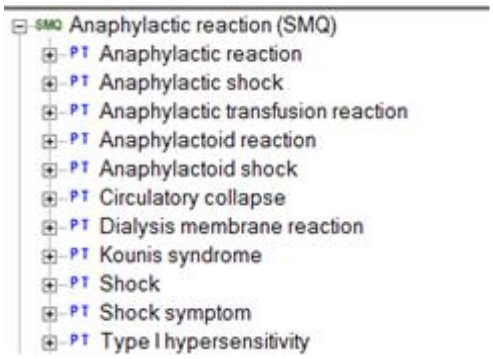
The timing and frequency of Step 2 should be outlines and agreed to by the study team at the beginning of the study. It is suggested that this process be executed multiple times throughout the course of the study, more frequently in the weeks leading up to database lock, and one final time immediately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

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

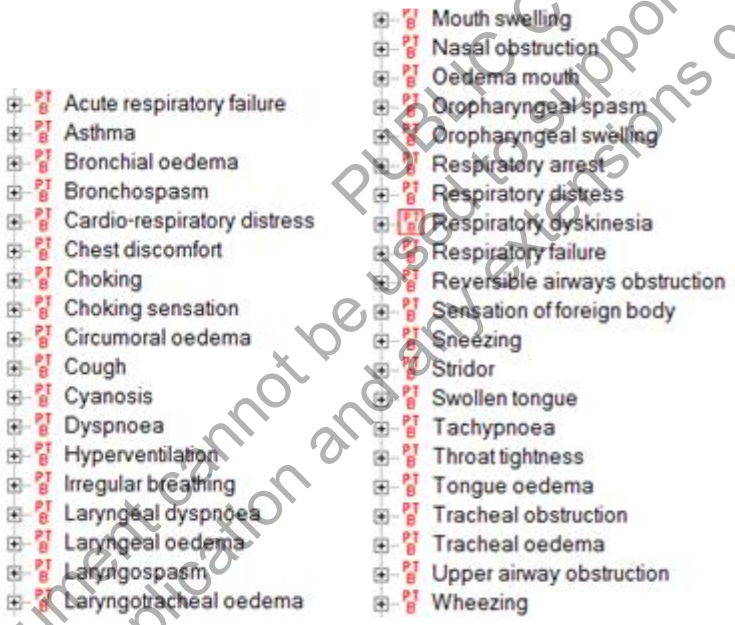
12.4 MedDRA algorithmic approach to anaphylaxis

The SMQ Anaphylactic reaction consists of three parts:

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

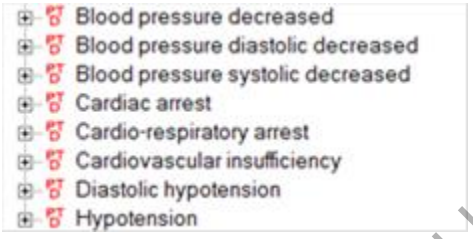


- A **broad search** that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction and categorized in B, C or D
  - Cat B



  - 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.

12.5 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 AMENDMENTS 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 06 Feb 2020. 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 following modifications and changes have been made:

- Efficacy measurements at the SFU visit have been removed from the list of assessments for the other efficacy endpoints (Section 2.2.2.3).
- 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 AS0009 EV for safety 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 AS0008 Baseline and from AS0009 EV for laboratory parameters (with the exception of CRP) will not be presented, due to a change in laboratory vendor between AS0008 and AS0009. Laboratory Baseline is defined as the earliest value in AS0009 at or prior to AS0009 Week 12.
- Summaries of ASAS40, ASAS20 and ASAS5/6 response at each post-AS0008 Baseline visit in AS0008 through to AS0009 Week 208 have been added for subjects who were responders at AS0008 Week 12. These summaries will be used to assess maintenance of response.
- The relative day will now be calculated twice, once relative to the start of study medication in AS0008 and once relative to the start of study medication in AS0009.
- A definition of the dosing period has been added.
- Baseline values (with the exception of AS0009-Laboratory Baseline values) will now be taken directly from the AS0008 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 protocol and previous version of the SAP describe the FAS as consisting of all enrolled subjects who receive at least 1 dose of IMP and have a valid measurement for at least 1 efficacy variable at AS0009 study entry. This has been updated to include all subjects in the ES who received at least one dose of study medication in AS0009 and have a valid measurement for at least one efficacy variable after AS0009 EV in order to identify subjects who have had assessments during AS0009.
- Summaries by randomized treatment in AS0008 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 AS0009 entry. Maintenance of response displays will be split by treatment sequence across AS0008 and AS0009. Safety displays using AS0008 information will incorporate exposure in AS0008.
- The protocol defines subgroups based on 'Concomitant non-steroidal anti-inflammatory drug (NSAID) status at AS0009 entry. This has been updated to 'Concomitant NSAID status at start of AS0008'.
- 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 AS0009. In addition the SAP has been updated to state that for NRI, the imputation will be re-derived at the AS0009 EV instead of using the AS0008 Week 48 imputed value; this is due to slight differences in the derivation rules for some endpoints between the AS0008 and AS0009 SAPs.
- The MI procedures have been updated for all endpoints to use OC data from both AS0008 and AS0009 studies such that missing data across both studies will be imputed. Thus, the procedure will estimate an imputation model at each post-AS0008 Baseline visit where efficacy variables are collected. The covariate for AS0009 EV has therefore been deleted from the model.
- 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 NSAID 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 AS0009. 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 ASAS40, 20, ASAS5/6 and BASDAI. Additional sensitivity analyses based on MI of component scores were added for ASAS40 and ASAS20 response variables.
- The data handling rules for ASAS response derivations have been updated and clarified to match the overall program conventions for bimekizumab
- Summaries of MASES were restricted to subjects with enthesitis (MASES > 0) at AS0008 Baseline
- CRP values below the LLOQ will now be set to half LLOQ (0.08mg/L) prior to reporting (rules for calculation of ASDAS-CRP use different conventions for values that are below the LLOQ).
- Plots of geometric mean bimekizumab plasma concentration versus time by treatment group and cumulative ADAb status have been added based on ADAb status in AS0008 and AS0009.
- 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 AS0008 and AS0009 combined, a corresponding AE overview table and a table of exposure across AS0008 and AS0009 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 AS0009 and ongoing TEAEs from AS0008 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

13.2.1 Rationale for the amendment

The main objectives of this SAP amendment are to incorporate relevant updates in order to align with the most recent bimekizumab program conventions and make other modifications following the review of the results from the interim analysis.

13.2.2 Modifications and changes

The following modifications and changes have been made:

- Section 3.3 was updated to clarify that local laboratory measurements will not be considered in the definition of Baseline for laboratory data.
- The endpoints/components for which MI will be performed have been updated in the section on handling missing data for the efficacy analyses; these now include each of the 8 individual domains of the SF-36, in addition to the PCS and MCS scores. The domain scores will also be summarized in a corresponding table. In addition, the minimum and maximum allowable ranges for PCS and MCS for imputation purposes have been updated using the most recently available norm-based scores.
- In Table 4–2, the OC analysis has been added as the secondary analysis for ASAS-PR; this was omitted in error in the previous version of the SAP.
- The disease categories for ASDAS-CRP have been updated to reference ‘low’ disease activity instead of ‘moderate’ disease activity.

- Section 8.1.12 has been updated to clarify that CRP assessments performed at local laboratories will not be considered for efficacy analyses (including ASDAS-CRP).
- The methodology for calculation of the BASMI scores has been updated in line with the most recent bimekizumab program conventions. The reference list has been updated accordingly.
- The analysis set used to present the impact of the COVID-19 pandemic on the conduct of the efficacy assessments has been updated from the SS to the FAS.
- Section 6.2 was updated to clarify that the summary of current corticosteroid therapy for AS0009 will include oral medications only.
- Section 6.5 was updated to clarify how different medication types will be identified and classified for reporting purposes.
- A summary of the injection setting and person performing the injection at each dosing visit has been added. An additional overall summary has been added showing the overall number of subjects having self- and home-administrations of study medication.
- The calculation rules for exposure time at risk relative to the COVID-19 pandemic have been updated to take into account treatment discontinuation within each period.
- The summaries of TEAEs by time of onset relative to the COVID-19 pandemic and by region have been removed due to the small number of events within each region.
- The data handling rules for PK concentration data have been updated with respect to the exclusion rules used for the summary statistics. In addition, the rules for determining cumulative ADAb positivity have been clarified.
- The method for calculating the fold change from Baseline for the ADAb titers has been added to the SAP.
- The summary table of ADAb status by visit has been updated to include a summary for the BKZ Total group in addition to the summaries by treatment at completion of AS0008.
- The reference to the use of Kaplan-Meier methods for the plot of time to treatment-emergent ADAb positivity has been removed as this is not applicable.
- The summary tables and corresponding figures for time to treatment-emergent ADAb positivity have been updated to include a summary for the BKZ Total group in addition to the summaries by treatment at completion of AS0008. Further details regarding the presentation of the figures were also added to the text for clarity.
- The categories for the figure of ASAS40 responders over time by ADAb status have been updated to exclude the AS0009 SFU visit in the derivations.
- The description of the figure for ASAS40 responders over time by ADAb status has been updated to clarify that the missing category will be omitted from the plot if there are <=5% of subjects in this category. Additional modifications to the text describing the ADAb-related figures have been made to clarify the requirements where needed.
- The summary table of TEAEs by timing of onset relative to ADAb status was clarified with respect to the ADAb categories to be included.

- An additional table was added to the SAP summarizing neuropsychiatric TEAEs by event type.
- Additional categories for the adjudicated IBD AESI have been added to the SAP, per the latest IBD adjudication committee criteria.
- The rules for handling safety laboratory data reported as below the LLOQ were updated in line with the most recent bimekizumab program conventions. Additional clarification was added regarding the presentation of markedly abnormal laboratory results and CTCAE grades to highlight that only central laboratory results will be included in these outputs.
- The criteria for TEMA laboratory results have been updated for creatinine and total cholesterol.
- The CTCAE grades for hemoglobin and creatinine have been updated.
- ALP was added to the list of elevated liver function tests and the text has been updated to clarify that results from both central and local laboratories will be considered in this tabulation.

13.3 Amendment 3

13.3.1 Rationale for the amendment

The purpose of this SAP amendment is to clarify the definition of the FAS in order to ensure that all subjects included in the FAS have data available to contribute to the efficacy analyses.

13.3.2 Modifications and changes

The following modifications and changes have been made:

- Section 2.2.2.3 was updated to remove the Week 132 visit for the ASQoL efficacy endpoint; this was an error in the previous versions of the SAP.
- Section 3.6.3 was updated to the following:

  The Full Analysis Set (FAS) will consist of all subjects in the ES who received at least one dose of study medication in AS0009 and have a valid measurement for at least one efficacy variable at any scheduled visit (excluding SFU visits) after AS0009 EV where efficacy is planned to be collected. This will include any data collected at an unscheduled or ET visit, and which has been remapped to a scheduled visit where efficacy data are planned. The protocol definition suggested that a valid measurement for at least one efficacy variable at AS0009 EV was required, but in order to identify subjects who have had assessments during AS0009, the requirement has been changed to 'after'. This has been further clarified to include scheduled visits in AS0009 (where efficacy data is planned), excluding SFU visits, in order to ensure that all subjects in the FAS have data available to contribute to any of the efficacy analyses.
- Section 3.10 was updated to add additional detail to the change from the protocol-defined definition of the FAS.

14 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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