STATISTICAL ANALYSIS PLAN AMENDMENT 5

Study: PA0008

Product: Bimekizumab

A MULTICENTER, PHASE 2B, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE-RANGING STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN ACTIVE PSORIATIC ARTHRITIS

SAP/Amendment Number	Date
Final SAP	12 May 2017
SAP Amendment 1	11 Aug 2017
SAP Amendment 2	7 Nov 2017
SAP Amendment 3	02 Mar 2018
SAP Amendment 4	09 Aug 2018
SAP Amendment 5	07 Sep 2018

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LIST OF ABBREVIATIONS

AbAb	anti-bimekizumab antibody
ACR	American College of Rheumatology
ACR20,50,70	American College of Rheumatology 20, 50, 70% response criteria
ACP	above the cut point
ADR	adverse drug reaction
AE	adverse event
AJ	assessed joints
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BCP	below the cut point
BKZ	bimekizumab
BLQ	below the level of quantification
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	cyclic citrullinated peptide
cDBRS	corrected Dose-Blind Responder Set
CDF	cumulative distribution function

CDISC	Clinical Data Interchange Standards Consortium
cESS	corrected Escape Subject Set
CI	confidence interval
CL/F	total body clearance
CP	confirmed positive
CPK	creatine phosphokinase
CRP	C-reactive protein
CV	coefficient of variance
DAP	data analysis plan
DAS28(CRP)	Disease Activity Score-28 joint count C-reactive protein
DBS	Dose-Blind Set
DBRS	Dose-Blind Responder Set
DEM	data evaluation meeting
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EAER	exposure adjusted event rate
AEIR	exposure adjusted incidence rate
ES	Enrolled Set
ESS	Escape Subject Set
ET	early termination
FAS	Full Analysis Set
GGT	gamma glutamyltransferase

H	high
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale—Anxiety
HADS-D	Hospital Anxiety and Depression Scale—Depression
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBcAb-IgM	Hepatitis B core antibody-IgM
HBsAg	Hepatitis B surface antigen
HIV	human immunodeficiency virus
HLGT	High-Level Group Term
HLT	High Level Term
HRQoL	Health-Related Quality of Life
hs-CRP	high sensitivity C-reactive protein
INR	international normalized ratio
ITT	Intent-to-treat
IMP	investigational medicinal product
L	low
LCL	lower confidence limit
LD	loading dose
LDH	lactate dehydrogenase
LDI	Leeds Dactylitis Index
LEF	leflunomide
IgM	immunoglobulin M
LLN	lower limit of normal
LLOQ	lower limit of quantification

LOCF	last observation carried forward
MAR	missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Index
MCH	mean corpuscular hemoglobin;
MCHC	mean corpuscular hemoglobin concentration
MCMC	Markov-Chain Monte Carlo
MCS	mental component summary
MCV	mean corpuscular volume
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTX	methotrexate
mNAPSI	modified Nail Psoriasis Severity Index
N	number of subjects
n	number of observations
N/A	not applicable
NCP	not confirmed positive
NRI	non-responder imputation
NRS	numerical rating scale
NSAID	nonsteroidal anti-inflammatory drug
OR	odds ratio
PASI	Psoriasis Area and Severity Index
PASI75, PASI90, PASI100	Psoriasis Area and Severity Index 75%, 90%, 100%
PCS	physical component summary

PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamics Per-Protocol Set
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic
PK-PPS	Pharmacokinetic Per-Protocol Set
PPS	Per-Protocol Set
PsA	psoriatic arthritis
PsAID-9	Psoriatic Arthritis Impact of Disease-9
PsAQoL	Psoriatic Arthritis Quality of Life
PT	preferred term
PtAAP	Patient's Assessment of Arthritis Pain
Q4W	every 4 weeks (monthly)
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RCTC	Rheumatology Common Toxicity Criteria
RNA	ribonucleic acid
RS	Randomized Set
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)

SD	standard deviation
SE	standard error
SF-36	Short-Form 36-item Health Survey
SFU	Safety Follow-up
SJC	swollen joint count
SMQ	Standard MedDRA query
SOC	system organ class
SS	Safety Set
TEAE	treatment-emergent adverse event
TJC	tender joint count
TFLs	tables, figures, and listings
TNF	tumor necrosis factor
TNFα	tumor necrosis factor-alpha
TB	tuberculosis
UCL	upper confidence limit
ULN	upper limit of normal
V/F	volume of distribution
VAS	visual analog scale
WBC	white blood cell
WHO-DD	World Health Organization Drug Dictionary
Z	critical value from the standard normal distribution

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required interim and final statistical analysis for study PA0008. It also defines the summary tables, figures, and listings (TFLs) to be generated in the clinical study report according to the final Protocol (29 Jul 2016), Protocol Amendment 1 (16 Dec 2016), and Protocol Amendment 2 (09 Mar 2018).

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

2 PROTOCOL SUMMARY

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

The study population will consist of adult subjects (≥18 years of age) fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR, Table 12–1) criteria and having active disease with tender joint count (TJC) ≥3 out of 78 and swollen joint count (SJC) ≥3 out of 76. Subjects must be rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies negative and have active psoriatic lesion(s) and/or a documented history of psoriasis. Subjects may be tumor necrosis factor (TNF) inhibitor naïve or may have received 1 prior TNF inhibitor.

Subjects who have been on a TNF inhibitor previously must have:

- experienced an inadequate response to previous treatment given for at least 3 months
- been intolerant to administration (eg, had a side-effect/adverse event (AE) that led to discontinuation)
- lost access to TNF inhibitor for other reasons

An estimated 70 sites in Europe and North America will randomize 200 subjects. Enrollment of TNF inhibitor experienced subjects will be limited to 30% of the total study population.

The study consists of a Screening Period (14 to 28 days), Double-Blind Period (12 weeks), Dose-Blind Period (36 weeks) and Safety Follow-up Period (20 weeks after last dose; only for subjects who do not enter the extension study). Therefore, the maximum duration of the study is 68 weeks.

2.1 Study objectives

2.1.1 Primary objective

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

2.1.2 Secondary objectives

The secondary objectives of the study are as follows:

- To assess the efficacy of the individual dose regimens of bimekizumab compared to placebo
- To assess skin and nail psoriasis in the subgroup of affected subjects at Baseline
- To assess the safety and tolerability of bimekizumab
- To assess the PK of bimekizumab
- To assess the PD of bimekizumab
- To assess the immunogenicity of bimekizumab
- To assess the exposure:response relationship of bimekizumab as it relates to efficacy and safety

2.1.3 Other objectives

Other objectives of the study are as follows:

- To assess the impact on patient-reported quality of life
- To assess the impact of bimekizumab treatment on axial disease
- To assess the impact of bimekizumab on dactylitis and enthesitis
- To assess the impact of administration of bimekizumab on biological pathways relating to disease biology, progression, and response to therapy via biomarker analysis and to enable genomic and related approaches for analysis of subject samples and evaluation of the potential for subject stratification approaches

2.2 Study variables

2.2.1 Efficacy variables

2.2.1.1 Primary efficacy variable

The primary efficacy variable for this study is as follows:

- American College of Rheumatology 50% (ACR50) response at Week 12

2.2.1.2 Secondary efficacy variable(s)

The secondary efficacy variables for this study are as follows:

- American College of Rheumatology 20% (ACR20) response at Week 12
- American College of Rheumatology 70% (ACR70) response at Week 12
- Psoriasis Area and Severity Index 90% (PASI90) response at Week 12 in the subgroup of subjects with psoriasis involving at least 3% of body surface area (BSA) at Baseline/Day 1
- Psoriasis Area and Severity Index 75% (PASI75) response at Week 12 in the subgroup of subjects with psoriasis involving at least 3% of BSA at Baseline/Day 1

2.2.1.3 Other efficacy variables

Other efficacy variables will be assessed as specified in Table 2–1:

- Time to ACR20 and ACR50 response

- Psoriasis Area and Severity Index 100% (PASI100) response in the subgroup of subjects with psoriasis involving at least 3% of BSA at Baseline/Day 1
- ACR20, ACR50, and ACR70 response
- Composite endpoint comprised of ACR50 and PASI90 response in the subgroup of subjects with psoriasis involving at least 3% of BSA at Baseline/Day 1
- Minimal Disease Activity (MDA) and modified MDA
- Change from Baseline in the Disease Activity Score-28 based on high sensitivity C-reactive protein (DAS28 [CRP])
- Change from Baseline in all individual American College of Rheumatology (ACR) score components:
  - SJC
  - TJC
  - Health Assessment Questionnaire—Disability Index (HAQ-DI)
  - Patient's Assessment of Arthritis Pain (PtAAP)
  - Physician's Global Assessment of Disease Activity (PhGADA)
  - Patient's Global Assessment of Disease Activity (PGADA)
  - high sensitivity C-reactive protein (hs-CRP)
- Change from Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Change from Baseline in the modified Nail Psoriasis Severity Index (mNAPSI)
- Change from Baseline in the Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index
- Change from Baseline in the Leeds Dactylitis Index (LDI)
- Psoriatic Arthritis Impact of Disease (PsAID)-9
- Psoriatic Arthritis Quality of Life (PsAQoL)
- Change from Baseline in Physical Component Summary (PCS) and Mental Component Summary (MCS) of the SF-36 (Short-Form 36-Item Health Survey)
- Change from Baseline in Hospital Anxiety and Depression Scale (HADS) HADS-Anxiety (A) and HADS-Depression (D) scores
- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores)

2.2.2 Pharmacokinetic/pharmacodynamic variables

2.2.2.1 Pharmacokinetic variable

The PK variable is plasma concentration of bimekizumab. The assessment schedule for plasma concentration is available in Table 2–1.

2.2.2.2 Pharmacodynamic variables

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

2.2.3 Pharmacogenomic variables

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

2.2.4 Immunological variables

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

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

2.2.5 Safety variables

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

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

2.3 Study design and conduct

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

- Subject has a documented diagnosis of adult-onset PsA classified by CASPAR criteria with symptoms for at least 6 months prior to Screening with active PsA and must have at Baseline TJC ≥3 out of 78 and SJC ≥3 out of 76 (dactylitis of a digit counts as 1 joint each).
- Subject must be rheumatoid factor and anti-CCP antibodies negative.
- Subject must have active psoriatic lesion(s) and/or a documented history of psoriasis.

- Subjects may be TNF inhibitor naïve or may have received 1 prior TNF inhibitor. Subjects who have been on a TNF inhibitor previously must have:
  - experienced an inadequate response to previous treatment given for at least 3 months
  - been intolerant to administration (eg, had a side-effect/AE that led to discontinuation)
  - lost access to TNF inhibitor for other reasons

Two hundred subjects will be randomized to 1 of 5 treatment arms. Subjects in any treatment group who complete the 12-week Double-Blind Period will enter the 36-week Dose-Blind Period. Treatment during the Dose-Blind Period will start at Week 12 and be administered Q4W thereafter through Week 44.

Screening Period/ Baseline

During the Screening Period, the Investigator will obtain laboratory data and verify that the doses of methotrexate (MTX), leflunomide (LEF), nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids, if used, are stable. The Screening Period will also enable washout of medications not permitted for use during the study. The Screening Period will last 14 to 28 days.

Double-Blind Period

During the Double-Blind Period, subjects will be randomized 1:1:1:1:1 (stratified by region and prior TNF inhibitor exposure) to receive the following blinded study treatment regimens:

- Placebo
- Bimekizumab 16mg administered sc Q4W
- Bimekizumab 160mg administered sc Q4W
- Bimekizumab 320mg administered sc Q4W
- Bimekizumab 320mg loading dose followed by 160mg administered sc starting at Week 4 and Q4W thereafter

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

Investigational medicinal product (IMP) will be administered sc in the clinic at Baseline, Week 4, and Week 8. Additional non-dosing study visits in the Double-Blind Period will occur at Week 1 and Week 2. At Week 12, subjects will transition from the Double-Blind Period into the 36-week Dose-Blind Period. Note that the other assessments are planned to be performed before the IMP administration and will be analyzed for the Double-Blind Period.

Dose-Blind Period

The first IMP for the Dose-Blind Period will be administered at Week 12. At the Week 12 Visit, subjects will be allocated to bimekizumab treatment regimens as follows:

- Subjects in the placebo group will be rerandomized 1:1 to bimekizumab 160mg or bimekizumab 320mg Q4W

- Subjects in the bimekizumab 16mg dose group will be rerandomized 1:1 to bimekizumab 160mg or bimekizumab 320mg Q4W
- Subjects in the bimekizumab 160mg dose group will continue to receive bimekizumab 160mg Q4W
- Subjects in the bimekizumab 320mg dose group will continue to receive bimekizumab 320mg Q4W
- Subjects in the bimekizumab 320mg (loading)/160mg dose group will continue to receive bimekizumab 160mg Q4W

All assessments for the Dose-Blind Period will be done from Week 18 to Week 48. The last IMP administration is on Week 44.

The total duration of treatment is 36 weeks.

During the 36-week Dose-Blind Period, subjects will be evaluated for inadequate response to treatment at defined time points. Subjects who do not show an improvement in tender and swollen joint count will be eligible to receive rescue therapy as defined in Section 6.5.

Safety Follow-up/Extension study

At the completion of the Dose-Blind Period, Investigators should discuss treatment options with the subject. Subjects will be given the opportunity to enter an extension study at Week 48, provided they do not qualify for rescue therapy.

Table 2–1: Schedule of assessments

Protocol activity / Visit[a]/ Week	Screening (V1) (14-28 days)	Baseline (Day 1, V2) (first dose)	Double-Blind Period (weeks after first dose)					Dose-Blind Period (weeks after first dose)									ET	SFU[b]
			3/1	4/2	5/4	6/8	7/12	8/16	9/20	10/24	11/28	12/32	13/36	14/40	15/44	16/48		
Written Informed consent	X																	
Demographic data	X																	
PsA history	X																	
Significant past medical history and concomitant diseases	X	X[c]																
Inclusion/exclusion criteria	X	X																
Prior medication	X																	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PsAQoL		X			X	X	X	X		X			X			X	X	X
BASDAI		X	X	X	X	X	X	X		X			X			X	X	X
HAQ-DI		X		X	X	X	X	X	X	X			X			X	X	X
SF-36		X			X		X	X		X			X			X	X	X

Table 2–1: Schedule of assessments

Protocol activity / Visit[a]/ Week	Screening (V1) (14-28 days)	Baseline (Day 1, V2) (first dose)	Double-Blind Period (weeks after first dose)					Dose-Blind Period (weeks after first dose)									ET	SFU[b]
			3/1	4/2	5/4	6/8	7/12	8/16	9/20	10/24	11/28	12/32	13/36	14/40	15/44	16/48		
PGADA		X	X	X	X	X	X	X	X	X			X			X	X	X
PsAID-9		X			X	X	X	X		X			X			X	X	X
Tuberculosis questionnaire	X	X					X			X			X			X	X	X
Height	X																	
Vital signs (pulse, temperature, BP)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X					X			X			X			X	X	X
Physical examination[e]	X						X			X						X	X	X
SJC and TJC	X	X		X	X	X	X	X	X	X			X			X	X	X
BSA affected by PSO (BSA palm method)		X					X			X						X	X	X
PASI[f]		X		X	X	X	X			X			X			X	X	X
mNAPSI		X					X			X			X			X	X	
MASES		X			X	X	X	X		X			X			X	X	X
LDI		X			X	X	X	X		X			X			X	X	X
PhGADA		X		X	X	X	X	X	X	X			X			X	X	X

Table 2–1: Schedule of assessments

Protocol activity / Visit[a]/ Week	Screening (V1) (14-28 days)	Baseline (Day 1, V2) (first dose)	Double-Blind Period (weeks after first dose)					Dose-Blind Period (weeks after first dose)									ET	SFU[b]
			3/1	4/2	5/4	6/8	7/12	8/16	9/20	10/24	11/28	12/32	13/36	14/40	15/44	16/48		
ECG	X						X									X	X	X
Hematology/biochemistry/ urinalysis	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
hs-CRP[g]	X	X	X	X	X	X	X	X	X	X			X			X	X	X
CRP[g]		X			X		X			X								
Pregnancy testing[h]	X	X														X	X	X
Hepatitis B and C testing	X																	
HIV testing	X																	
RF, anti-CCP antibodies	X																	
Blood sample for bimekizumab plasma concentrations[i]		X	X	X	X	X	X	X	X	X			X			X	X	X
Bimekizumab antibody detection[i]		X			X	X	X	X	X	X			X			X	X	X
Blood samples for cytokines, complement, and biomarker analysis[i]		X	X		X		X			X						X	X	

Table 2–1: Schedule of assessments

Protocol activity / Visit[a]/ Week	Screening (V1) (14-28 days)	Baseline (Day 1, V2) (first dose)	Double-Blind Period (weeks after first dose)					Dose-Blind Period (weeks after first dose)									ET	SFU[b]
			3/1	4/2	5/4	6/8	7/12	8/16	9/20	10/24	11/28	12/32	13/36	14/40	15/44	16/48		
Blood samples for genomic, proteomic/metabolomics analyses[i,j]		X	X		X		X			X						X	X	
For participating centers: Blood samples for flow cytometry[i]		X	X		X		X			X						X	X	
Blood samples for genetic/epigenetic analysis[i,j]		X	X				X			X								
IGRA Tuberculosis test[k]	X														X		X	X
Evaluation for rescue[l]								X		X			X					
Chest x-ray[m]	X																	
Hand and foot x-rays[n]	X																	
Enter IXRS[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bimekizumab or placebo administration[p,q]		X			X	X	X	X	X	X	X	X	X	X	X			

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BP=blood pressure; BSA=body surface area; CCP= cyclic citrullinated peptide; CRP=C-reactive protein; eCRF=electronic Case Report Form; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram;

Table 2–1: Schedule of assessments

Protocol activity \ Visit[a]/ Week	Screening (V1) (14-28 days)	Baseline (Day 1, V2) (first dose)	Double-Blind Period (weeks after first dose)					Dose-Blind Period (weeks after first dose)								ET	SFU[b]
			3/1	4/2	5/4	6/8	7/12	8/16	9/20	10/24	11/28	12/32	13/36	14/40	15/44	16/48	
Informed consent[c]	X																
Medical history[c]	X																
Demography	X																
Randomization		X															
Vital signs[d]	X	X	X			X		X		X				X		X	X
Physical examination	X															X	
Height	X																
Weight	X	X				X		X		X				X		X	X
Tuberculosis[e]	X																
Pregnancy test[h]	X	X														X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests	X	X				X		X		X				X		X	X
Urinalysis	X	X				X		X		X				X		X	X
Hepatitis B and C	X																
HIV	X																
IGRA	X																
Psoriasis assessments[f]	X	X				X		X		X				X		X	X
PASI	X	X				X		X		X				X		X	X
PGADA	X	X				X		X		X				X		X	X
PhGADA	X	X				X		X		X				X		X	X
mNAPSI	X	X				X		X		X				X		X	X
Psoriatic arthritis assessments	X	X				X		X		X				X		X	X
PsAID	X	X				X		X		X				X		X	X
PtAAP	X	X				X		X		X				X		X	X
LDI	X	X				X		X		X				X		X	X
SJC	X	X				X		X		X				X		X	X
TJC	X	X				X		X		X				X		X	X
Quality of life assessments	X	X				X		X		X				X		X	X
SF-36	X	X				X		X		X				X		X	X
PsAQoL	X	X				X		X		X				X		X	X
HAQ-DI	X	X				X		X		X				X		X	X
HADS	X	X				X		X		X				X		X	X
Hs-CRP[g]	X	X				X		X		X				X		X	X
Blood samples for bimekizumab and anti-bimekizumab antibody detection[i]		X				X		X		X				X		X	X
Genetic testing[j]		X															
IXRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X		

ET=Early Termination; HADS=Hospital Anxiety and Depression Scale; HAQ-DI=Health Assessment Questionnaire—Disability Index; HIV=human immunodeficiency virus; hs-CRP=high sensitivity CRP; IGRA=interferon gamma release assay; IMP=investigational medicinal product; IXRS=interactive voice or web response system; mNAPSI=modified Nail Psoriasis Severity Index; LDI=Leeds Dactylitis Index; PASI=psoriasis area severity index; PGADA=Patient's Global Assessment of Disease Activity; PhGADA=Physician's Global Assessment of Disease Activity; PsA=psoriatic arthritis; PsAID=Psoriatic Arthritis Impact of Disease; PsAQoL=Psoriatic Arthritis Quality of Life; PSO=psoriasis; PtAAP=Patient's Assessment of Arthritis Pain; RF=rheumatoid factor; SF-36=short form-36; SFU=Safety Follow-Up; SJC=swollen joint count; TB=tuberculosis; TJC=tender joint count

a Visit windows of +/-3 days from the first dose at all visits through Week 12 and +/-4 days for all visits after Week 12 except SFU. The Safety Follow-up Visit window is -3 and +7 days from last dose.

b Safety Follow-Up Visit occurs 20 weeks after the last dose for all subjects who complete the study and do not enter the extension study or who discontinue early, including those withdrawn from study treatment.

c Ensure there are no significant changes in medical history that would exclude the subject based on the exclusion criteria.

d At Baseline/Day 1, 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. All other procedures are done prior to dosing.

e Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.

f PASI will be assessed in all subjects with Baseline/Day 1 BSA affected by PSO ≥3% as determined by the BSA palm method.

g High sensitivity-CRP is performed at Screening, Baseline, and all other study visits as marked with an X. CRP will be performed at Baseline, Week 4, Week 12, and Week 24 only. After Screening, the hs-CRP and CRP data will not be sent to the Investigator to protect the blinded nature of the treatment assignments.

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

i At dosing visits, all blood samples are taken prior to dosing. Blood samples for bimekizumab and anti-bimekizumab antibody detection will be processed as per instructions in the laboratory manual.

j A separate Informed Consent Form will be required for subjects who provide samples for genetic testing. The Informed Consent Form must be signed prior to collecting samples.

Table 2–1: Schedule of assessments

Protocol activity / Visit[a]/ Week	Screening (V1) (14-28 days)	Baseline (Day 1, V2) (first dose)	Double-Blind Period (weeks after first dose)					Dose-Blind Period (weeks after first dose)								ET	SFU[b]
			3/1	4/2	5/4	6/8	7/12	8/16	9/20	10/24	11/28	12/32	13/36	14/40	15/44	16/48		

k It is recommended that Quantiferon TB GOLD test be performed.

l At Weeks 16, 24, and 36, subjects will be evaluated for inadequate response to treatment. Subjects who do not show an improvement in tender and swollen joint counts will be eligible to receive rescue therapy.

m If a subject has had a recent radiograph of the chest within 3 months prior to the Screening Visit, it may be used as the Screening chest x-ray.

n Hand and foot x-rays are not required if the subject has hand and/or foot x-rays (only hand OR foot is required) that are no more than 2 years from the date of Screening, and are available for submission within the Screening Period to the central radiology reader and whose reading is consistent with CASPAR Criteria #5 showing ill-defined ossification near joint margin (but excluding osteophyte formation). For those subjects without prior x-rays that meet this Criterion and those whose submitted films are not read with changes consistent with CASPAR, hand and foot x-rays may be done during the Screening Period.

o IXRS is used to register the Subject at Screening, randomize the Subject at Baseline/Day 1, rerandomize the Subject at Week 12 (Subjects in the placebo or bimekizumab 16mg treatment groups), and to register all visits.

p The minimum time between doses during the Double-Blind Period should be no less than 25 days and no more than 31 days and during the Dose-Blind Period should be no less than 24 days and no more than 32 days.

q At Week 12, the Dose-Blind Period dosing will start.

2.4 Determination of sample size

A total of 200 subjects (40 in each treatment group) are planned to be randomized in this study.

The sample size is calculated based on the ACR50 response data from the Phase 2 bimekizumab study in subjects with PsA (PA0007). The ACR50 responses at Week 12 were reported to be 80.0% (95% CI: 37.6%; 96.4%), 52.6% (95% CI: 31.7%; 72.7%), and 33.3% (95% CI: 9.7%; 70.0%) for the bimekizumab 560/320mg, bimekizumab 240/160mg, and bimekizumab 80/40mg doses, respectively. Placebo ACR50 response at Week 12 is based on the PA0007 study (0%), the FUTURE 1 study (8.0%; Mease et al, 2015) and FUTURE 2 study (6.0%; McInnes et al, 2015).

Since the uncertainty of ACR50 responder rates of PA0007 is high due to the small number of subjects, the midpoint of the point estimate and the lower 95% CI was used for the sample size calculation of all active dose groups as a conservative assumption. For the bimekizumab 16mg dose, the midpoint of the 80/40mg dose was reduced by 6.5%.

Hence, ACR50 responder rates of 58.5%, 42.2%, 15.0%, and 8% at the end of a 12-week treatment period for bimekizumab 320mg, bimekizumab 160mg, bimekizumab 16mg, and placebo have been assumed, respectively. Since those ACR50 responder rates are based on a study population of TNF inhibitor naïve subjects, an adjustment was made for a reduction in ACR50 response of 25% by a maximum of 30% of subjects with TNF inhibitor experience (ie, 12 subjects per group).

The sample size for the primary objective of evaluating the dose response relationship was calculated using a 2-sided test for detecting a linear trend across proportions (Nam, 1987) at a 2-sided significance level of 0.05. With 40 subjects in each treatment group, the test for detecting the overall dose response based on ACR50 response is powered at >99%.

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

3 DATA ANALYSIS CONSIDERATIONS

3.1 General presentation of summaries and analyses

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

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

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

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

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

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

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

In the Double-Blind Period the order of treatment groups will be presented in tables from left to right will be

- Placebo
- Bimekizumab 16mg
- Bimekizumab 160mg
- Bimekizumab 160mg with loading dose 320mg
- Bimekizumab 320mg

The general principle is to go from the lowest to highest dose when moving from left to right. Tables may also include columns for all subjects or all subjects on bimekizumab. An overview of the treatment group assignment is available in Section 12.3.

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

- Placebo to bimekizumab 160mg at Week 12
- Placebo to bimekizumab 320mg at Week 12
- Bimekizumab 16mg to bimekizumab 160mg at Week 12
- Bimekizumab 16mg to bimekizumab 320mg at Week 12
- Bimekizumab 160mg with loading dose 320mg to bimekizumab 160mg at Week 12
- Bimekizumab 160mg
- Bimekizumab 320mg

The abbreviation for bimekizumab is BKZ and will be used in tables and listings headers. In the TFLs subjects on bimekizumab 160mg with loading dose 320mg will be displayed as "BKZ 160mg w/LD". All subjects on bimekizumab will be labeled as "All BKZ" in the TFLs.

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

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

3.2 General study level definitions

3.2.1 Relative day

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

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

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

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

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

3.2.2 Study Periods

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

- Pre-treatment period (Screening period): up to 28 days, ends with the visit date of the first dose of study medication (Visit 2)
- Double-Blind treatment period: starts with the visit date of the first dose of study medication (Visit 2), ends at Week 12 visit date
- Dose-Blind treatment period: starts at the Week 12 visit, ends at Week 48 visit.
- Post-treatment period: the post-treatment period (Follow-up period) is the period after the Week 48 visit

3.3 Definition of Baseline values

The last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value. If a scheduled Baseline assessment is taken on the same day and after the first

administration of study medication, it will be analyzed as the first post-Baseline assessment. If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken prior to study medication.

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

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

3.4 Protocol deviations

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

3.5 Mapping of assessments performed at early termination visit

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

3.6 Analysis sets

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

At the time of the Week 48 interim it was discovered that the Dose-Blind Responder Set (DBRS) and Escape Subject Set (ESS) were defined incorrectly from the original intent. The original

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

3.6.1 Enrolled Set (ES)

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

3.6.2 Randomized Set (RS)

The RS consists of all randomized subjects.

3.6.3 Safety Set (SS)

The SS consists of all randomized subjects who received at least 1 dose of the IMP.

3.6.4 Full Analysis Set (FAS)

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

3.6.5 Per-Protocol Set (PPS)

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

3.6.6 Pharmacokinetics Per-Protocol Set (PK-PPS)

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

3.6.7 Pharmacodynamics Per-Protocol Set (PD-PPS)

The PD-PPS consists of all randomized subjects who took at least one dose of the IMP and provided at least 1 PD measurement post-dose that is without important protocol deviation affecting that time point.

3.6.8 Dose-Blind Set (DBS)

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

3.6.9 Escape Subject Set (ESS)

The ESS consists of all subjects who started the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have not achieved at least a 10% reduction from Baseline in SJC and TJC at Week 16, Week 24, or Week 36.

3.6.10 Dose-Blind Responder Set (DBRS)

The DBRS consists of all subjects who started the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have achieved at least a 10% reduction from Baseline in SJC and TJC at Week 16, Week 24, and Week 36.

3.6.11 Corrected Escape Subject Set (cESS)

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

3.6.12 Corrected Dose-Blind Responder Set (cDBRS)

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

3.7 Treatment assignment and treatment groups

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

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

- All subjects screened/ES: planned treatment
- RS: planned treatment
- SS: actual treatment
- FAS: planned treatment
- PPS: planned treatment
- PK-PPS: actual treatment
- PD-PPS: actual treatment
- DBS: planned treatment (demographics, baseline characteristics, and efficacy analyses) or actual treatment
- ESS: planned treatment
- DBRS: planned treatment
- cESS: planned treatment
- cDBRS: planned treatment

3.8 Center pooling strategy

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

3.9 Coding dictionaries

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

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

3.10 Changes to protocol-defined analyses

The PK variables total body clearance (CL/F) and volume of distribution (V/F) will be analyzed separately. CL/F and V/F variables were removed from the PK variable list.

Following two subgroup analyses were added: time since first diagnosis of PsA and body weight.

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

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

The other efficacy variable modified MDA was added to the analysis. The definition for the modified MDS is available in Section 8.3.1.

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

Two addition analyses were added in the section analysis of other efficacy variables. A frequencies table counting the number of subjects with PSAID-9 $\leq$ 3 as well as cumulative distribution function (CDF) plots of PSAID-9 change from Baseline to Week 12 and Week 12 to Week 48 by treatment group.

4 STATISTICAL/ANALYTICAL ISSUES

4.1 Adjustments for covariates

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

4.2 Handling of dropouts or missing data

4.2.1 Handling of missing data for efficacy analysis

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

Sensitivity analysis will be performed for the secondary analysis of the primary variable (ACR50 response at Week 12) using MI assuming that missingness is missing at random (MAR). The MI method will be applied as follows:

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

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

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

     Note: To avoid that imputed values are outside of the pre-defined range of values for the ACR components (eg, HAQ-DI [0-3]) maximum and minimum values for imputed variable values are specified.
   - If the intermediate missing data are imputed, the monotone missing data will be imputed for all patients with monotone regression including geographic region, and prior TNF inhibitor exposure as covariates. The dataset is the output dataset of the partial imputation. Since this dataset already has 100 imputed values at each visit, only one imputation will be performed.

     Note: Maximum and minimum values are specified for imputed variable values to avoid values outside of the pre-defined range of values.
2. The ACR50 response will be calculated using the complete datasets. That is, the values of the ACR components at Week 12 based on the complete datasets will be compared to their corresponding Baseline values to calculate an ACR50 response for each subject (as described in Section 8.1.1). Each complete imputed data set will then be analyzed based on a logistic regression model with factors of treatment group, geographic region, and prior TNF inhibitor exposure as fixed effects.
3. The Week 12 results from the logistic regression analysis of each of the 100 imputed data sets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987).

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

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

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

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

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

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

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

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

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

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

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

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

4.2.2 Handling of missing data for AE

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

Partial AE start dates will be imputed as follows:

Imputation of Partial Start Dates:

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

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

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

- If first treatment allocation visit date is missing then the all activities events will be assumed to be treatment emergent.

Imputation of Partial Stop Dates:

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

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

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

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

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

4.2.3 Handling of missing data for prior and concomitant medication

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

Imputation of partial start dates:

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date and the subject did not switch treatment during that month and year, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the month and year are specified and the subject did switch treatment during that month and year, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is not the same as the year of the start date and the subject did not switch treatment during that year, then use the 1st of January of the year of the start date.
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose.
- If only the year is specified, and the year of first dose is the same as the year the subject did switch treatment, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is the same as the year of the start date and the same as the year the subject did switch treatment, then use the date of first dose.

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

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

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

Imputation of Partial Stop Dates:

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

There will be no imputation of any other missing data.

4.3 Interim analysis and data monitoring

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

4.3.1 Interim analysis Week 12

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

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

The interim analysis will summarize disposition, demographics, PsA history, Baseline characteristics, PsA concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). Not all collected hematology and biochemistry laboratory variables will be summarized. For the interim analysis only selected

hematology and biochemistry variables will be provided as listed in Table 12–4. Listings of AEs, hematology, biochemistry and C-SSRS data will be provided.

The interim efficacy analysis will focus on the primary and secondary efficacy analyses including supportive and sensitivity analysis. In addition, summary tables for the primary and secondary efficacy variables, the ACR components, and MDA will be provided. Categorical variables will be summarized using frequency tables by each visit. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive statistics by each visit. Time to onset of ACR50 response and ACR20 response will be summarized and plotted as described in Section 8.3.

PK and AbAb data will be analyzed in the interim analysis as described in Section 9.1 and Section 9.2 .Biomarker data will not be analyzed in the interim analysis.

The interim analysis includes selected data up to Week 12 and in addition data up to Week 24. The data up to Week 24 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. Following variables will be analyzed: primary and secondary efficacy variables, ACR components, MDA, PK, AbAb, TEAEs, biochemistry and hematology laboratory results, and Hy's Law. It depends on the variable how those additional time points will be presented in the interim analysis.

The efficacy analyses and the plasma concentration analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Two summary tables for each of the primary and secondary efficacy variables, the ACR components, and MDA will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 24 by the following treatment groups: bimekizumab 160mg and bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. The summary table for plasma concentration will present only data up to Week 12 for the Baseline treatment groups Placebo and bimekizumab 16mg. Data up to Week 24 will be presented for bimekizumab 160mg, bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. All Listings which include data up to Week 24 will use the same approach as for plasma concentration tables.

The safety analysis (TEAEs, biochemistry and hematology laboratory results, and Hy's Law) will be handled as follows: Two summary tables for each of the safety analysis will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 24 and will also present subjects under their Baseline treatment group. For the second table any event/finding that is unique to a treatment group should only be presented in the "All subjects" column and the treatment columns should remain blank. Following rules will be applied for the TEAEs: If the relative TEAE start date is less or equal to 84 (12*7) days, then the TEAE will be presented in the up to Week 12 table. If the relative start date is less or equal to 168 (24*7) days, then the TEAE will be presented in the up to Week 24 table.

The treatment group information will not be displayed for the interim listings.

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

AEs occur on the same days as the treatment switch, the AEs will be allocated to the Dose-Blind treatment and will not be presented for the interim analysis.

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

For the interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The Investigators and subjects will remain blind to the assigned bimekizumab dosing regimen until the subject completes the Dose-Blind Period at Week 48. Further details are available in the PA0008 blinding plan.

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

4.3.1.1 Changes from interim analysis to SAP-defined analyses

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

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

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

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

Following AEs are defined as TEAEs of special monitoring:

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

- Hepatic events

Fungal Infectious disorder

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

Opportunistic infection

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

Malignant or unspecified tumor

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

Malignant tumor

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

Major cardiovascular events

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

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

Haematopoietic cytopenias

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

Neuropsychiatric events

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

Inflammatory bowel disease

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

Hypersensitivity reactions and anaphylactic reactions

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

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

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

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

Hepatic events

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

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

4.3.2 Interim analysis Week 48

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

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

The snapshot for the PA0008 interim analysis Week 48 will occur before all subjects have completed the PA0008 study. Specifically, subjects who do not enter the extension study will need to complete the SFU Visit, which occurs 20 weeks after the last dose of study treatment. The Week 48 interim database lock will be performed based on the last subject completing the Week 48 visit. It is anticipated that there will be some subjects still awaiting the SFU at that time. The number of subjects in the SFU period is expected to be low, and the minimal data to be collected from their SFU visits is not considered mandatory to evaluation of the key efficacy and safety objectives of the study.

4.3.2.1 Changes from interim analysis to SAP-defined analyses

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

4.3.2.2 Changes during interim analysis to SAP-defined analyses

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

4.4 Multicenter studies

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

4.5 Multiple comparisons/multiplicity

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

4.6 Use of an efficacy subset of subjects

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

4.7 Active-control studies intended to show equivalence

Not applicable.

4.8 Examination of subgroups

The following variables for subgroup analyses will be used:

- Age (<45 years, ≥45 to <65 years, ≥65 years)
- Gender (male, female)
- Geographic region (North America, Europe)
- BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])
- Prior TNF inhibitor exposure (yes, no)
- Treatment-emergent AbAb status (positive, negative)

- Extent of psoriasis involvement (<3%, ≥3% to <10%, ≥10%)
- hs-CRP level (<= upper limit normal, > upper limit normal)
- Time since first diagnosis of PsA (< 2 years, ≥ 2 years)
- Body weight (<100 kg, ≥100 kg)

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

The derivation of time since first diagnosis of PsA is described in Section 6.2.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject disposition

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

The number and percentage of subjects who discontinued study medication, who discontinued the study, and who discontinued due to AEs will be summarized for subjects in the RS and DBS. The table using RS will analyze subjects for the complete study as well as the Double-Blind Period. Completed study is defined as completed the 12-week Double-Blind Period and the 36-week Dose-Blind Period including the safety follow-up visit. Subjects will be allocated to the treatment group at Baseline. The table using DBS will only summarize subjects in the Dose-Blind Period.

Study eligibility criteria will be listed and a separate listing of subjects who did not meet the eligibility criteria will be presented.

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

5.2 Protocol deviations

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

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

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

6 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

6.1 Demographics

Tables with descriptive statistics (number of subjects, mean, SD, minimum, median, and maximum) and listings will be given for the demographic variables age (at time of informed consent), gender, racial group, ethnicity, weight at Screening, height at Screening, body mass index (BMI), country, and geographic region. Age and BMI will be summarized as a continuous variable and as categorical variables. Age will be combined based on the following categories: ≤18, 19-<65, ≥65 years (clinicaltrials.gov requirement), 18-<65, 65-<85, ≥85 years (EudraCT requirement), and 18-<45, ≥45-<65, ≥65 years. BMI will be summarized based on the following categories: <25, 25-<30, ≥30 kg/m^2.

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

For adults:

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

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

A frequency table for Lifestyle will be presented as well as a corresponding listing. Data collected in the CRF for subject's childbearing potential and birth control will only be listed.

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

6.2 Other Baseline characteristics

PsA history will be summarized for subjects in the FAS and SS including the time since first diagnosis of PsA, age at first diagnosis date, and PsA subtype (polyarticular – symmetric arthritis, oligoarticular – asymmetric arthritis, distal interphalangeal, joint predominant, spondylitis predominant, arthritis mutilans). Time since first diagnosis will be summarized as a continuous variable and as categorical variables based on following categories: <2, ≥2 years. The history will be listed for all subjects in the RS.

Time since first diagnosis of PsA will be calculated as:

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

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

Age at first diagnosis will be calculated as:

$$Age\ at\ first\ diagnosis = \frac{Date\ of\ first\ diagnosis - Date\ of\ birth}{365.25} \quad (7)$$

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

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

- TJC
- SJC
- hs-CRP
- Rheumatoid factor
- Anti-CCP antibodies
- Prior NSAID therapy, and prior anti-TNF therapy
- Psoriasis BSA
- Nail psoriasis
- Dactylitis
- NSAID therapy
- Synthetic DMARDs
- MTX
- Sulfasalazine
- Hydroxychloroquine

A rheumatoid factor value < 15 IU/mL is defined as negative and a value ≥ 15 IU/mL is defined as positive. Anti-CCP antibodies negative is a value < 5 U/mL and a value ≥ 5 U/mL is defined as positive.

For hs-CRP following rules will be applied:

- If Baseline hs-CRP values are missing, then take the Screening hs-CRP values.
- If Screening hs-CRP values are missing, then take the median hs-CRP values.

The corresponding listings will be presented for the RS.

6.3 Medical history and concomitant diseases

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

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

6.4 Prior and concomitant medications

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

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

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

The number and percentage of subjects taking concomitant medications will be summarized similarly. Tables for prior and concomitant medications will be presented for SS and FAS.

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

6.5 Prohibited medication and rescue medication

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

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

The SS and FAS will be used for both summary tables and the RS will be used for the listings.

7 MEASUREMENTS OF TREATMENT COMPLIANCE

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

$$Percent\ compliance = 100 * \frac{\text{Number of doses received}}{\text{Number of doses expected}} \quad (8)$$

where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes treatment 12 doses are expected (Baseline and every 4th week

afterwards until Week 44). If a subject discontinues early, then the number of expected doses is based on the time of early discontinuation relative to the dosing visits. If a dose is not completely given at a specific visit (eg, subject only received one injection instead of the two planned injections), then the subject will be considered to have no compliance for the visit. In the formula above it will be counted as no dose received at this visit.

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

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

8 EFFICACY ANALYSES

8.1 Statistical analysis of the primary efficacy variable

8.1.1 Derivations of primary ACR score and response

ACR20/50/70 response represents at least 20%, 50%, or 70% respective improvement from Baseline for each of the following:

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

For all non-missed visits, if any of the component scores are missing, then those scores will be considered as not having met the criteria for improvement for the respective component. For component scores with a Baseline value of 0, the percentage improvement is not calculable and is treated as missing. However, if ACR20, ACR50, or ACR70 response is used as the primary endpoint in a study, consideration should be given to requiring a value >0 for each of the component endpoints in order to enter the study. 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.

Missing items for TJC, SJC, and HAQ-DI will be handled as described in Section 8.1.1.1 and Section 8.1.1.5.

8.1.1.1 Tender joint count (TJC) and swollen joint count (SJC)

8.1.1.1.1 78/76 joint evaluation for ACR response

The Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly assesses the following joints for tenderness: the distal interphalangeal, proximal interphalangeal and metacarpophalangeal joints of the hands, and metatarsophalangeal joints of the feet, the carpometacarpal and wrist joints (counted separately), the elbows, shoulders, acromioclavicular, sternoclavicular, hip, knee, talo-tibial, and midtarsaljoints. All of these except for the hips are assessed for swelling.

Artificial and ankylosed joints, as well as missing joints (ie, amputated joints), are excluded from both tenderness and swelling assessments.

One dactylitic digit is to be counted as 1 swollen joint (instead of counting as 3 in the finger or 2 in the toe).

Table 8–1 summarizes the swelling and tenderness grading criteria.

Table 8–1: Swelling and tenderness grading

[redacted]

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

$$SJC = n * \sum_{i=1}^{n} SJ \Big/ \sum_{i=1}^{n} AJ \quad (9)$$

$$TJC = n * \sum_{i=1}^{n} TJ \Big/ \sum_{i=1}^{n} AJ \quad (10)$$

where n is the number of total joints. If a joint is missing at Baseline, then that joint is set to missing throughout the study. If more than 50% of the tender joint assessments or 50% of the

swollen joint assessments are missing at the time of a given assessment, then no imputation will be done and the total TJC or SJC will be set to missing for that visit.

Injected joints will be counted as swollen and tender from the date of injection up to 52 weeks after injection, ie, swelling and tenderness grading is 1.

8.1.1.1.2 28 joint evaluation for determination of DAS28(CRP)

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

- Upper extremity (26)-bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), MCP I, II, III, IV, and V, thumb interphalangeals (IP), PIP II, III, IV, and V
- Lower extremity (2)-knees

Injected joints will be counted as swollen and tender from the date of injection up to 52 weeks after injection, ie, swelling and tenderness grading is 1.

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

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

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

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

8.1.1.4 Patient's Assessment of Arthritis Pain (PtAAP)

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

8.1.1.5 Health Assessment Questionnaire-Disability Index (HAQ-DI) score

The HAQ-DI contains 20 items divided into 8 domains that measure: dressing and grooming (2 items), arising (2 items), eating (3 items), walking (2 items), hygiene (3 items), reach (2 items), grip (3 items), and common daily activities (3 items). The questionnaire is available in the Appendix Section 12.5. Subjects are required to indicate the degree of difficulty they have experienced in each domain in the past week on a 4-point scale that ranges from 0 (without difficulty) to 3 (unable to do). The highest score in each category is then summed (0 to 24) and divided by the number of categories scored to give a score that ranges from 0 to 3.

Any individual score of less than 2 is adjusted to 2 if the activity requires assistance from another individual or the use of an assistive device. If the category score is already a 2, and a device related to that category is used, or help from another person is provided for the category, the

score for that category remains 2. The following list details how each aid and device is associated with the category scores (Table 8–2):

Table 8–2: Aid or Device associated with HAQ-DI domain

If all questions within a given category are unanswered, no score will be provided for that category (this rule applies even if aids and devices are non-missing). The HAQ-DI will be calculated by dividing the sum of the category scores by the number of categories with at least 1 question answered. If fewer than 6 categories have responses, no disability score will be calculated. A lower HAQ disability score indicates an improvement in function.

8.1.1.6 Body surface area (BSA)-Psoriaris

The BSA palm method will be used for the evaluation of BSA affected by psoriasis as follows:

The subject's hand, including the palm, fingers and thumb, is used as the reference point for measuring how much of their skin is affected by psoriasis, representing roughly 1% of the body's surface.

- Subject's palm=1%
- Head and neck=10% (10 palms)
- Upper extremities=20 % (20 palms)
- Trunk=30% (30 palms)
- Lower extremities=40 % (40 palms)

Total BSA=100%.

8.1.2 Primary analysis of the primary efficacy variable

The primary efficacy variable (ACR50 at Week 12) will be analyzed for all subjects in the FAS.

The dose-response relationship between treatment and ACR50 response will be assessed with an ordered categorical analysis using a nonparametric correlation statistic of Mantel and Haenszel

(Mantel and Haenszel, 1959) and modified ridit scores (Bross, 1958) with the corresponding p-value.

The analysis will include geographic region and prior TNF inhibitor exposure as stratification factors. Prior TNF inhibitor exposure will be used as a stratification factor as it may have an impact on efficacy. The use of geographic region as a stratification factor is intended to combine study centers in similar geographic regions. The geographic regions are defined in Section 3.8. The correlation between dose and ACR50 response will be evaluated at a two-sided significance level of α=0.05. This evaluation of dose-response will constitute the primary efficacy analysis.

Bimekizumab 160mg with loading dose will be excluded from the dose-response analysis. A table will present the responder rates for placebo, BKZ 16mg, BKZ 160mg, BKZ 320mg, and the correlation statistic of Mantel and Haenszel (ridit score) with the corresponding p-value.

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

8.1.3 Secondary analyses of the primary efficacy variable

As the secondary analysis for the primary efficacy variable, a logistic regression model will be used to assess the effect of each individual dose versus placebo on ACR50 response. The model will include fixed effects for treatment, geographic region, and prior TNF inhibitor exposure (yes/no). To avoid the problem of the so-called monotone likelihood resulting in infinite large confidence intervals (eg, if one of the cell counts in the 2x2 table is equal to zero), a penalized maximum likelihood approach based on the modified score procedure of Firth (eg, Heinze and Schemper, 2002) will be used in the logistic models. If the logistic regression model is unable to converge, then geographic region may be dropped from the model to facilitate convergence. If the logistic regression model is unable to converge after dropping the geographic region, then prior TNF inhibitor exposure may be dropped as well. Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% CI, and the corresponding p-value will be calculated. In addition, a comparison will be made for the bimekizumab 320mg loading dose followed by bimekizumab 160mg Q4W versus bimekizumab 160mg Q4W using the same logistic model described above.

The pairwise comparisons of bimekizumab versus placebo will be formally evaluated for statistical significance only if the primary dose response efficacy analysis is statistically significant. Once the dose response has been established, pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose. If the dose-response relationship fails to reach significance at a significance level of α=0.05, then the further pairwise comparisons are seen as non-significant.

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

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

8.1.4 Supportive analyses of the primary efficacy variable

The following supportive analyses are planned:

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

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

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

8.1.5 Sensitivity analyses of the primary efficacy variable

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

1. This analysis evaluates the effectiveness of the treatment (de facto hypothesis) and will be based on the ordered categorical analysis to evaluate dose-response as specified in the primary analysis. In an attempt to prevent missing data during the study, efforts will be made to collect data from subjects that withdraw early from the study. An analysis will be performed in which all available data at Week 12 will be considered. In this case, subjects will be analyzed according to their randomized treatment, even if they discontinued prior to Week 12 and were no longer on the randomized study treatment when the assessment was performed at Week 12. If Week 12 data for the ACR50 response are not collected, the subject will be assumed to be a non-responder. It should be noted that this measures something different from the primary analysis and could be confounded by placebo subjects who withdraw and are subsequently on another active medication at the time of the Week 12 assessment.
2. An additional sensitivity analysis will be based on observed data only for subjects who are still on the initially randomized treatment at Week 12. Subjects with missing data or who have prematurely discontinued study treatment will be excluded from the analysis. The same procedure described for the primary efficacy analysis of dose response will be used.

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

1. Missing data will be imputed using MI. In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by monotone regression for monotone missing data to evaluate the effect of the method for handling missing data on the analysis. The ACR components will be imputed individually and then the ACR response will be calculated using the complete datasets. The multiply imputed data sets will be analyzed using a logistic regression model with fixed effects fixed effects for treatment, geographic region, and prior TNF inhibitor exposure. Finally, the results will be combined into a single inference using Rubin's rule (Carpenter and Kenward, 2013). This procedure assumes a MAR pattern of missingness and corresponds to an estimand of what has been called the difference in outcome improvement if all subjects tolerated or adhered to treatment (Mallinckrodt et al, 2012). More details are available in Section 4.2.1.
2. The logistic regression model will be applied where all available data at Week 12 will be considered, as described in sensitivity analysis (1) for the primary efficacy variable.
3. The logistic regression model will be applied where only observed data for subjects still on the initially randomized treatment at Week 12 will be considered, as described in sensitivity analysis (2) for the primary efficacy variable.

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

8.2 Statistical analysis of the secondary efficacy variables

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

All categorical variables (ie, ACR20/70 response and PASI75/90 response) will be analyzed for treatment effects using pairwise comparisons using the same logistic model as described in the secondary analysis of the primary variable (Section 8.1.3).

The responder rates for placebo, BKZ 16mg, BKZ 160mg w/ LD, BKZ 160mg, BKZ 320mg, and for each dose the odds ratios (differences to placebo), 95% CIs, and corresponding p-values from the logistic regression will be provided.

The categorical efficacy variables will be analyzed using observed cases as treated and imputed with NRI.

8.2.1 Derivation of Psoriasis Area and Severity Index (PASI), PASI75, PASI90, and PASI100

PASI will be assessed in all subjects with Baseline BSA affected by psoriasis ≥3% determined by the method described in Section 8.1.1.6 (ie, the BSA palm method).

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

Table 8–3: Body areas for calculation of percent BSA for PASI

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

BSA=body surface area; PASI=Psoriasis Area and Severity Index

[a] Where 0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected

The body is divided into 4 sections (head (h) (10% of a person's skin); arms (a) (20%); trunk (t) (30%); legs (l) (40%), Table 8–3). Each of these sections is scored by itself, and then the 4 scores are combined into the final PASI. For each section, the percent of area of skin affected (A), is estimated and then transformed into a grade from 0 to 6:

- 0% of involved area, grade: 0
- < 10% of involved area, grade: 1
- 10-29% of involved area, grade: 2
- 30-49% of involved area, grade: 3
- 50-69% of involved area, grade: 4
- 70-89% of involved area, grade: 5
- 90-100% of involved area, grade: 6

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

$$PASI = 0.1 * Ah * (Rh + Th + Sh) + 0.2 * Au * (Ru + Tu + Su) + 0.3 * At * (Rt + Tt + St) + 0.4 * Al * (Rl + Tl + Sl) \quad (11)$$

where

Rh, Ru, Rt, and Rl is the redness score of plaques on the head, upper limbs, trunk, and lower limbs;

Th, Tu, Tt, and Tl is the thickness score of plaques on the head, upper limbs, trunk, and lower limbs;

Sh, Su, St, and Sl is the scaliness score of plaques on the head, upper limbs, trunk, and lower limbs;

Ah, Au, At, and Al is the degree of involvement for the head, upper limbs, trunk, and lower limbs.

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

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

The PASI50, PASI75, PASI90, and PASI100 responses are based on at least 50%, 75%, 90%, and 100% improvement from Baseline in the PASI score.

8.3 Analysis of other efficacy variables

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

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

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

Subgroup of subjects will be used for the analyses of mNAPSI, MASES, and LDI. The MASES will be analyzed for subjects with enthesitis at Baseline (MASES > 0). The LDI will be summarized for subjects with dactylitis at Baseline (LDI > 0) and the mNAPSI will be analyzed on a subgroup of subjects with nail disease at Baseline (mNAPSI > 0).

CDF plots of PSAID-9 change from Baseline to Week 12 and from Week 12 to Week 48 by treatment group will be presented as well as a frequency table with number of subjects with PSAID-9 ≤ 3.

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

Time to onset of ACR20/50 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates. Subjects who discontinue study prior to achieving a response will be censored at the date of study discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

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

Summary tables will be presented for the time to onset of ACR20 response and ACR50 response including following information: number of subjects achieving ACR20/ACR50 response, number of subjects censored, descriptive statistics (minimum, 25th percentile, median, 75th percentile, maximum) for the Kaplan-Meier estimates including the p-value (difference to placebo). Additional Kaplan-Meier Plots will be provided.

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

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

In order to assess the potential bias of the potentially unblinded subjects based on data, the results of the final analysis will be utilized. Results of the ACR50 and PASI90 response of the rerandomized 320mg and 160mg treatment group at Week 48 will be compared to the potentially unblinded, randomized 320mg and 160mg treatment groups. If the percentage of ACR50 and PASI90 responders is comparable as assessed by overlapping 95% confidence intervals, the potential bias is estimated to be at minimum.

8.3.1 Minimal disease activity (MDA)

MDA is a state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations. Criteria shown in Table 8–4 covering all of the domains of the disease have been developed to determine whether or not patient has reached MDA based on key outcome measures in PsA. A subject is considered as having MDA if 5 or more of the following 7 criteria in Table 8–4 are fulfilled:

Table 8–4: MDA criteria in PsA

A subject is classified as in MDA when they meet 5 of 7 of the following criteria:
TJC ≤1
SJC ≤1
PASI ≤1 or BSA ≤3
PtAAP ≤15
PGADA ≤20
HAQ-DI ≤0.5
Tender enthesial points ≤1

BSA=body surface area; HAQ=Health Assessment Questionnaire; MDA=minimal disease activity; PASI=Psoriasis Area and Severity Index; PGADA=Patient's Global Assessment of Disease Activity; PtAAP=Patient's Assessment of Arthritis Pain; SJC=swollen joint count; TJC=tender joint count

Following rule will be applied for subjects with BSA < 3 at Baseline due to missing post-Baseline measurements for BASI and PASI: Subjects with BSA < 3 will always meet the criteria PASI ≤ 1 or BSA ≤ 3.

The MASES items will be used to check whether a subject has less or equal one tender enthesial point.

8.3.1.1 Modified MDA

Subjects are classified as in modified MDA when they meet the criteria PASI ≤ 1 or BSA ≤ 3 and 4 of the following criteria: TJC ≤1, SJC ≤ 1, PtAAP ≤ 15, PGADA ≤ 20, HAQ-DI ≤ 0.5 or tender enthesial points ≤ 1. The difference between the MDA and the modified MDA is that the PASI/BSA criteria is a mandatory criteria.

8.3.2 Disease Activity Score-28 joint count C-reactive protein (DAS28[CRP])

The components for DAS28(CRP) include the TJC and SJC based on 28 joints, hs-CRP (mg/L), and the PGADA (mm). DAS28(CRP) is calculated as follows:

$$DAS28(CRP) = 0.56 * \sqrt{TJC} + 0.28 * \sqrt{SJC} + 0.014 * PGADA + 0.36 * \ln(hsCRP + 1) + 0.96 \quad (12)$$

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

8.3.3 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI is the most commonly used instrument to measure the disease activity of ankylosing spondylitis. 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. The BASDAI questionnaire is available in the Appendix Section 12.6. 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:

$$BASDAI = \frac{Q1 + Q2 + Q3 + Q4 + (\frac{Q5 + Q6}{2})}{5} \quad (13)$$

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

If 1 of the 2 morning stiffness measurements (ie, questions: [redacted] and [redacted]) is missing, the other one will be used for the morning stiffness calculation.

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.

8.3.4 Modified Nail Psoriasis Severity Index (mNAPSI)

Subjects with psoriatic nail disease will have a target nail selected at the Baseline visit for evaluation using the mNAPSI. The nail selected should be the most affected nail observed at Baseline and should be the only one assessed throughout the study. The target nail will be scored (0 to 3) for onycholysis/oil drop dyschromia, nail plate crumbling, and pitting and will be scored (0 for "no" or 1 for "yes") for leukonychia, nail bed hyperkeratosis, splinter haemorrhages and red spots in the lunula. The score for an individual nail ranges from 0 to 13 with higher scores indicative of more severe nail disease. Subjects with nail disease at Baseline are defined as those with a mNAPSI score >0 at Baseline.

If 1 or 2 response items scored on the 0 to 1 scale are missing, the missing response(s) will be imputed by the average of the available responses. Otherwise, the total mNAPSI score will be set to missing.

8.3.5 Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index

The MASES Index comprises 13 items (bilateral costochondral 1, costochondral 7, anterior superior iliac spine, posterior iliac spine, iliac crest and proximal insertion of the achilles tendon sites, and the fifth lumbar vertebral body spinous process) (Heuft-Dorenbosch et al, 2003) each scored as 0 = yes or 1 = no and then summed for a possible score of 0 to 13, with higher scores indicating worse enthesitis. The questionnaire is available in Section 12.7.

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

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

8.3.6 Leeds Dactylitis Index (LDI)

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation, is a characteristic of inflammatory spondyloarthropathies, including PsA. Presence of dactylitis will be assessed using the LDI basic which evaluates for a ≥10% difference in the circumference of the digit compared to the opposite digit (Healy and Helliwell, 2007; Helliwell et al, 2005). The percent difference between circumferences will be multiplied by a tenderness score (0 for non-tender, 1 for tender). The digits involved and the matching contralateral digit will also be recorded at the same visits. The results from each digit with dactylitis will then be summed to produce a final score.

The following is a table of normative values, which will be used to provide the comparison, if matching digits are thought to be involved (Table 8–5).

Table 8–5: Normative values for LDI

	Digit	Men	Women
Hand	Thumb	70	58

Table 8–5: Normative values for LDI

	Digit	Men	Women
	Index	63	54
	Middle	63	54
	Ring	59	50
	Little	52	44
Foot	Great toe	82	72
	Second	52	46
	Middle	50	44
	Fourth	50	44
	Little	52	45

The following rules will be applied for the LDI calculation in case of unclear data. If both digits of a given pair are recorded as affected, then each digit will be compared to the normative value. If both comparisons result in a difference greater than 10%, then both digits will contribute to the LDI score. If the circumference of the affected digit is smaller than the unaffected digit, then the LDI will be calculated by comparing the smaller digit to the normative value. If a digit is recorded as affected and the circumference of the contralateral digit is missing, the normative value will be used for comparison with the affected digit.

If the LDI CRF page is left empty at Baseline, it will be assumed that no digits were affected. At post-Baseline visits, when LDI cannot be determined, last observation carried forward (LOCF) imputation should be applied.

8.3.7 Psoriatic Arthritis Impact of Disease-9 (PsAID-9)

The PsAID-9 is a patient-reported outcome measure for assessing the impact of PsA in 9 physical and psychological domains, including pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, and anxiety/fear/uncertainty. The questionnaire is available in the Appendix Section 12.8.

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

$$\begin{aligned} PsAID = {} & Pain * 0.174 + Fatigue * 0.131 + Skin * 0.121 \\ & + Work\ and/or\ Leisure\ Activities * 0.110 + Function \\ & * 0.107 + Discomfort * 0.098 + Sleep * 0.089 + Coping \\ & * 0.087 + Anxiety * 0.085 \end{aligned} \quad (14)$$

The total score ranges from 0 to 10, with higher scores indicating a worse status. A score below 4 out of 10 is considered a patient-acceptable status. A change of 3 or more points is considered relevant absolute change.

If one of the 9 domains is missing, the missing value is imputed using the mean value of the 8 other (non-missing) domains. The imputed value will be used to calculate the PsAID with the formula above. If 2 or more of the domains are missing, the PsAID will be treated as missing.

8.3.8 Psoriatic Arthritis Quality of Life (PsAQoL)

The use of the PsAQoL is recommended by the health regulatory authorities as one of the disease specific Health-Related Quality of Life (HRQoL) measures in PsA (CHMP/EWP/438/04). The questionnaire is available in Section 12.9. The PsAQoL comprises 20 items (0 for "not true" or 1 for "true") so that the score ranges from 0 to 20 with higher scores indicating worse HRQoL.

If 6 or less item responses are missing, the missing responses will be imputed with the mean of available responses to calculate a total score. If more than 6 items responses are missing, the total score will be left missing.

8.3.9 Short Form – 36 Items Health Survey

The SF-36 measures the following 8 health domains as rated by the subjects over the past four weeks: Physical Functioning, role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. The questionnaire is available in Section 12.10 and the classification of the questionnaire items to the health domains is shown in Section 12.11.

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

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

The SF-36 will be calculated using QualityMetric's Health Outcomes™ Scoring Software 4.5. The software uses updates 2009 U.S. population norms and applies a Full Missing Score Estimation method as follows:

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

8.3.10 Hospital Anxiety and Depression Scale (HADS)

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 scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal whereas a score of 15 and above is considered severe (Snaith and Zigmond, 1994).

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

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

$$CV = \sqrt{e^{SD_{ln}^2} - 1} \quad (15)$$

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

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

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

8.4 Subgroup analysis

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

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

The derivation of time since first diagnosis of PsA is described in Section 6.2.

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

9 PHARMACOKINETICS AND PHARMACODYNAMICS

9.1 Pharmacokinetics

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

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

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

The bimekizumab concentrations will also be listed.

9.2 Pharmacodynamics and Immunogenicity

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

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

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

At each visit:

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

In addition, overall AbAb status should be determined:

- Subject AbAb positivity is defined as having with AbAb+ at any time in the treatment period. This does not include Baseline/pre-treatment
- Subject AbAb negativity is defined with AbAb- at any time in the treatment period. This does also include AbAb+ at Baseline/pre-treatment
- If there is AbAb+ at Baseline/pre-treatment and there is a 4-fold increase in titre at least at one visit during the treatment period, then the subject has also an overall AbAb positivity status.

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

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

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

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

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

10 SAFETY ANALYSES

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

10.1 Extent of exposure

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

Duration of exposure Double-Blind Period

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

$$\begin{aligned} &Duration\ of\ exposure \\ &\quad = Date\ of\ last\ injection\ (double-blind\ period) \\ &\quad - Date\ of\ first\ injection\ (double-blind\ period) + 28 \end{aligned} \qquad (16)$$

28 days refer to one half-life of bimekizumab.

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

$$\begin{aligned} &Duration\ of\ exposure \\ &\quad = Date\ of\ first\ injection\ (dose-blind\ period) \\ &\quad - Date\ of\ first\ injection\ (double-blind\ period) + 1 \end{aligned} \qquad (17)$$

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

$$\begin{aligned} &Duration\ of\ exposure \\ &\quad = Date\ of\ death - Date\ of\ first\ injection\ (double \\ &\quad - blind\ Period) + 1 \end{aligned} \qquad (18)$$

Duration of exposure entire treatment period

For subjects who do not switch study treatments, who receive bimekizumab 160mg with loading dose at Baseline, or who receive bimekizumab 16mg and will be summarized under all bimekizumab group:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection + 28 \quad (19)$$

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

$$Duration\ of\ exposure = Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection + 1 \quad (20)$$

For subjects who die, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection + 1 \quad (21)$$

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

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 28 \quad (22)$$

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

$$Duration\ of\ exposure = Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (23)$$

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

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (24)$$

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

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

Time at risk Double-Blind Period

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

$$Time\ at\ risk = Date\ of\ first\ injection\ (dose - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (25)$$

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

$$Date\ of\ last\ injection\ (double - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 140 \quad (26)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (27)$$

$$Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (28)$$

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

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

$$Date\ of\ death - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (29)$$

Time at risk entire treatment period

For subjects who do not switch study treatments, who receive bimekizumab 160mg with loading dose at Baseline, or who receive bimekizumab 16mg and will be summarized under all bimekizumab group:

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

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

For subjects who die prior to the final visit:

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

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

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

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

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

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

$$Time\ at\ risk = Date\ of\ Visit\ 16\ (Week\ 48) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (34)$$

For subjects who die during the Dose-Blind Period:

$$Time\ at\ risk = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (35)$$

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

$$Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 140 \quad (36)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (37)$$

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

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

$$Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \quad (38)$$

$$Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose\ + 1 \quad (39)$$

10.2 Adverse events

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

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

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

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

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

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

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

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

Exposure adjusted incidence rate (EAIR) and exposure adjusted event rate (EAER) will only be calculated for the complete treatment period for following tables in the final analysis: all TEAEs, serious TEAEs, TEAEs leading to study discontinuation and/or permanent withdrawal, adverse drug reactions, fungal infectious disorder TEAEs, opportunistic infection (including tuberculosis) TEAEs, malignant or unspecified tumor TEAEs, malignant tumor TEAEs, major cardiovascular event TEAEs, haematopoietic cytopenias TEAEs, neuropsychiatric events

TEAEs, inflammatory bowel disease TEAEs, hypersensitivity and anaphylactic Reaction TEAEs, hepatic events TEAEs, and TEAEs by timing of onset relative to AbAb Status.

10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (40)$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \quad (41)$$

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

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (42)$$

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

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (41 and 42) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

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

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

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

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [40] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (Section 10.1).

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

considered from the start of Dose-Blind Period, when presenting AEs for the bimekizumab 160mg and bimekizumab160mg with loading dose, or bimekizumab 320mg groups. All exposure time on any bimekizumab dose is considered for the all bimekizumab column.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (44)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (45)$$

$$CI_{Lower} = 100 * \frac{LCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (46)$$

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (47)$$

where n_{AE} is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [40] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (Section 10.1).

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (48)$$

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 AE of Special Interest and AE of Special Monitoring

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

AE of special monitoring for this study include:

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

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

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

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

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

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

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

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

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

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

10.3 Clinical laboratory evaluations

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

Different summary tables for hematology and biochemistry variables will be provided, based on data from scheduled visits: observed values and change from Baseline, shift from Baseline to maximum post-Baseline value (in Double-Blind Period), shift from Baseline to maximum post-Baseline value (in Dose-Blind Period), shift from Baseline to minimum post-Baseline value (in Double-Blind Period), shift from Baseline to minimum post-Baseline value (in Dose-Blind Period), shift from Baseline to end of treatment (in Double-Blind Period), shift from Baseline to end of treatment (in Dose-Blind Period), and markedly abnormal laboratory data.

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

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

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

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

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

Table 10–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	Bacteria
Eosinophils	Chloride	Crystals
Lymphocytes	Magnesium	Glucose
Monocytes	Potassium	pH
Neutrophils	Sodium	RBC
Hematocrit	Glucose	WBC

Table 10–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Hemoglobin	BUN	Urine dipstick for pregnancy testing[b]
MCH	Creatinine	
MCHC	hs-CRP/CRP[a]	
MCV	AST	
Platelet count	ALT	
RBC count	GGT	
WBC count	ALP	
	Total bilirubin	
	LDH	
	Total cholesterol	
	Uric acid	
	Albumin	
	Serum pregnancy testing[b]	

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

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

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

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

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

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

Table 10–2: Definitions of markedly abnormal hematology values

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

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

Table 10–3: Definitions of Markedly Abnormal Biochemistry Values

Variable (RCTC Units)	Markedly Abnormal Definition	
	Low	High
ALP	N/A	>3 x ULN
ALT	N/A	>3 x ULN
AST	N/A	>3 x ULN
Calcium (mg/dL)	<7.0	>12.5
Creatinine (mg/dL)	N/A	>1.8 x ULN
Glucose (mg/dL)	<40	>250
Potassium (mmol/L)	<3.0	>6.4
Sodium (mmol/L)	<125	N/A
Total bilirubin	N/A	≥2 x ULN
Uric acid	N/A	≥3 x ULN

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

10.4 Potential drug-induced liver injury (PDILI) assessment

All potential drug-induced liver injury (PDILI) events require immediate action, testing, and monitoring. The measurements and additional information required for the assessment of PDILI

events when there is a reasonable possibility that they may have been caused by the IMP are included but not limited to those listed in Table 10–4 (laboratory measurements) and Table 10–5 (additional information).

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

Table 10–4: PDILI laboratory measurements

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

Table 10–4: PDILI laboratory measurements

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

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).

Table 10–5: Additional PDILI information

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

Table 10–5: Additional PDILI information

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

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

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

10.5.1 Vital signs

The following vital signs measurements will be assessed:

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

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

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

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

10.5.2 Electrocardiograms

The following ECG variables will be assessed:

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

- QTcB interval (ms)

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

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

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

10.5.3 Other safety variables

Physical Examination

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

Assessment of Tuberculosis

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

Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)

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

- Category 1 – [redacted]
- Category 2 – [redacted]
- Category 3 – [redacted]
- Category 4 – [redacted]
- Category 5 – [redacted]
- Category 6 – [redacted]
- Category 7 – [redacted]
- Category 8 – [redacted]
- Category 9 – [redacted]

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

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

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

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

11 REFERENCES

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12 APPENDICES

12.1 Classification Criteria for Psoriatic Arthritis (CASPAR) Criteria

A score will be derived by adding the points from each of the 5 categories. The maximum score will be 6. The CASPAR criteria are fulfilled, if the score is ≥3 and Inflammatory articular disease (joint, spine, or entheseal):

Table 12–1: CASPAR Criteria

Category	Definition	Points
1) Evidence of psoriasis:		
Current psoriasis or	Psoriatic skin or scalp disease present today as judged by a dermatologist or rheumatologist	2 points
Personal history of psoriasis or	A history of psoriasis that may be obtained from the subject, family physician, dermatologist, rheumatologist, or other qualified health care provider	1 point
Family history of psoriasis	A history of psoriasis in a first- or second-degree relative according to subject report	1 point
2) Psoriatic nail dystrophy	Typical psoriatic nail dystrophy, including onycholysis, pitting, and hyperkeratosis, observed on current physical examination	1 point
3) A negative test for rheumatoid factor	By any method except latex, but preferably by enzyme-linked immunosorbent assay (ELISA) or nephelometry, according to the local laboratory reference range	1 point
4) Dactylitis:		
Current dactylitis or	Swelling of an entire digit	1 point
History of dactylitis	A history of dactylitis recorded by a rheumatologist	1point
5) Radiologic evidence of juxta-articular new bone formation	Ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	1 point

CASPAR=Classification Criteria for Psoriatic Arthritis

12.2 Calculation rules for duration of adverse events

The calculation rules for duration of AEs are presented in Table 12–2. AE duration is computed and reported in day.

Table 12–2: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Complete data	D1	D2	Duration = D2 – D1 + 1

Table 12–2: Calculation rules for duration of adverse events

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

12.3 Treatment group assignment for tables and figures

Table 12–3 displays the treatment group labels for each data type. This overview clarifies what kind of treatment groups will be used for producing the tables and figures separated between the different table types.

Table 12–3: Treatment group assignment for tables and figures

	Placebo	BKZ 16mg, BKZ 160mg w/LD / BKZ 160mg/ BKZ 320mg	All BKZ	All subjects
Subject disposition	X	X		X
Important protocol deviation	X	X		X
Demographics/Lifestyle	X	X		X
Ankylosing spondylitis history	X	X		X
Baseline characteristics	X	X		X
Tuberculosis testing	X	X		X
Previous and ongoing medical history	X	X		X
Prior and concomitant medication	X	X		X

Table 12–3: Treatment group assignment for tables and figures

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

BKZ=bimekizumab; eC-SSRS= Electronic Columbia-Suicide Severity Rating Scale; LD=loading dose.

12.4 Hematology and biochemistry variables for the interim analysis

Table 12–4: Selected hematology and biochemistry variables for the interim analysis

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

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

12.7 Maastricht Ankylosing Spondylitis Enthesitis Index (MASES) questionnaire

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

12.8 Psoriatic Arthritis Impact of Disease-9 (PsAID-9)

The EULAR Psoriatic Arthritis Impact of Disease: PsAID9 for clinical trials

We want you to indicate how much your psoriatic arthritis impacts your health. Please tell us how you have been feeling this last week.

1. Pain

Circle the number that best describes the pain you felt due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

2. Fatigue

Circle the number that best describes the overall level of fatigue due to your psoriatic arthritis you have experienced during the last week:

No fatigue	0	1	2	3	4	5	6	7	8	9	10	Totally exhausted

3. Skin problems

Circle the number that best describes the skin problems including itching you felt due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

4. Work and/or leisure activities

Circle the number that best describes the difficulties you had to participate fully in work and/or leisure activities due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

5. Functional capacity

Circle the number that best describes the difficulty you had in doing daily physical activities due to your psoriatic arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

6. Discomfort

Circle the number that best describes the feeling of discomfort and annoyance with everyday tasks due to your psoriatic arthritis during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

7. Sleep disturbance

Circle the number that best describes the sleep difficulties (i.e., resting at night) you felt due to your psoriatic arthritis during the last week:

No difficulty	0	1	2	3	4	5	6	7	8	9	10	Extreme difficulty

8. Coping

Considering your psoriatic arthritis overall, how well did you cope (manage, deal, make do) with your psoriatic arthritis during the last week?

Very well	0	1	2	3	4	5	6	7	8	9	10	Very poorly

9. Anxiety, fear and uncertainty

Circle the number that best describes the level of anxiety, fear and uncertainty (for example about the future, treatments, fear of loneliness) due to your psoriatic arthritis you have experienced during the last week:

None	0	1	2	3	4	5	6	7	8	9	10	Extreme

THANK YOU FOR ANSWERING THIS QUESTIONNAIRE

[redacted]

12.13 Identification of Opportunistic infections

Opportunistic infections are identified in two steps:

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

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

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

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

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

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

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

12.14 MedDRA algorithmic approach to anaphylaxis

The SMQ Anaphylactic reaction consists of three parts:

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

  Category A

- Anaphylactic reaction (SMQ)
  - Anaphylactic reaction
  - Anaphylactic shock
  - Anaphylactic transfusion reaction
  - Anaphylactoid reaction
  - Anaphylactoid shock
  - Circulatory collapse
  - Dialysis membrane reaction
  - Kounis syndrome
  - Shock
  - Shock symptom
  - Type I hypersensitivity

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

  Category B

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

  Category C

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

Category D

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

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

13 AMENDMENT(S) TO THE STATISTICAL ANALYSIS PLAN

13.1 Amendment 1

13.1.1 Rationale for the amendment

The main objectives of this SAP amendment are to describe and specify the extension of time point up to Week 24 for the interim analysis. The SAP has been amended to:

- Add additional analyses for the time points up to Week 24 for ACR, PASI, MDA, TEAEs, Hy's Law, PK, and AbAb data
- Add the definition for rheumatoid factor and anti-CCP antibodies positivity and negativity
- Add clarification for handling injected joints for the swollen and tender grading
- Add assessment of potential bias of potentially unblinding at the entry of Dose-Blind phase
- Refine the categories of the subgroup variable Psoriasis BSA

13.1.2 Modifications and changes

Change # 1:

Section 4.3 Interim analysis and data monitoring

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

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

The interim analysis will summarize disposition, demographics, PsA history, Baseline characteristics, PsA concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). Corresponding listings will be provided. Not all collected hematology and biochemistry laboratory variables will be summarized and listed. For the interim analysis only selected variables will be provided as listed in Table 12–4.

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

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

The interim efficacy analysis will focus on the primary and secondary efficacy analyses including supportive and sensitivity analysis. In addition, summary tables for the primary and secondary efficacy variables, and the ACR components will be provided. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive statistics by each visit. Time to onset of ACR50 response and ACR20 response will be summarized and plotted as described in Section 8.3.

PK and PD data will not be analyzed in the interim analysis. A separate PKPD analysis based on a separate Data Analysis Plan (DAP) will be performed after Week 12.

…

Has been changed to

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

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

The interim analysis will summarize disposition, demographics, PsA history, Baseline characteristics, PsA concomitant medication, efficacy analysis, AEs and treatment-emergent AEs (derivation Section 10.2), hematology and biochemistry laboratory data, and Electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). ~~Corresponding listings will be provided.~~ Not all collected hematology and biochemistry laboratory variables will be summarized ~~and listed~~. For the interim analysis only selected **hematology and biochemistry** variables will be provided as listed in Table 12–4. **Listings of AEs, hematology, biochemistry and C-SSRS data will be provided.**

The interim efficacy analysis will focus on the primary and secondary efficacy analyses including supportive and sensitivity analysis. In addition, summary tables for the primary and secondary efficacy variables, ~~and~~ the ACR components**, and MDA** will be provided. Categorical variables will be summarized using frequency tables by each visit. Continuous variables will be summarized using descriptive statistics by each visit. Time to onset of ACR50 response and ACR20 response will be summarized and plotted as described in Section 8.3.

PK and ~~PD data~~ **AbAb data** will ~~not~~ be analyzed in the interim analysis **as described in** Section 9.1 **and** Section 9.2 . ~~A separate PKPD analysis based on a separate Data Analysis Plan (DAP) will be performed after Week 12.~~ **Biomarker data will not be analyzed in the interim analysis.**

The interim analysis includes selected data up to Week 12 and in addition data up to Week 24. The data up to Week 24 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. All analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Following variables will be analyzed: primary and secondary efficacy variables, ACR components, MDA, PK, AbAb, TEAEs and Hy's Law. It depends on the analysis how those additional

time points will be presented in the interim analysis. Two summary tables for each of the primary and secondary efficacy variables, the ACR components, and MDA will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 24 by following treatment groups: bimekizumab 160mg and bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. The same approach will be done for all TEAEs tables and the Hy's Law criteria tables. The summary table for plasma concentration will present only data up to Week 12 for the Baseline treatment groups Placebo and bimekizumab 16mg. Data up to Week 24 will be presented for bimekizumab 160mg, bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. All Listings which include data up to Week 24 will use the same approach as for plasma concentration tables.

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

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

…

Change # 2:

Section 8.1.2.1 Tender joint count (TJC) and swollen joint count (SJC)

Section 8.1.2.1.1 78/76 joint evaluation for ACR response

The Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly assesses the following joints for tenderness: the distal interphalangeal, proximal interphalangeal and metacarpophalangeal joints of the hands, and metatarsophalangeal joints of the feet, the carpometacarpal and wrist joints (counted separately), the elbows, shoulders, acromioclavicular, sternoclavicular, hip, knee, talo-tibial, and midtarsaljoints. All of these except for the hips are assessed for swelling.

Artificial and ankylosed joints, as well as missing joints (ie, amputated joints), are excluded from both tenderness and swelling assessments.

One dactylitic digit is to be counted as 1 swollen joint (instead of counting as 3 in the finger or 2 in the toe).

Table 8–1 summarizes the swelling and tenderness grading criteria.

Table 13–1: Swelling and tenderness grading

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

$$SJC = n * \sum_{i=1}^{n} SJ \Big/ \sum_{i=1}^{n} AJ \quad (9)$$

$$TJC = n * \sum_{i=1}^{n} SJ \Big/ \sum_{i=1}^{n} AJ \quad (10)$$

where n is the number of total joints. If a joint is missing at Baseline, then that joint is set to missing throughout the study. If more than 50% of the tender joint assessments or 50% of the swollen joint assessments are missing at the time of a given assessment, then no imputation will be done and the total TJC or SJC will be set to missing for that visit.

Section 8.1.2.1.2 28 joint evaluation for determination of DAS28(CRP)

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

- Upper extremity (26)-bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), MCP I, II, III, IV, and V, thumb interphalangeals (IP), PIP II, III, IV, and V
- Lower extremity (2)-knees

Has been changed to

Section 8.1.2.1 Tender joint count (TJC) and swollen joint count (SJC)

Section 8.1.2.1.1 78/76 joint evaluation for ACR response

The Principal Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly assesses the following joints for tenderness: the distal interphalangeal, proximal interphalangeal and metacarpophalangeal joints of the hands, and metatarsophalangeal joints of the feet, the carpometacarpal and wrist joints (counted separately), the elbows, shoulders, acromioclavicular, sternoclavicular, hip, knee, talo-tibial, and midtarsaljoints. All of these except for the hips are assessed for swelling.

Artificial and ankylosed joints, as well as missing joints (ie, amputated joints), are excluded from both tenderness and swelling assessments.

One dactylitic digit is to be counted as 1 swollen joint (instead of counting as 3 in the finger or 2 in the toe).

Table 8–1 summarizes the swelling and tenderness grading criteria.

Table 13–1: Swelling and tenderness grading

[redacted]

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

$$SJC = n * \sum_{i=1}^{n} SJ \Big/ \sum_{i=1}^{n} AJ \quad (9)$$

$$TJC = n * \sum_{i=1}^{n} TJ \Big/ \sum_{i=1}^{n} AJ \quad (10)$$

where n is the number of total joints. If a joint is missing at Baseline, then that joint is set to missing throughout the study. If more than 50% of the tender joint assessments or 50% of the swollen joint assessments are missing at the time of a given assessment, then no imputation will be done and the total TJC or SJC will be set to missing for that visit.

Injected joints will be counted as swollen and tender from the date of injection up to 52 weeks after injection, ie, swelling and tenderness grading is 1.

Section 8.1.2.1.2 28 joint evaluation for determination of DAS28(CRP)

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

- Upper extremity (26)-bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), MCP I, II, III, IV, and V, thumb interphalangeals (IP), PIP II, III, IV, and V
- Lower extremity (2)-knees

Injected joints will be counted as swollen and tender from the date of injection up to 52 weeks after injection, ie, swelling and tenderness grading is 1.

Change # 3

Section 6.2 Other Baseline characteristics

…

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

- TJC
- SJC
- hs-CRP
- Rheumatoid factor
- Anti-CCP antibodies
- Prior NSAID therapy, and prior anti-TNF therapy
- Psoriasis BSA
- Nail psoriasis
- Dactylitis
- NSAID therapy
- Synthetic DMARDs
- MTX
- Sulfasalazine
- Hydroxychloroquine

The corresponding listings will be presented for the RS.

Has been changed to

…

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

- TJC
- SJC
- hs-CRP
- Rheumatoid factor
- Anti-CCP antibodies
- Prior NSAID therapy, and prior anti-TNF therapy
- Psoriasis BSA
- Nail psoriasis

- Dactylitis
- NSAID therapy
- Synthetic DMARDs
- MTX
- Sulfasalazine
- Hydroxychloroquine

A rheumatoid factor value < 15 IU/mL is defined as negative and a value ≥ 15 IU/mL is defined as positive. Anti-CCP antibodies negative is a value < 5 U/mL and a value ≥ 5 U/mL is defined as positive.

The corresponding listings will be presented for the RS.

Change # 4:

Following text has been added at the end of

Section 8.3 Analysis of other efficacy variables

…

In order to assess the potential bias of the potentially unblinded subjects based on data, the results of the final analysis will be utilized. Results of the ACR50 and PASI90 response of the rerandomized 320mg and 160mg treatment group at Week 48 will be compared to the potentially unblinded, randomized 320mg and 160mg treatment groups. If the percentage of ACR50 and PASI90 responders is comparable as assessed by overlapping 95% confidence intervals, the potential bias is estimated to be at minimum.

Change # 5:

Section 8.4 Subgroup analysis

and

Section 4.8 Examination of subgroups

…

- Extent of psoriasis involvement >3% (yes, no)

…

Has been changed to

…

- Extent of psoriasis involvement **(<3%, ≥3% to <10%, ≥10%)**

…

13.2 Amendment 2

13.2.1 Rationale for the amendment

The SAP has been amended to:

- Add 'End of Treatment' visit for the final analysis
- Add clarification for the different handling of additional time points in the interim analysis
- Add rule for missing hs-CRP values at Baseline
- Correct inflammatory bowel disease coding
- Add rule for handling missing data for prior and concomitant medication
- Modify Section 10

13.2.2 Modifications and changes

Section 3.5 Mapping of assessments performed at early termination visit

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

Has been changed to

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

A visit called 'End of Treatment' will be added for the TFLs in the final analysis. The visit will display the Week 48 assessments or the early termination assessment depending if the subject discontinued early or not.

Section 4.2.3 Handling of missing data for prior and concomitant medication

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

Imputation of partial start dates:

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

…

Has been changed to

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

Imputation of partial start dates:

- If only the month and year are specified and the month and year of first dose is not the same as the month and year of the start date and the subject did not switch treatment during that month and year, then use the 1st of the month.
- If only the month and year are specified and the month and year of first dose is the same as the month and year of the start, then use the date of first dose.
- If only the month and year are specified and the subject did switch treatment during that month and year, then use the date of first switch treatment.
- If only the year is specified, and the year of first dose is not the same as the year of the start date and the subject did not switch treatment during that year, then use the 1st of January of the year of the start date.
- If only the year is specified, and the year of first dose is the same as the year of the start date, then use the date of first dose.

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

…

Section 4.3 Interim analysis and data monitoring

…

The interim analysis includes selected data up to Week 12 and in addition data up to Week 24. The data up to Week 24 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. All analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Following variables will be analyzed: primary and secondary efficacy variables, ACR components, MDA, modified MDA, PK, AbAb, TEAEs and Hy's Law. It depends on the variable how those additional time points will be presented in the interim analysis. Two summary tables for each of the primary and secondary efficacy variables, the ACR components, MDA and modified MDA will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 24 by following treatment groups: bimekizumab 160mg and bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. The same approach will be done for all TEAEs tables and the Hy's Law criteria tables. The summary table for plasma concentration will present only data up to Week 12 for the Baseline treatment groups Placebo and bimekizumab 16mg. Data up to Week 24 will be presented for bimekizumab 160mg, bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. All Listings which include data up to Week 24 will use the same approach as for plasma concentration tables.

…

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

…

Has been changed to

…

The interim analysis includes selected data up to Week 12 and in addition data up to Week 24. The data up to Week 24 may include partial results up to the time the database for Week 12 was locked for ongoing subjects. ~~All analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized.~~ **The analysis of following variables will include data up to Week 24**~~Following variables will be analyzed~~: primary and secondary

efficacy variables, ACR components, MDA~~, modified MDA,~~ PK, AbAb, TEAEs, **biochemistry and hematology laboratory results,** and Hy's Law. It depends on the variable how those additional time points will be presented in the interim analysis.

The efficacy analyses and the plasma concentration analyses for the period between Week 12 and Week 24 are only for those treatment groups that are not rerandomized. Two summary tables for each of the primary and secondary efficacy variables, the ACR components, **and** MDA ~~and modified MDA~~ will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 24 by **the** following treatment groups: bimekizumab 160mg and bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. ~~The same approach will be done for all TEAEs tables and the Hy's Law criteria tables.~~ The summary table for plasma concentration will present only data up to Week 12 for the Baseline treatment groups Placebo and bimekizumab 16mg. Data up to Week 24 will be presented for bimekizumab 160mg, bimekizumab 160mg with loading dose 320mg, and bimekizumab 320mg. All Listings which include data up to Week 24 will use the same approach as for plasma concentration tables.

The safety analysis (TEAEs, biochemistry and hematology laboratory results, and Hy's Law) will be handled as follows: Two summary tables for each of the safety analysis will be presented. The first table will include data up to Week 12 by treatment group at Baseline. The second table will include data up to Week 24 and will also present subjects under their Baseline treatment group. For the second table any event/finding that is unique to a treatment group should only be presented in the "All subjects" column and the treatment columns should remain blank. Following rules will be applied for the TEAEs: If the relative TEAE start date is less or equal to 84 (12*7) days, then the TEAE will be presented in the up to Week 12 table. If the relative start date is less or equal to 168 (24*7) days, then the TEAE will be presented in the up to Week 24 table.

The treatment group information will not be displayed for the interim listings.

…

For the interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The Investigators and subjects will remain blind to the assigned bimekizumab dosing regimen until the subject completes the Dose-Blind Period at Week 48. **Further details are available in the PA0008 blinding plan.**

…

Section 6.2 Other Baseline characteristics

…

Time since first diagnosis of PsA will be calculated as:

$$Time\ since\ first\ diagnosis = Date\ of\ diagnosis - Date\ of\ Informed\ Consent \quad (6)$$

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

…

A rheumatoid factor value < 15 IU/mL is defined as negative and a value ≥ 15 IU/mL is defined as positive. Anti-CCP antibodies negative is a value < 5 U/mL and a value ≥ 5 U/mL is defined as positive.

The corresponding listings will be presented for the RS.

Has been changed to

…

Time since first diagnosis of PsA will be calculated as:

$$Time\ since\ first\ diagnosis = Date\ of\ diagnosis - Date\ of\ Informed\ Consent \quad (6)$$

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

The absolute values of the formula (6) will be used to display positive values.

…

A rheumatoid factor value < 15 IU/mL is defined as negative and a value ≥ 15 IU/mL is defined as positive. Anti-CCP antibodies negative is a value < 5 U/mL and a value ≥ 5 U/mL is defined as positive.

For hs-CRP following rules will be applied:

- **If Baseline hs-CRP values are missing, then take the Screening hs-CRP values.**
- **If Screening hs-CRP values are missing, then take the median hs-CRP values.**

The corresponding listings will be presented for the RS.

Section 8.4 Subgroup analysis

Subgroup analyses will be performed on the primary and secondary efficacy variables. The following variables for subgroup analyses will be defined:

- Age (<45 years, ≥45 to <65 years, ≥65 years)
- Gender (male, female)
- Geographic region (North America, Europe)
- BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])
- Prior TNF inhibitor exposure (yes, no)
- Treatment-emergent AbAb status (positive, negative)
- Extent of psoriasis involvement (<3%, ≥3% to <10%, ≥10%)
- hs-CRP level (<= upper limit normal, > upper limit normal)
- Time since first diagnosis of PsA (< 2 years, ≥ 2 years)

- Body weight (<100 kg, ≥100 kg)

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

The derivation of time since first diagnosis of PsA is described in Section 6.2.

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

Has been changed to

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

- ~~Age (<45 years, ≥45 to <65 years, ≥65 years)~~
- ~~Gender (male, female)~~
- ~~Geographic region (North America, Europe)~~
- ~~BASDAI (<4 [mild disease]; ≥4 to ≤7 [moderate disease]; >7 to ≤10 [severe disease])~~
- ~~Prior TNF inhibitor exposure (yes, no)~~
- ~~Treatment-emergent AbAb status (positive, negative)~~
- ~~Extent of psoriasis involvement (<3%, ≥3% to <10%, ≥10%)~~
- ~~hs-CRP level (<= upper limit normal, > upper limit normal)~~
- ~~Time since first diagnosis of PsA (< 2 years, ≥ 2 years)~~
- ~~Body weight (<100 kg, ≥100 kg)~~

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

The derivation of time since first diagnosis of PsA is described in Section 6.2.

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

Section 8.3 Analysis of other efficacy variables

…

Time to onset of ACR20/50 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

…

Has been changed to

…

Time to onset of ACR20/50 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. **Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates.** Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

…

Section 10.1 Extent of exposure

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

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

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

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ Injection \quad (16)$$

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

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ Injection + 1 \quad (17)$$

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

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

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (18)$$

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

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

Has been changed to

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

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

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

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ Injection \quad (16)$$

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

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ Injection + 1 \quad (17)$$

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

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

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (18)$$

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

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

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

$$\textbf{\textit{Days on treatment}} = \textbf{\textit{Date of last/latest dose}} - \textbf{\textit{Date of first placebo or bimekizumab dose}} + \mathbf{1} \quad \textbf{(19)}$$

$$\textbf{\textit{Days on bimekizumab treatment}} = \textbf{\textit{Date of last/latest dose}} - \textbf{\textit{Date of first bimekizumab dose}} + \mathbf{1} \quad \textbf{(20)}$$

Section 10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (19)$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \quad (20)$$

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

$$\begin{aligned} &Time\ since\ most\ recent\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset \\ &\quad - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \end{aligned} \quad (21)$$

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

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (20 and 21) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

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

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose + 1 \end{aligned} \quad (22)$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose + 1 \end{aligned} \quad (23)$$

Has been changed to

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (\text{~~19~~}\underline{\mathbf{21}})$$

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

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

$$\begin{aligned} &Time\ since\ first\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \end{aligned} \quad (2\underline{\mathbf{2}}\text{~~0~~})$$

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

$$\begin{aligned} &Time\ since\ most\ recent\ dose\ (days) \\ &\quad = Date\ of\ AE\ onset \\ &\quad - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \end{aligned} \quad (2\underline{\mathbf{3}}\text{~~1~~})$$

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

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (20 and 21) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

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

~~*Days on treatment*~~
~~*= Date of last/latest dose*~~ ~~(22)~~
~~*− Date of first placebo or bimekizumab dose* + 1~~

~~*Days on bimekizumab treatment*~~
~~*= Date of last/latest dose*~~ ~~(23)~~
~~*− Date of first bimekizumab dose* + 1~~

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

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (24)$$

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

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

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (25)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (26)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (27)$$

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

No CI will be computed for EAER.

Has been changed to

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (24)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest **(equation [21] in years)** **at the level of coding evaluated**.

If a subject has multiple events **at the level of coding evaluated**, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk **(15)** is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (25)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (26)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (27)$$

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

No CI will be computed for EAER.

Section 10.2.3 AE of Special Monitoring

…

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLGT of "Colitis excl infective".

…

Has been changed to

…

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HL~~G~~T of "Colitis excl infective".

13.3 Amendment 3

13.3.1 Rationale for the amendment

The SAP has been amended to:

- Add Section with changes from interim analysis to SAP-defined analyses
- Change definition of AE of special monitoring for final analysis
- Add rule for value below limit of quantification for DAS28(CRP)
- Add Section for CRP and hs-CRP
- Update AE section to apply the interim rules to the final analysis
- Update markedly abnormal laboratory units and add the RCTC reference
- Update AbAb Section to clarify the overall AbAb status and the first occurrence of AbAb positivity
- Change subgroup analysis sections to change the definitions of treatment-emergent AbAb status
- Remove rounding information for BMI
- Update prohibited medication section to remove the rule that efficacy results should be set to missing after receiving prohibited medication
- Update pharmacokinetics section to be aligned with TFLs shells

13.3.2 Modification and changes

List of abbreviation

…	
CDF	cumulative distribution function
CI	confidence interval
…	
RBC	red blood cell
RNA	ribonucleic acid
…	

Has been changed to

…	
CDF	cumulative distribution function
CDISC	**Clinical Data Interchange Standards Consortium**
CI	confidence interval

…

RBC	Red blood cell
RCTC	**Rheumatology Common Toxicity Criteria**
RNA	Ribonucleic acid

…

Section 4.3.1 has been added

Section 4.3.1 Changes from interim analysis to SAP-defined analyses

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

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

The definition of time since first diagnosis of PsA was updated with the third SAP Amendment after the interim analysis. In the previous definitions the date of informed consent was subtracted from the date of diagnosis which results in negative values. For the interim analysis another calculations were used:

$$\textit{Time since first diagnosis (years)} = \frac{\textit{Date of Treatment Start Date} - \textit{Date of diagnosis} + 1}{365.25}$$

Section 4.3.2 has been added

Section 4.3.2 Search and selection criteria for AE of special monitoring for interim analysis

Following AEs are defined as TEAEs of special monitoring:

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

Fungal Infectious disorder

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

Opportunistic infection

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

Malignant or unspecified tumor

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

Malignant tumor

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

Major cardiovascular events

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

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

Haematopoietic cytopenias

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

Neuropsychiatric events

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

Inflammatory bowel disease

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

Hypersensitivity reactions and anaphylactic reactions

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

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

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

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

Hepatic events

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

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

Section 4.8 Examination of subgroups

…

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

Has been changed to

…

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

Section 6.1 Demographics

…

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

For adults:

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

Even if they are available in the database, these variables are calculated during analysis (if applicable). These calculated values are used in the statistical analysis since they are considered more accurate. BMI is rounded to 1 decimal.

…

Has been changed to

…

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

For adults:

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

Even if they are available in the database, these variables are calculated during analysis (if applicable). These calculated values are used in the statistical analysis since they are considered more accurate. ~~BMI is rounded to 1 decimal~~.

…

Section 6.2 Other Baseline characteristics

….

Time since first diagnosis of PsA will be calculated as:

$$Time\ since\ first\ diagnosis = Date\ of\ diagnosis - Date\ of\ Informed\ Consent \quad (6)$$

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

The absolute values of the formula (6) will be used to display positive values.

…

Has been changed to

….

Time since first diagnosis of PsA will be calculated as:

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

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

~~The absolute values of the formula (6) will be used to display positive values~~.

…

Section 6.5 Prohibited medication and rescue medication

Prohibited medications are defined in the Protocol (Section 7.8.2). All efficacy data collected at assessments after the use of prohibited medications should be treated as missing. Prohibited medication use and date of first usage should be determined and documented during the data evaluation meeting (DEM) prior to the database lock. The number and percentage of subjects who used prohibited medication will be summarized and also be listed.

…

Has been changed to

Prohibited medications are defined in the Protocol (Section 7.8.2). ~~All efficacy data collected at assessments after the use of prohibited medications should be treated as missing. Prohibited medication use and date of first usage should be determined and documented during the data evaluation meeting (DEM) prior to the database lock. The number and percentage of subjects who used prohibited medication will be summarized and also be listed.~~

…

Section 8.3.2 Disease Activity Score-28 joint count C-reactive protein (DAS28[CRP])

The components for DAS28(CRP) include the TJC and SJC based on 28 joints, hs-CRP (mg/L), and the PGADA (mm). DAS28(CRP) is calculated as follows:

$$DAS28(CRP) = 0.56 * \sqrt{TJC} + 0.28 * \sqrt{SJC} + 0.014 * PGADA + 0.36 * \ln(hsCRP + 1) + 0.96 \quad (12)$$

Has been changed to

The components for DAS28(CRP) include the TJC and SJC based on 28 joints, hs-CRP (mg/L), and the PGADA (mm). DAS28(CRP) is calculated as follows:

$$DAS28(CRP) = 0.56 * \sqrt{TJC} + 0.28 * \sqrt{SJC} + 0.014 * PGADA + 0.36 * \ln(hsCRP + 1) + 0.96 \quad (12)$$

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

Section 8.3.11 has been added

Section 8.3.11 C-reactive protein (CRP) and high-sensitivity C-reactive protein (CRP)

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

$$CV = \sqrt{e^{SD_{ln}^2} - 1} \quad (15)$$

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

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

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

Section 9.2 Pharmacodynamics and Immunogenicity

…

In addition, overall AbAb status should be determined:

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

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

…

Has been changed to

…

In addition, overall AbAb status should be determined:

- Subject AbAb positivity is defined as having with AbAb+ at any time in the treatment period. This does not include Baseline/pre-treatment
- Subject AbAb negativity is defined with AbAb- at any time in the treatment period. This does also include AbAb+ at Baseline/pre-treatment
- ~~Treatment-emergent~~ AbAb positivity is defined ~~when a subject is AbAb+ for the first time during treatment period excluding Baseline/pre-treatment.~~ If there is AbAb+ at Baseline/pre-treatment and there is a ~~pre-defined~~ **4-**fold increase in titre at least at one visit during the treatment period, then the subject has also a**n** ~~treatment-emergent~~ **overall** AbAb positivity status.

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

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

…

Section 8.4 Subgroup analysis

…

Subjects will be counted to have a positive treatment-emergent AbAb status in case the positivity occurred between the first dose and Visit 7 (Week 12).

…

Has been changed to

…

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

…

Section 9.1Pharmacokinetics

…

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

…

Has been changed to

…

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

…

Section 10.1 Extent of exposure

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

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

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

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ Injection \quad (16)$$

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

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ Injection + 1 \quad (17)$$

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

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

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (18)$$

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

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

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

$$Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \quad (19)$$

$$Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose\ + 1 \quad (20)$$

Has been changed to

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

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ Injection + 28 \quad (15\underline{\mathbf{6}})$$

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

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ Injection \quad (16\underline{\mathbf{7}})$$

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

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ Injection + 1 \quad (17\underline{\mathbf{8}})$$

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

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

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (18\underline{\mathbf{9}})$$

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

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

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

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \end{aligned} \quad (\text{~~19~~}\mathbf{20})$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose\ + 1 \end{aligned} \quad (\text{~~20~~}\mathbf{1})$$

Section 10.2 Adverse events

…

The following code lists will be used for AE recording:

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

For all TEAEs the following variables will be calculated:

- Duration
- Time since first dose

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

…

Has been changed to

…

~~The following code lists will be used for AE recording:~~

- ~~Pattern of event: intermittent or continuous~~
- ~~Intensity of event: mild, moderate or severe~~
- ~~Relationship: related or not related~~

~~• Action taken with IMP: dose not changed, dose reduced, dose increased, drug temporarily, interrupted, drug permanently withdrawn or not applicable~~

~~• Outcome: resolving, not resolved, resolved, resolved with sequelae, worsened, fatal or unknown~~

~~For all TEAEs the following variables will be calculated:~~

~~• Duration~~

~~• Time since first dose~~

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

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

…

Section 10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (19)$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \quad (20)$$

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

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (21)$$

…

Has been changed to

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (~~19~~**22**)$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \quad (\text{~~20~~}\underline{\mathbf{23}})$$

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

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (\text{~~21~~}\underline{\mathbf{24}})$$

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

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (24)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [21] in years) at the level of coding evaluated.

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (15) is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (25)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (26)$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (27)$$

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

No CI will be computed for EAER.

Has been changed to

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (24\underline{5})$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [21] in years) at the level of coding evaluated.

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (15) is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (25\underline{6})$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (26\underline{7})$$

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

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{i=1}^{n} T_{Risk,i}} \quad (27\underline{8})$$

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

No CI will be computed for EAER.

Section 10.2.3 AE of Special Interest and AE of Special Monitoring

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

AEs of special monitoring for this study include: serious infections (including opportunistic infections and tuberculosis [TB]), cytopenias, hypersensitivities, suicide ideation or behavior

(assessed using the eC-SSRS), depression and anxiety (assessed using the HADS), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin), malignancies, and inflammatory bowel diseases.

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

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

Fungal infectious disorder

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

Opportunistic infection

Opportunistic infections (including TB) will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs identified using UCB-defined search criteria as described in Section 12.13.

Malignant or unspecified tumor

These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)".

The output table will include 2 different overall incidence rows:

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

Malignant tumor

These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria SMQ=”Malignant tumours (SMQ)”.

Note that the events included in the “Malignant tumours” table will be a subset of the events included in the “Malignant or unspecified tumours” table. The SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each SMQ.

The output table will include 2 different overall incidence rows:

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

Major cardiovascular events

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

- All serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups of the following SMQs:
  - Haemorrhagic central nervous system vascular conditions (SMQ)
  - Ischaemic central nervous system vascular conditions (SMQ)
- All serious TEAEs which code to a PT included in the HLT “Ischaemic coronary artery disorders” except events coding to PT “Chest Pain” or “Chest discomfort”
- All serious TEAEs which code to a PT of “Cardiac failure congestive”

Haematopoietic cytopenias

These events will be presented in a stand-alone table that is based on the SMQ = “Haematopoietic cytopenias”. The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Neuropsychiatric events

These events will be presented in a stand-alone table including EAIR and EAER. The table will be based on the SMQ = “Depression and suicide/self-injury (SMQ)”. The SMQ search will include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLT of “Colitis excl infective”.

Hypersensitivity reactions and anaphylactic reactions

Anaphylactic reactions will be summarized together in a stand-alone table.

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

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

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

Following these three overall incidence rows, all TEAEs that have been identified as either a hypersensitivity reaction or an anaphylactic reaction will be summarized (together – not broken out by type) by SOC, HLT and PT.

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

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

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

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

Hepatic events

Although not officially considered to be AEs of special monitoring but hepatic events are nonetheless considered to be interesting enough to be summarized in stand-alone tables.

Hepatic events will be summarized in a stand-alone table that includes all TEAEs in the SMQ "Drug related hepatic disorders - comprehensive search (SMQ)". Note that the following two sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps)" and "Liver neoplasms, malignant and unspecified (SMQ)".

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

Has been changed to

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

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

AE of special monitoring for this study include:

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

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

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

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

• The first overall incidence row will summarize "Any malignancies (including unspecified)" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.

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

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

• The first overall incidence row will summarize "Any malignancies" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.

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

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

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

• The second row within the body of the table will be labeled "Any hypersensitivity reaction" and will represent the overall incidence of subjects who reported at least one hypersensitivity reaction.

• The third row within the body of the table will be labeled "Any anaphylactic reaction" and will represent the overall incidence of subjects who reported at least one anaphylactic reaction.

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

~~**Fungal infectious disorder**~~

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

~~**Opportunistic infection**~~

~~Opportunistic infections (including TB) will be summarized in a stand-alone table which presents EAIR and EAER. The table will include all TEAEs identified using UCB-defined search criteria as described in Section 12.13.~~

~~**Malignant or unspecified tumor**~~

~~These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria Standardized MedDRA Query (SMQ) = "Malignant or unspecified tumours (SMQ)".~~

~~The output table will include 2 different overall incidence rows:~~

8. ~~The first overall incidence row will summarize "Any malignancies (including unspecified)" and this row will summarize the incidence of all AEs flagged for inclusion in the table, regardless of the High Level Term (HLT) it codes to.~~

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

Malignant tumor

These events will be presented in one stand-alone table which will include EAIR and EAER. The table will be based on the criteria SMQ="Malignant tumours (SMQ)".

Note that the events included in the "Malignant tumours" table will be a subset of the events included in the "Malignant or unspecified tumours" table. The SMQ search should include all TEAEs which code to a PT included in the Scope=Narrow group within each SMQ.

The output table will include 2 different overall incidence rows:

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

Major cardiovascular events

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

- All serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups of the following SMQs:
  - Haemorrhagic central nervous system vascular conditions (SMQ)
  - Ischaemic central nervous system vascular conditions (SMQ)
- All serious TEAEs which code to a PT included in the HLT "Ischaemic coronary artery disorders" except events coding to PT "Chest Pain" or "Chest discomfort"
- All serious TEAEs which code to a PT of "Cardiac failure congestive"

Haematopoietic cytopenias

These events will be presented in a stand-alone table that is based on the SMQ = "Haematopoietic cytopenias". The SMQ search should include all serious TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Neuropsychiatric events

These events will be presented in a stand-alone table including EAIR and EAER. The table will be based on the SMQ = "Depression and suicide/self-injury (SMQ)". The SMQ search will include all TEAEs which code to a PT included in the Scope=Broad and/or Scope=Narrow groups within the SMQ.

Inflammatory bowel disease

These events will be presented in a stand-alone table which includes EAIR and EAER. The table will include all TEAEs which code into the HLT of "Colitis excl infective".

Hypersensitivity reactions and anaphylactic reactions

Anaphylactic reactions will be summarized together in a stand-alone table.

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

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

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

Following these three overall incidence rows, all TEAEs that have been identified as either a hypersensitivity reaction or an anaphylactic reaction will be summarized (together – not broken out by type) by SOC, HLT and PT.

Hypersensitivity reactions and anaphylactic reactions will be identified as follow:

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

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

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

Hepatic events

Although not officially considered to be AEs of special monitoring but hepatic events are nonetheless considered to be interesting enough to be summarized in stand-alone tables.

Hepatic events will be summarized in a stand-alone table that includes all TEAEs in the SMQ "Drug-related hepatic disorders – comprehensive search (SMQ)". Note that the following two sub-SMQs are to be excluded: "Liver neoplasms, benign (incl cysts and polyps)" and "Liver neoplasms, malignant and unspecified (SMQ)".

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

Section 10.3 Clinical laboratory evaluations

…

Markedly abnormal values for biochemistry and hematology are defined in Table 10–2 and Table 10–3.The markedly abnormal laboratory results will be listed separately.

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

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

Table 13–2: Definitions of Markedly Abnormal Biochemistry Values

Variable (Standard international units)	Markedly abnormal definition	
	Low	High
ALP	N/A	>3 x ULN
ALT	N/A	>3 x ULN
AST	N/A	>3 x ULN
Calcium (mg/dL)	<7.0	>12.5
Creatinine (mg/dL)	N/A	>1.8 x ULN
Glucose (mg/dL)	<40	>250
Potassium (mmol/L)	<3.0	>6.4
Sodium (mmol/L)	<125	N/A
Total bilirubin	N/A	≥2 x ULN
Uric acid	N/A	≥3 x ULN

ALP=alkaline phosphatase; AST=aspartate aminotransferase; N/A=Not applicable; ULN=upper limit of normal.

Table 13–3: Definitions of Markedly Abnormal Hematology Values

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

Table 13–2: Definitions of Markedly Abnormal Biochemistry Values

Variable (Standard international units)	Markedly abnormal definition	
	Low	High
Platelets (x 1000)	<50	N/A

LLN=lower limit of normal; N/A = not applicable.

Has been changed to

…

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

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

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

Table 13–4: Definitions of Markedly Abnormal Biochemistry Values

Variable (~~Standard international~~ RCTC units)	Markedly abnormal definition	
	Low	High
ALP	N/A	>3 x ULN
ALT	N/A	>3 x ULN
AST	N/A	>3 x ULN
Calcium (mg/dL)	<7.0	>12.5
Creatinine (mg/dL)	N/A	>1.8 x ULN
Glucose (mg/dL)	<40	>250
Potassium (mmol/L)	<3.0	>6.4
Sodium (mmol/L)	<125	N/A
Total bilirubin	N/A	≥2 x ULN
Uric acid	N/A	≥3 x ULN

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

Table 13–4: Definitions of Markedly Abnormal Biochemistry Values

Variable (~~Standard international~~ RCTC units)	Markedly abnormal definition	
	Low	High

Table 13–5: Definitions of Markedly Abnormal Hematology Values

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

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

13.4 Amendment 4

13.4.1 Rationale for the amendment

The main objectives of this SAP amendment are to describe an additional interim analysis Week 48 and correct small errors.

13.4.2 Modification and changes

Section 1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required interim and final statistical analysis for study PA0008. It also defines the summary tables, figures, and listings (TFLs) to be generated in the clinical study report according to the final Protocol (29 Jul 2016) and Protocol Amendment 1 (16 Dec 2016).

…

Has been changed to

The purpose of this statistical analysis plan (SAP) is to provide all necessary information to perform the required interim and final statistical analysis for study PA0008. It also defines the summary tables, figures, and listings (TFLs) to be generated in the clinical study report according to the final Protocol (29 Jul 2016)**,** ~~and~~ Protocol Amendment 1 (16 Dec 2016)**, and Protocol Amendment 2 (09 Mar 2018)**.

…

Section 2.3 Study design and conduct

Table 2-1 updated to align with Table 5-1 from the Protocol Amendment 2.

Section 3.1 General presentation of summaries and analyses

…

All original and derived variables will be listed and described using summary statistics (number of observations [n], mean, standard deviation [SD], median, minimum and maximum, unless otherwise stated) or frequency counts (number of subjects [N] and percentages).

…

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than 0.9999 will be presented as ">0.9999." Statistical comparisons will be performed by two-sided statistical tests at the 0.0500 level of significance.

…

Has been changed to

…

All original and derived variables will be listed and described using summary statistics (number of observations [n], mean, standard deviation [SD], median, minimum and maximum, unless otherwise stated) or frequency counts (number of subjects [N] and percentages). **For multiple**

post-Baseline assessments at a specific visit, the first non-missing measurement will be used for summary statistics or frequency counts.

…

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to **3**~~0~~4 decimal places. P-values less than 0.00~~0~~1 will be presented as "<0.00~~0~~1" and p-values greater than 0.999~~9~~ will be presented as ">0.999~~9~~." Statistical comparisons will be performed by two-sided statistical tests at the 0.050~~0~~ level of significance.

…

Section 3.2.2 Study Periods

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

- Pre-treatment period (Screening period): up to 28 days, ends with the first dose of bimekizumab.
- Double-Blind treatment period: starts with the first dose of study medication (Visit 2), ends at Week 12 prior to the treatment re-randomization.
- Dose-Blind treatment period: starts at the Week 12 visit after the treatment re-randomization, ends at Week 48.
- Post-treatment period: The post-treatment period (Follow-up period) is the period after the last dose of bimekizumab administration.

Has been changed to

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

- Pre-treatment period (Screening period): up to 28 days, ends with the **visit date of the first dose of study medication (Visit 2)** ~~first dose of bimekizumab.~~
- Double-Blind treatment period: starts with the **visit date of the** first dose of study medication (Visit 2), ends at Week 12 **visit date** ~~prior to the treatment re-randomization~~.
- Dose-Blind treatment period: starts at the Week 12 visit ~~after the treatment re-randomization~~, ends at Week 48 **visit**~~.~~
- Post-treatment period: The post-treatment period (Follow-up period) is the period after the **Week 48 visit**~~last dose of bimekizumab administration~~.

Section 3.3 Definition of Baseline values

Unless otherwise specified, the last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value. The same Baseline definition will be used for the Follow-up period. However, for some variables, assessments may be scheduled for Screening only and not for Baseline. In this case the Screening value will be utilized as Baseline value. If a Baseline measurement is missing, and a Screening value available, the Screening value will be utilized as Baseline instead.

If a scheduled Baseline assessment is taken on the same day and after the first administration of study medication, it will be analyzed as the first post-Baseline assessment. If a scheduled

Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken after the study medication.

Has been changed to

~~Unless otherwise specified, t~~ **T**he last valid measurement before first dose of study drug (Visit 2) will be used as the Baseline value. **If a scheduled Baseline assessment is taken on the same day and after the first administration of study medication, it will be analyzed as the first post-Baseline assessment. If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken after the study medication.** ~~The same Baseline definition will be used for the Follow-up period~~.

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

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

~~If a scheduled Baseline assessment is taken on the same day and after the first administration of study medication, it will be analyzed as the first post-Baseline assessment. If a scheduled Baseline assessment is taken on the same day as first administration of study medication and no time is collected, it will be assumed to have been taken after the study medication.~~

Section 3.5 Mapping of assessments performed at early termination visit

…

A visit called 'End of Treatment' will be added for the TFLs in the final analysis. The visit will display the Week 48 assessments or the early termination assessment depending if the subject discontinued early or not.

Has been changed to

…

~~A visit called 'End of Treatment' will be added for the TFLs in the final analysis. The visit will display the Week 48 assessments or the early termination assessment depending if the subject discontinued early or not.~~

Section 3.6 Analysis sets

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

…

Section 3.6.9 Escape Subject Set (ESS)

The Escape Subject Set (ESS) consists of all subjects who started the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have not achieved at least a 10% reduction from Baseline in SJC and TJC at Week 16, Week 24, or Week 36.

Section 3.6.10 Dose-Blind Responder Set (DBRS)

The Dose-Blind Responder Set (DBRS) consists of all subjects who started the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have achieved at least a 10% reduction from Baseline in SJC and TJC at Week 16, Week 24, and Week 36.

Has been changed to

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

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

…

Section 3.6.9 Escape Subject Set (ESS)

The ~~Escape Subject Set (~~ESS~~)~~ consists of all subjects who started the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have not achieved at least a 10% reduction from Baseline in SJC and TJC at Week 16, Week 24, or Week 36.

Section 3.6.10 Dose-Blind Responder Set (DBRS)

The ~~Dose-Blind Responder Set (~~DBRS~~)~~ consists of all subjects who started the Dose-Blind Period and who received at least 1 dose of the IMP during the Dose-Blind Period and who have achieved at least a 10% reduction from Baseline in SJC and TJC at Week 16, Week 24, and Week 36.

3.6.11 Corrected Escape Subject Set (cESS)

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

3.6.12 Corrected Dose-Blind Responder Set (cDBRS)

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

Section 3.7 Treatment assignment and treatment groups

…

For AE tables and listings, AEs for each subject will be summarized based on the treatment actually received at the onset of each particular AE. It should be noted that this could result in one subject being summarized in two different treatment groups within one output if they were on a treatment regimen that involved treatment switching and experienced AEs under both treatment allocations.

Efficacy analyses will be performed according to randomization and not actual treatment received.

Has been changed to

…

~~For AE tables and listings, AEs for each subject will be summarized based on the treatment actually received at the onset of each particular AE. It should be noted that this could result in one subject being summarized in two different treatment groups within one output if they were on a treatment regimen that involved treatment switching and experienced AEs under both treatment allocations.~~

~~Efficacy analyses will be performed according to randomization and not actual treatment received.~~

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

- **All subjects screened/ES: planned treatment**
- **RS: planned treatment**
- **SS: actual treatment**
- **FAS: planned treatment**
- **PPS: planned treatment**
- **PK-PPS: actual treatment**
- **PD-PPS: actual treatment**

- **DBS: planned treatment (demographics, baseline characteristics, and efficacy analyses) or actual treatment**
- **ESS: planned treatment**
- **DBRS: planned treatment**
- **cESS: planned treatment**
- **cDBRS: planned treatment**

Section 4.2.3 Handling of missing data for prior and concomitant medication

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

Imputation of partial start dates:

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

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

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

- If both the day and month of first study medication or switch treatment are unknown, then this date will be imputed to be the date of first treatment allocation visit.
- If first treatment allocation visit date is missing then the all activities events will be assumed to be treatment emergent..

…

Has been changed to

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

Imputation of partial start dates:

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

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

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

…

Section 4.3 Interim analyses and data monitoring

…

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

…

Section 4.3.1 Changes from interim analysis to SAP-defined analyses

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

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

The definition of time since first diagnosis of PsA was updated with the third SAP Amendment after the interim analysis. In the previous definitions the date of informed consent was subtracted from the date of diagnosis which results in negative values. For the interim analysis another calculations were used:

$$Time\ since\ first\ diagnosis\ (years) = \frac{Date\ of\ Treatment\ Start\ Date - \ Date\ of\ diagnosis + 1}{365.25}$$

Section 4.3.2 Search and selection criteria for AE of special monitoring for interim analysis

…

Has been changed to

Section 4.3 Interim analyses and data monitoring

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

Section 4.3.1 Interim analysis Week 12

….

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

…

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

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

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

~~The definition of time since first diagnosis of PsA was updated with the third SAP Amendment after the interim analysis. In the previous definitions the date of informed consent was subtracted from the date of diagnosis which results in negative values. For the interim analysis another calculations were used:~~

$$\text{Time since first diagnosis (years)} = \frac{\text{Date of Treatment Start Date} - \text{Date of diagnosis} + 1}{365.25}$$

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

Section 4.3.2 Interim analysis Week 48

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

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

The snapshot for the PA0008 interim analysis Week 48 will occur before all subjects have completed the PA0008 study. Specifically, subjects who do not enter the extension study will need to complete the SFU Visit, which occurs 20 weeks after the last dose of study treatment. The Week 48 interim database lock will be performed based on the last subject completing the Week 48 visit. It is anticipated that there will be some subjects still awaiting

the SFU at that time. The number of subjects in the SFU period is expected to be low, and the minimal data to be collected from their SFU visits is not considered mandatory to evaluation of the key efficacy and safety objectives of the study.

Section 4.3.2.1 Changes from interim analysis to SAP-defined analyses

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

Section 4.3.2.2 Changes during interim analysis to SAP-defined analyses

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

Section 6.1 Demographics

…

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

Has been changed to

…

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

Section 6.2 Other Baseline characteristics

…

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

…

Has been changed to

…

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

…

Section 6.4 Prior and concomitant medications

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

In the case of missing data, the classification of medications as prior or concomitant will be performed as described in Section 4.2.3. Imputations of missing data will be performed before calculation of relative study days.

…

Has been changed to

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

In the case of missing data, the classification of medications as prior or concomitant will be performed as described in Section 4.2.3. ~~Imputations of missing data will be performed before calculation of relative study days.~~

…

Section 7 Measurements of treatment compliance

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

$$Percent\ compliance = 100 * \frac{\text{Number of doses received}}{\text{Number of doses expected}} \quad (8)$$

where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes treatment 12 doses are expected (Baseline and every 4th week afterwards until Week 48). If a subject discontinues early, then the number of expected doses is based on the time of early discontinuation relative to the dosing visits. If a dose is not completely given at a specific visit (eg, subject only received one injection instead of the two planned injections), then the subject will be considered to have no compliance for the visit. In the formula above it will be counted as no dose received at this visit.

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group.

…

Has been changed to

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

$$Percent\ compliance = 100 * \frac{\text{Number of doses received}}{\text{Number of doses expected}} \quad (8)$$

where the total number of expected doses is derived relative to when the subject finishes treatment. If a subject completes treatment 12 doses are expected (Baseline and every 4th week afterwards until Week **44**~~48~~). If a subject discontinues early, then the number of expected doses is based on the time of early discontinuation relative to the dosing visits. If a dose is not completely given at a specific visit (eg, subject only received one injection instead of the two planned injections), then the subject will be considered to have no compliance for the visit. In the formula above it will be counted as no dose received at this visit.

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group **for the overall treatment period as well as for double-blind treatment period.**

…

Section 8.1.1.3 Physician's Global Assessment of Disease Activity (PhGADA)

The Investigator will assess the overall status of the subject with respect to their PsA signs and symptoms and functional capacity (considering both joint and skin components) using a numerical rating scale (NRS) where 0 is "very good, asymptomatic and no limitation of normal activities" and 10 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities".

Has been changed to

The Investigator will assess the overall status of the subject with respect to their PsA signs and symptoms and functional capacity (considering both joint and skin components) using a numerical rating scale (NRS) where 0 is "very good, asymptomatic and no limitation of normal activities" and 10**0** is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities".

Section 8.3 Analysis of other efficacy variables

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

…

Time to onset of ACR20/50 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

…

Has been changed to

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

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

…

Time to onset of ACR20/50 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in weeks from Baseline until the first date when the response is achieved. Following derivation will be used: Days from Baseline until the first date divided by 7. There will be no rounding for the Kaplan Meier estimates. Subjects who discontinue study ~~treatment~~ prior to achieving a response will be censored at the date of study ~~treatment~~ discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit. Missing response data will be imputed with NRI.

…

Section 10.1 Extent of exposure

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

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ Injection + 28 \quad (16)$$

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

$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ Injection \quad (17)$$

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

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ Injection + 1 \quad (18)$$

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

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

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (19)$$

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

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

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

$$Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose + 1 \quad (20)$$

$$Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose + 1 \quad (21)$$

Has been changed to

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

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ Injection + 28 \quad (16)$$

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

~~$$Duration\ of\ exposure = Date\ of\ treatment\ change - Date\ of\ first\ Injection \quad (17)$$~~

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

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ Injection + 1 \quad (\mathbf{17}\sout{18})$$

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

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

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (\underline{18}\sout{19})$$

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

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

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

$$Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose + 1 \quad (\underline{19}\sout{20})$$

$$Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose + 1 \quad (\underline{20}\sout{21})$$

Section 10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (22)$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \quad (23)$$

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

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (24)$$

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

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (20 and 21) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

Has been changed to

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (\underline{21}\sout{22})$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \quad (\underline{22}\sout{23})$$

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

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (\underline{23}\sout{24})$$

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

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (**22**~~20~~ and **23**~~21~~) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

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

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

$$EAIR = 100 * \frac{n}{\sum_{i=1}^{n} T_{Exp,i}} \quad (25)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [21] in years) at the level of coding evaluated.

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (15) is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (26)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (27)$$

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

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

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

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

No CI will be computed for EAER.

Has been changed to

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

$$EAIR = 100 * \frac{n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (\underline{24}\sout{25})$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [21] in years) at the level of coding evaluated, **$\underline{n_{noAE}}$ the number of subjects without the specific AE and $\underline{T_{Risk,j}}$ the total time at risk scaled to 100 patient-years (equation [18] in years).**

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (**18**~~15~~) **in years** is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (\underline{25}\sout{26})$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (\underline{26}\sout{27})$$

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

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (\underline{28})$$

where n is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, **$\underline{T_{Exp,i}}$ is a subject's exposure time in years up to the first occurrence of the**

AE of interest (equation [21] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (equation [18] in years).

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (29\text{~~28~~})$$

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

No CI will be computed for EAER.

Section 10.3 Clinical laboratory evaluations

…

Different summary tables for hematology and biochemistry variables will be provided: observed values and change from Baseline, from Baseline to maximum post-Baseline value, from Baseline to minimum post-Baseline value, shift from Baseline to end of treatment, shift from Baseline to end of double-blind treatment, and markedly abnormal laboratory data.

…

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	Albumin
Eosinophils	Chloride	Bacteria
Lymphocytes	Magnesium	Crystals
Atypical lymphocytes	Potassium	Glucose
Monocytes	Sodium	pH
Neutrophils	Glucose	RBC
Hematocrit	BUN	WBC
Hemoglobin	Creatinine	Urine dipstick for pregnancy testing[b]
MCH	hs-CRP/CRP[a]	
MCHC	AST	
MCV	ALT	
Platelet count	GGT	
RBC count	ALP	

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
WBC count	Total bilirubin	
	LDH	
	Total cholesterol	
	Serum pregnancy testing[b]	

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

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

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

Has been changed to

…

Different summary tables for hematology and biochemistry variables will be provided**, based on data from scheduled visits**: observed values and change from Baseline, from Baseline to maximum post-Baseline value, from Baseline to minimum post-Baseline value, shift from Baseline to end of treatment~~, shift from Baseline to end of double-blind treatment~~, and markedly abnormal laboratory data.

End of treatment will be defined as the Week 48 visit or the early termination assessment depending if the subject discontinued early or not.

…

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	~~Albumin~~
Eosinophils	Chloride	Bacteria
Lymphocytes	Magnesium	Crystals
~~Atypical lymphocytes~~	Potassium	Glucose
Monocytes	Sodium	pH

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Neutrophils	Glucose	RBC
Hematocrit	BUN	WBC
Hemoglobin	Creatinine	Urine dipstick for pregnancy testing[b]
MCH	hs-CRP/CRP[a]	
MCHC	AST	
MCV	ALT	
Platelet count	GGT	
RBC count	ALP	
WBC count	Total bilirubin	
	LDH	
	Total cholesterol	
	Albumin	
	Serum pregnancy testing[b]	

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

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

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

…

Table 10-4 updated to align with Table 12-4 from the Protocol Amendment 2.

Table 10-5 updated to align with Table 12-5 from the Protocol Amendment 2.

Section 12.2 Calculation rules for duration of adverse events

The calculation rules for duration of AEs are presented in Table 12–2. AE duration is computed and reported in day.

Table 13–2: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Complete data	D1	D2	Duration = D2 – D1 + 1
Start date missing	-	D2	Duration = < D2 – D0 Where, for a subject in the FAS, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day
End date missing	D1	-	Duration = > Discharge day – D1 For resolved and ongoing AE Duration Where discharge refers to the date of Visit 16 (Week 48) or date of discontinuation
Start and end date missing	-	-	Duration = > Discharge day – D0 For resolved and ongoing AE Duration Where, for a subjects in the FAS, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day, Discharge refers to the date of Visit 16 (Week 48) or date of discontinuation.

Has been changed to

The calculation rules for duration of AEs are presented in Table 12–2. AE duration is computed and reported in day.

Table 13–3: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Complete data	D1	D2	Duration = D2 – D1 + 1
Start date missing	-	D2	Duration = < D2 – D0 **+ 1** Where, for a subject in the **SS**~~FAS~~, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day
End date missing	D1	-	Duration = > **Final contact date**~~Discharge day~~ – D1 **+ 1** For resolved and ongoing AE Duration ~~Where discharge refers to the date of Visit 16 (Week 48) or date of discontinuation~~

Table 13–3: Calculation rules for duration of adverse events

Data Availability	Onset Date	Outcome Date	Calculation Rules
Start and end date missing	-	-	Duration = > **Final contact date** ~~Discharge day~~ – D0 + **1** For resolved and ongoing AE Duration Where, for ~~a~~ subjects in the **SS**~~FAS~~, D0 is the date of the first intake of IMP, and for screen failures, D0 is the date of the Screening visit day, ~~Discharge refers to the date of Visit 16 (Week 48) or date of discontinuation.~~

13.5 Amendment 5

13.5.1 Rationale for the amendment

The main objectives are to describe the different presentation of the safety assessments.

13.5.2 Modification and changes

Text added for Section 4.2.1 Handling of missing data for efficacy analysis

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

Section 6.4 Prior and concomitant medications

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

…

Has been changed to

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

…

Section 7 Measurements of treatment compliance

…

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group for the overall treatment period as well as for Double-Blind treatment period.

A by-subject listing of treatment compliance will be provided.

Has been changed to

…

A summary of percent treatment compliance categorized as ≤80% and >80% will be provided by treatment group for the overall treatment period as well as for Double-Blind treatment period.

For the Double-Blind treatment period compliance will refer to the first 12 weeks and will be presented by treatment received at baseline. For the overall treatment period, the compliance will be calculated for the following three groups: bimekizumab 160mg and 160mg with loading dose, bimekizumab 320mg, and all bimekizumab. Treatment compliance for the bimekizumab 160mg and 160mg with loading dose group will be calculated for the time the subject receives 160mg or 160mg with loading dose, eg for a subject who switches from Placebo or bimekizumab 16mg to bimekizumab 160mg at Week 12, the compliance will only be calculated for the time the subject receives bimekizumab 160mg. The same approach will be done for bimekizumab 320mg. The all bimekizumab group will consist of all the doses of bimekizumab including bimekizumab 16mg, and will only exclude the time subjects receive Placebo.

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

Section 9.1 Pharmacokinetics

Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit using the PK-PPS analysis set.

…

Has been changed to

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

…

Section 9.2 Pharmacodynamics and Immunogenicity

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

…

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

…

Has been changed to

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

…

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

…

Section 10.1 Extent of exposure

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

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ Injection + 28 \quad (16)$$

28 days refer to one half-life of bimekizumab.

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

$$Duration\ of\ exposure = Date\ of\ Death - Date\ of\ first\ Injection + 1 \quad (17)$$

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

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

Time at risk (in days) is defined as:

$$Time\ at\ risk = Date\ of\ last\ injection - Date\ of\ first\ injection + 140 \quad (18)$$

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

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

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

$$Days\ on\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ placebo\ or\ bimekizumab\ dose + 1 \quad (19)$$

$$Days\ on\ bimekizumab\ treatment = Date\ of\ last/latest\ dose - Date\ of\ first\ bimekizumab\ dose + 1 \quad (20)$$

Has been changed to

The duration of exposure and time at risk will be summarized for the Double-Blind Period and the entire treatment period. For the entire treatment period the duration of exposure and time at risk will be calculated for bimekizumab 160mg and 160mg with loading dose, bimekizumab 320mg, and all bimekizumab. The calculation of exposure duration and time at risk for the all bimekizumab group is different from that of the other two groups. For all bimekizumab the duration of exposure and time at risk will include the time a subject

received any dose of bimekizumab (including 16mg) while for the other two treatment groups only the time a subject received 160mg, 160mg with loading dose, or 320mg will be included into the calculation.

Duration of exposure Double-Blind Period

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

$$\begin{aligned} &Duration\ of\ exposure \\ &= Date\ of\ last\ injection\ (double-blind\ period) \\ &- Date\ of\ first\ injection\ (double-blind\ period) + 28 \end{aligned} \quad (16)$$

28 days refer to one half-life of bimekizumab.

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

$$\begin{aligned} &Duration\ of\ exposure \\ &= Date\ of\ first\ injection\ (dose-blind\ period) \\ &- Date\ of\ first\ injection\ (double-blind\ period) + 1 \end{aligned} \quad (17)$$

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

$$\begin{aligned} &Duration\ of\ exposure \\ &= Date\ of\ death - Date\ of\ first\ injection\ (double \\ &- blind\ Period) + 1 \end{aligned} \quad (18)$$

Duration of exposure entire treatment period

For subjects who do not switch study treatments, who receive bimekizumab 160mg with loading dose at Baseline, or who receive bimekizumab 16mg and will be summarized under all bimekizumab group:

$$\begin{aligned} &Duration\ of\ exposure \\ &= Date\ of\ last\ injection\ - Date\ of\ first\ injection + 28 \end{aligned} \quad (19)$$

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

$$\begin{aligned} &Duration\ of\ exposure \\ &= Date\ of\ last\ visit\ (not\ including\ SFU) \\ &- Date\ of\ first\ injection + 1 \end{aligned} \quad (20)$$

For subjects who die, then this calculation reverts to:

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection + 1 \quad (21)$$

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

bimekizumab 160mg or 320mg, or subjects who received Placebo and will be summarized in the overall table under their Dose-Blind treatment:

$$Duration\ of\ exposure = Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 28 \quad (22)$$

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

$$Duration\ of\ exposure = Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (23)$$

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

$$Duration\ of\ exposure = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (24)$$

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

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

Time at risk Double-Blind Period

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

$$Time\ at\ risk = Date\ of\ first\ injection\ (dose - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (25)$$

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

$$Date\ of\ last\ injection\ (double - blind\ period) - Date\ of\ first\ injection\ (double - blind\ period) + 140 \quad (26)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (27)$$

$$Date\ of\ last\ visit\ (not\ including\ SFU) - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (28)$$

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

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

$$Date\ of\ death - Date\ of\ first\ injection\ (double - blind\ period) + 1 \quad (29)$$

Time at risk entire treatment period

For subjects who do not switch study treatments, who receive bimekizumab 160mg with loading dose at Baseline, or who receive bimekizumab 16mg and will be summarized under all bimekizumab group:

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

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

For subjects who die prior to the final visit:

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

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

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

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

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

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

$$Time\ at\ risk = Date\ of\ Visit\ 16\ (Week\ 48) - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (34)$$

For subjects who die during the Dose-Blind Period:

$$Time\ at\ risk = Date\ of\ death - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (35)$$

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

$$Date\ of\ last\ injection - Date\ of\ first\ injection\ (dose - blind\ period) + 140 \quad (36)$$

$$Date\ of\ final\ contact - Date\ of\ first\ injection\ (dose - blind\ period) + 1 \quad (37)$$

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

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

$$\begin{aligned} &Days\ on\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ placebo\ or\ bimekizumab\ dose\ + 1 \end{aligned} \quad \textbf{(38)}$$

$$\begin{aligned} &Days\ on\ bimekizumab\ treatment \\ &\quad = Date\ of\ last/latest\ dose \\ &\quad - Date\ of\ first\ bimekizumab\ dose\ + 1 \end{aligned} \quad \textbf{(39)}$$

Section 10.2 Adverse events

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

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

Has been changed to

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

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

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

Section 10.2.1 Exposure duration

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \quad (21)$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \quad (22)$$

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

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \quad (23)$$

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

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (22 and 23) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

Has been changed to

The duration of each AE will be calculated as follows:

$$Duration\ (days) = Date\ of\ outcome - Date\ of\ onset + 1 \qquad (\underline{40}\sout{21})$$

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

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

$$Time\ since\ first\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ first\ dose + 1 \qquad (\underline{41}\sout{22})$$

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

$$Time\ since\ most\ recent\ dose\ (days) = Date\ of\ AE\ onset - Date\ of\ most\ recent\ dose\ prior\ to\ AE + 1 \qquad (\underline{42}\sout{23})$$

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

For the calculation of time to first bimekizumab and time to most recent bimekizumab dose the same formulas as above (**41**~~22~~ and **42**~~23~~) will be used but the date of first bimekizumab dose will be used instead of the date of first dose. The time to first dose and time to first bimekizumab dose differs only for those subjects who receive placebo at Baseline.

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

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

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

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [21] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (equation [18] in years).

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (18) in years is used.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \qquad (25)$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (26)$$

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

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (28)$$

where n_{AE} is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [21] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (equation [18] in years).

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (29)$$

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.

Has been changed to

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

$$EAIR = 100 * \frac{n_{AE}}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (**43**~~24~~)$$

where $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [**40**~~21~~] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (~~equation [18] in years~~Section 10.1).

If a subject has multiple events at the level of coding evaluated, the time of exposure is calculated to the first occurrence of the AE of interest. If a subject has no events, the total time at risk (~~18~~ Section 10.1) in years is used. **As indicated above, exposure-adjusted incidence rates will only be calculated for the overall treatment period. These presentations do not include**

AEs that occur under Placebo treatment. Therefore, a subject's exposure time will only start at the first dose of bimekizumab in the Dose-Blind Period for subjects randomized to Placebo at Baseline. Also, for subject's randomized to bimekizumab 16mg at Baseline, exposure time will only be considered from the start of Dose-Blind Period, when presenting AEs for the bimekizumab 160mg and bimekizumab160mg with loading dose, or bimekizumab 320mg groups. All exposure time on any bimekizumab dose is considered for the all bimekizumab column.

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

$$LCL = \frac{\chi^2_{2n,\frac{\alpha}{2}}}{2} \quad (44\text{~~25~~})$$

$$UCL = \frac{\chi^2_{2(n+1),1-\alpha/2}}{2} \quad (45\text{~~26~~})$$

$$CI_{Lower} = 100 * \frac{LCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (46\text{~~27~~})$$

$$CI_{Upper} = 100 * \frac{UCL}{\sum_{i=1}^{n_{AE}} T_{Exp,i} + \sum_{j=1}^{n_{noAE}} T_{Risk,j}} \quad (47\text{~~28~~})$$

where n_{AE} is the number of subjects with a specific AE for the incidence rate of interest and is the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2, $T_{Exp,i}$ is a subject's exposure time in years up to the first occurrence of the AE of interest (equation [40~~21~~] in years) at the level of coding evaluated, n_{noAE} the number of subjects without the specific AE and $T_{Risk,j}$ the total time at risk scaled to 100 patient-years (~~equation [18] in years~~ Section 10.1).

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

$$EAER = 100 * \frac{N_{AE}}{\sum_{j=1}^{n_{All}} T_{Risk,j}} \quad (48\text{~~29~~})$$

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.

Section 10.3 Clinical laboratory evaluations

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Different summary tables for hematology and biochemistry variables will be provided, based on data from scheduled visits: observed values and change from Baseline, from Baseline to maximum post-Baseline value, from Baseline to minimum post-Baseline value, shift from Baseline to end of treatment, and markedly abnormal laboratory data.

End of treatment will be defined as the Week 48 visit or the early termination assessment depending if the subject discontinued early or not.

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Table 13–1: Laboratory measurements

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

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis

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

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

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

Has been changed to

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Different summary tables for hematology and biochemistry variables will be provided, based on data from scheduled visits: observed values and change from Baseline, **shift** from Baseline to maximum post-Baseline value **(in Double-Blind Period), shift from Baseline to maximum post-Baseline value (in Dose-Blind Period), shift** from Baseline to minimum post-Baseline value **(in Double-Blind Period)**, **shift from Baseline to minimum post-Baseline value (in Dose-Blind Period)**, shift from Baseline to end of treatment **(in Double-Blind Period), shift from Baseline to end of treatment (in Dose-Blind Period),** and markedly abnormal laboratory data.

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

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

…

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	Bacteria
Eosinophils	Chloride	Crystals
Lymphocytes	Magnesium	Glucose
Monocytes	Potassium	pH
Neutrophils	Sodium	RBC

Table 13–1: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Hematocrit	Glucose	WBC
Hemoglobin	BUN	Urine dipstick for pregnancy testing[b]
MCH	Creatinine	
MCHC	hs-CRP/CRP[a]	
MCV	AST	
Platelet count	ALT	
RBC count	GGT	
WBC count	ALP	
	Total bilirubin	
	LDH	
	Total cholesterol	
	Uric acid	
	Albumin	
	Serum pregnancy testing[b]	

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

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

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

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.