PROTOCOL PA0008 AMENDMENT 2

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

PHASE 2B

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ACR	American College of Rheumatology
ACR20, 50, 70	American College of Rheumatology 20, 50, 70% response criteria
AE	adverse event
AESI	adverse event of special interest
AESM	adverse event for special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BP	blood pressure
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	cyclic citrullinated peptide
CD	cluster of differentiation
CDC	Centers for Disease Control
CDMS	clinical data management system
CI	confidence interval
CL/F	total body clearance
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRF/eCRF	Case Report Form/electronic CRF
CRO	Contract Research Organization
CRP	C-reactive protein
C-SSRS/eC-SSRS	Columbia-Suicide Severity Rating Scale/electronic C-SSRS
CZP	certolizumab pegol
DAS28(CRP)	Disease Activity Score-28 joint count C-reactive protein
DBS	Dose-Blind Set
DBRS	Dose-Blind Responder Set
DIP	distal interphalangeals
DMARD	disease-modifying antirheumatic drug

DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	electronic data capture
ES	Enrolled Set
ESS	Escape Subject Set
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
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
HBV	hepatitis B virus
HbsAg	hepatitis B surface antigen
HbcAB	hepatitis B core antibody
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	Health-Related Quality of Life
hs	high sensitivity
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Council on Harmonisation
IEC	independent ethics committee
IGRA	interferon-gamma release assay
IIV	interindividual variability
IP	interphalangeal
IL	interleukin
im	intramuscular
IMP	investigational medicinal product

IMS	International Menopause Society
IRB	institutional review board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
iv	intravenous
IXRS	interactive voice or web response system
LDI	Leeds Dactylitis Index
LEF	leflunomide
LTB	latent tuberculosis
LTBI	latent tuberculosis infection
MAR	missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Index
MCID	minimal clinically important difference
MCP-Mod	Multiple Comparison Procedure – Modeling
MCP	metacarpophalangeal
MCS	mental component summary
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMR	measles-mumps-rubella
mNAPSI	modified Nail Psoriasis Severity Index
MTB	mycobacterium tuberculosis
MTP	metatarsophalangeal
MTX	methotrexate
NOAEL	no adverse effect level
NRI	nonresponder imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria
OPV	oral polio vaccine
PASI	Psoriasis Area and Severity Index
PASI75, PASI90, PASI100	Psoriasis Area and Severity Index 75%, 90%, 100%

PCS	physical component summary
PD	pharmacodynamics
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamics Per-Protocol Set
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PIP	proximal interphalangeal
PK	pharmacokinetics
PK-PPS	Pharmacokinetic Per-Protocol Set
PPS	Per-Protocol Set
PS	Patient Safety
PSO	psoriasis
PsA	psoriatic arthritis
PsAID-9	Psoriatic Arthritis Impact of Disease-9
PsAQoL	Psoriatic Arthritis Quality of Life
PtAAP	Patient's Assessment of Arthritis Pain
PUVA	psoralen plus ultraviolet A light therapy
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
RA	receptor A
RCTC	Rheumatology Common Toxicity Criteria
RF	rheumatoid factor
RIF	rifampin
RS	Randomized Set
RUV	residual unexplained variability
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SF-36	Short-Form 36-item Health Survey
SFU	Safety Follow-up

SJC	swollen joint count
SOC	standard of care
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
Th17	T helper 17
TJC	tender joint count
TNF	tumor necrosis factor
TNFα	tumor necrosis factor-alpha
ULN	upper limit of normal
UVA	ultraviolet A
VAS	visual analog scale
V/F	volume of distribution

1 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) 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 PSO. 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

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. The primary efficacy variable is the American College of Rheumatology 50% (ACR50) response at Week 12, with a responder defined as a subject with an improvement from Baseline of ≥50% in the swollen and tender joint counts and at least 3 of the other 5 components of the core set of American College of Rheumatology (ACR) response measures.

The secondary objectives are to assess efficacy of the individual dose regimens of bimekizumab compared to placebo, skin and nail psoriasis in the subgroup of affected subjects at Baseline, safety and tolerability, PK, PD, immunogenicity, and the exposure:response relationship of bimekizumab as it relates to efficacy and safety. The secondary efficacy variables are American College of Rheumatology 20% (ACR20) response, American College of Rheumatology 70% (ACR70) response, Psoriasis Area and Severity Index 90% (PASI90) response, and Psoriasis Area and Severity Index 75% (PASI75) response, all at Week 12. Safety variables include incidence of adverse events (AEs) and serious adverse events (SAEs), withdrawal due to AEs, change from Baseline in vital signs, body weight, physical examination, ECG, and clinical laboratory variables.

Other objectives are to assess the impact of treatment on patient-reported quality of life, axial disease and biological pathways relating to disease biology, progression, and response to therapy via biomarker analysis, as well as to enable genomic and related approaches for analysis of subject samples and evaluation of the potential for subject stratification approaches.

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.

Screening Period/Baseline

The Screening Period will last 14 to 28 days. 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 any medications not permitted for use during the study.

Double-Blind Period

Subjects will be randomized in a 1:1:1:1:1 ratio (stratified by region and prior TNF inhibitor exposure) to receive the following blinded study treatment regimens:

- 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. Therefore, each arm will have approximately 12 TNF inhibitor experienced subjects in a total of 40 subjects per arm.

Investigational medicinal product (IMP) will be administered sc in the clinic at Baseline/Day 1, Week 4, Week 8, and Week 12. Additional nondosing 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.

Dose-Blind Period

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

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 5.1.4.

Safety Follow-Up Visit/Extension Study

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

2 INTRODUCTION

Psoriatic arthritis, a chronic inflammatory musculoskeletal disorder, occurs in approximately 6 to 41% of people affected by PSO (Ogdie and Weiss, 2015). A substantial proportion of subjects have polyarthritis (McHugh et al, 2003). Disease-modifying antirheumatic drugs and biological agents targeting TNFα, interleukin (IL)-17, and IL-12/23 are effective in PsA (Kavanaugh et al, 2012; Kavanaugh et al, 2009; Gottlieb et al, 2009; Gladman et al, 2007; Genovese et al, 2007; Kavanaugh et al, 2006; Antoni et al, 2005a; Antoni et al, 2005b; Mease et al, 2005; Mease et al, 2004, McInnes et al, 2015; Mease et al, 2015). However, some subjects are not responsive to these treatments, do not maintain a clinical response (defined as achieving ACR20 response criteria), or have contraindications or intolerance to these agents.

Recent work has implicated various isoforms comprising the IL-17 cytokine family in the pathophysiology of psoriasis (PsO) and of PsA (Raychaudhuri et al, 2012; Fujishima et al, 2010; Watanabe et al, 2009; Harper et al, 2009; Johansen et al, 2009). Numbers of IL-17A positive cells are increased and localized in psoriatic skin lesions (Fujishima et al, 2010; Watanabe et al, 2009; Harper et al, 2009; Johansen et al, 2009), and IL-17A and IL-17F are overexpressed in the serum and skin lesions of subjects with PSO (Johansen et al, 2009), while IL-17F in particular is a key inflammatory cytokine contributing to PSO pathology (Fujishima et al, 2010; Watanabe et al, 2009). Cluster of differentiation (CD) 4 + T helper 17 (Th17) cells, IL-17A, and IL-17 receptor A (IL-17-RA) have recently been shown to play a role in PsA (Raychaudhuri et al, 2012). Anti-IL-17 antibodies have been shown to be effective treatments for PSO (Papp et al, 2012; Leonardi et al, 2012; Hueber et al, 2010) and have also shown activity in subjects with rheumatoid arthritis, PsA, and ankylosing spondylitis (McInnes et al, 2014; Mease et al, 2015; Hueber et al, 2010; Genovese et al, 2010). Taken together these data suggest that inhibition of both IL-17A and IL-17F could be therapeutically effective in subjects with PSO and PsA, as well as spondyloarthritis disease, including axial spondylitis (axSpA).

Bimekizumab (UCB4940) is an engineered, humanized full-length monoclonal antibody of IgG1 subclass of approximately 150,000 Dalton which is expressed in a genetically engineered Chinese Hamster Ovarian (CHO) cell line. Bimekizumab has high affinity for human IL-17A and human IL-17F and selectively and potently inhibits the activity of both isoforms in vitro. Therefore, it permits an evaluation of the potential for additional efficacy, which may be conferred by dual inhibition of both cytokines, in patients suffering from diseases in which both cytokines are active. As a consequence, a Phase 2b dose-ranging study (PA0008) was designed to investigate the efficacy and safety of various bimekizumab dose regimens in subjects with active PsA. Furthermore, a proof-of-concept study with bimekizumab in patients with

moderate-to-severe PsA demonstrated an efficacy signal that warrants further exploration of bimekizumab in this indication.

2.1.1 Clinical

Three clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, and PA0007 in 53 subjects with PsA.

UP0008 was a Phase 1, single ascending dose study in adults with mild to moderate PSO affecting ≤5% body surface area (BSA). In this blinded study, single doses of up to 640mg (approximately 8mg/kg in an 80kg adult) were evaluated. A total of 26 subjects with PSO with less than 5% of body surface involvement were treated with a range of single intravenous (iv) doses from 8 to 640mg. The PK of bimekizumab was linear in the tested dose range. There were no clinically relevant safety findings identified at any dose and all doses were well tolerated. The pre-specified exploratory assessment of disease activity showed clinically relevant and statistically significant improvements at the higher doses studied.

RA0124 was a Phase 1, open-label, parallel-group, single-dose study in healthy subjects. The primary objective of this study was to determine the absolute bioavailability of single sc doses of bimekizumab (80mg and 160mg). The secondary objectives were to evaluate the dose proportionality of bimekizumab 80mg and 160mg sc, and to evaluate the safety and tolerability of these sc doses and 160mg given by iv infusion. In RA0124, the absolute bioavailability was similar for the 2 doses tested (0.656 and 0.631 for the bimekizumab 80mg and 160mg sc doses, respectively). The median $t_{1/2}$ following sc administration was similar to that following iv administration (27.81 days and 28.25 days for bimekizumab 160mg sc and bimekizumab 160mg iv, respectively).

Bimekizumab has also been investigated in a proof of concept, randomized, placebo-controlled, multiple dose study (PA0007). The primary objective of PA0007 was to assess the safety and PK of multiple dose administration of iv bimekizumab in subjects with PsA. Four active doses and a placebo were tested. Drug was administered as a loading dose of bimekizumab 80mg, 160mg, 240mg, or 560mg at Week 1, and 2 additional doses of bimekizumab 40mg, 80mg, 160mg, or 320mg at Week 4 and Week 7, respectively. In each treatment group, subjects received a total of 3 doses of bimekizumab, administered every 3 weeks. In this study, there were no unexpected clinically relevant safety findings and all doses were well tolerated. The PK was linear across the tested dose range and no change in PK was observed following multiple doses. Observed changes in inflammatory biomarkers were consistent with expectations based on the IL-17A and IL-17F mechanism of action. The exploratory analysis showed clinically relevant improvement in activity of PsA and in skin involvement in those subjects with concomitant active psoriatic lesions. Data from the top 3 bimekizumab dose groups pooled showed that by Week 9 80% [95% CI: 62.7, 90.5] of subjects achieved an ACR20 response (versus 16.7% [95% CI: 4.7, 44.8] in the placebo group) and 100% [95% CI: 79.6, 100.0] of subjects with active psoriatic lesions had achieved a PASI75 response (versus 0% [95% CI: 0.0, 43.4] in the placebo group).

Infections (mostly nasopharyngitis) were the most commonly reported events in both the active treatment and the placebo group. None of the infections were considered serious or required treatment with antibiotics. Two subjects in the active treatment group experienced 1 local candida infection each (oropharyngitis and vulvovaginitis, respectively) that were nonserious and resolved with topical therapy. There was a reduction in mean neutrophil count in the active

treatment group, although this drop was not clinically relevant and a clear relationship with dose or time was not evident. Some increases in liver function tests were reported, but none had a convincing relationship to exposure to study medication.

In the bimekizumab clinical studies to date, the most commonly reported GI AEs were abdominal distension, abdominal pain, diarrhea, flatulence, nausea, and vomiting. All of these events, except 1 event of vomiting, were mild or moderate in intensity. T helper-17 and other IL-17-producing cell types are present in a high frequency in the physiologic, healthy state of the intestinal mucosa. Interleukin-17 is recognized as an important player in the pathophysiology of infectious and immune-mediated GI diseases, and has been shown to contribute to the gut barrier function (Ivanov et al, 2008). Clinical data with secukinumab suggest that the drug may worsen symptoms of co-existing Crohn's disease in patients with psoriasis and ankylosing spondylitis (Baeten et al 2015).

Two additional studies are ongoing. RA0123 is a Phase 2a, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the safety, PK, PD, and efficacy of multiple doses of bimekizumab administered as add-on therapy to stable certolizumab pegol (CZP; Cimzia®) therapy in subjects with moderate to severe rheumatoid arthritis. UP0031 is an open-label, parallel-group, single-dose study designed to evaluate the relative bioavailability and tolerability of 2 dose levels of UCB4940 (bimekizumab) given as 2 x80mg or 1x 160mg given via sc injection in healthy subjects.

Additional information on the clinical data for bimekizumab is available in the current version of the Investigator's Brochure (IB).

2.1.2 Nonclinical

Parallel inhibition of IL-17A and IL-17F have shown potent effects in a variety of animal models of inflammatory disease. Intravenously administered bimekizumab was well tolerated in repeat dose toxicology studies in Cynomolgus monkeys with a no adverse effect level (NOAEL) of 200mg/kg/week. The findings of note in toxicity studies were diarrhea related to infectious enteritis (observed in the single dose study) and asymptomatic mild colonic ulceration in a proportion of animals (in the repeat-dose study); this latter finding was not associated with hematology abnormalities. Data suggest that bimekizumab has induced primary lesions to the mucosa-associated lymphoid tissue via a pharmacologically-related mechanism. In a second repeat-dose study, none of the minor apoptosis/necrosis findings observed in gut associated lymph nodes were seen. In animals given the highest dose of bimekizumab in the study (20mg/kg/week), a slightly higher number of protozoa (*Balantidium coli*) was observed in the cecum and colon as compared to the control animals and low dose animals. Therefore gut associated lymph node lesions observed in the first study are considered to be accidental and/or linked to exaggerated pharmacology and proliferation of *Balantidium coli* and are considered the result of a change in local mucosal immunity..

Additional information on the nonclinical data for bimekizumab is available in the current version of the IB.

3 STUDY OBJECTIVES

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

3.1 Primary objective

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

3.2 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

3.3 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

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable for this study is as follows:

- ACR50 response at Week 12

4.1.2 Secondary efficacy variables

The secondary efficacy variables for this study are as follows:

- ACR20 response at Week 12
- ACR70 response at Week 12
- PASI90 response at Week 12 in the subgroup of subjects with psoriasis involving at least 3% of body surface area at Baseline/Day 1
- PASI75 response at Week 12 in the subgroup of subjects with psoriasis involving at least 3% of body surface area at Baseline/Day 1

4.1.3 Other efficacy variables

Other efficacy variables will be assessed as specified in Table 5–1 (analyses at all time points not specified in Section 4.1.1 or Section 4.1.2 are exploratory):

- 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 body surface area at Baseline/Day 1
- ACR20, ACR50, and ACR70 response
- Composite endpoint comprised of ACR50 and PASI90 response in the subgroup of subjects with PSO involving at least 3% of body surface area at Baseline/Day 1
- Minimal Disease Activity (MDA), as defined in Table 9–3.
- Change from Baseline in the Disease Activity Score-28 based on CRP (DAS28 [CRP])
- Change from Baseline in all individual ACR core 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)
  - 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)

4.2 PK and PD variables

4.2.1 PK variables

The PK variables are plasma concentrations of bimekizumab, total body clearance (CL/F) and volume of distribution (V/F).

4.2.2 PD 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 TNFα.

4.3 Pharmacogenomic variables

4.3.1 Genomic, proteomic, and metabolite 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.

4.4 Immunological variables

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

- Anti-bimekizumab antibody 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

4.5 Safety variables

Safety variables to be assessed as specified in Table 5–1 are as follows:

- Incidence of AEs and SAEs
- Withdrawal due to AEs
- Change from Baseline in vital signs (blood pressure [BP] 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 Electrocardiogram (ECG) variables
- Change from Baseline in clinical laboratory variables (hematology, biochemistry, and urinalysis)

5 STUDY DESIGN

5.1 Study description

This is a multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy and safety of bimekizumab in subjects with active PsA. 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-cyclic citrullinated peptide (CCP) antibodies negative.
- Subject must have active psoriatic lesion(s) and/or a documented history of PSO.
- 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 (Section 5.1.2). Subjects in any treatment group who complete the 12-week Double-Blind Period will enter the 36-week Dose-Blind Period (Section 5.1.3). Treatment during the Dose-Blind Period will start at Week 12 and be administered Q4W thereafter through Week 44 (for subjects who will not enter the extension study or Week 48 (for subjects who enter the 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.

A schematic diagram of the study design is presented in Figure 5–1.

5.1.1 Screening Period/Baseline

The Screening Period will last 14 to 28 days. During the Screening Period, the Investigator will obtain laboratory data and verify that the doses of MTX (for those taking MTX), LEF (for those taking LEF), NSAIDs (if used), and corticosteroids are stable. The Screening Period will also enable washout of medications not permitted for use during the study (Section 7.8.2). The assessments at the Screening Period Visit are presented in Table 5–1.

5.1.2 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. Therefore, each arm will have approximately 12 TNF inhibitor experienced subjects in a total of 40 subjects per arm.

The Double-Blind Period is 12 weeks in duration. Study medication will be administered sc in the clinic at Baseline, Week 4, Week 8, and Week 12.

Additional study visits (without dosing) will occur at Week 1 and Week 2.

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

The assessments at each Double-Blind Period Visit are presented in Table 5–1.

At 12 weeks, subjects will transition from the double-blind placebo-controlled treatment into the 36-week Dose-Blind Period as discussed in Section 5.1.3.

5.1.3 Dose-Blind Period

After the 12-week Double-Blind Period, subjects will enter the 36-week Dose-Blind Period. 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

The assessments at each Dose-Blind Period Visit are presented in Table 5–1.

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 5.1.4.

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 as outlined in Section 5.1.4.

5.1.4 Rescue therapy

At Week 16, Week 24, and Week 36 of the Dose-blind Period, subjects will be evaluated for their response to treatment to determine eligibility for rescue therapy.

Subjects who have shown <10% improvement from Baseline in TJC and SJC will be eligible for rescue therapy. Rescue therapy for eligible subjects will be at the Investigator's discretion, with the following options:

- Nonsteroidal anti-inflammatory drugs, DMARDs (MTX, sulfasalazine, LEF, apremilast), and/or joint injections may be given as rescue therapy if deemed appropriate by the Investigator as outlined below. Subjects may receive these add-on therapies while continuing to receive their randomized dose of bimekizumab.
  - For subjects taking NSAID/COX-2 inhibitors at Baseline or at Week 16, Week 24, or Week 36, a change can be made to a different NSAID/COX-2. Changes from an NSAID to a COX-2 or from a COX-2 to an NSAID are permitted up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 may be taken at a given time.
  - For subjects not taking NSAID/COX-2 inhibitors at Baseline, Week 16, Week 24, or Week 36, either a NSAID or COX-2 inhibitor can be initiated, up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 may be taken at a given time.
  - Methotrexate may be added or increased to a maximum dose of 25mg/week, or the maximum tolerated dose, whichever is lower. The route of administration may be changed from oral to sc.
  - Sulfasalazine may be given up to a maximum dose of 3g/day, or the maximum tolerated dose, whichever is lower.
  - Leflunomide may be given at a maximum dose of 20mg/day (or an average of 20mg/day if not dosed daily), or the maximum tolerated dose, whichever is lower.

  - Apremilast may be given at a maximum dose of 30mg twice daily, or the maximum tolerated dose, whichever is lower.
  - Combination DMARDs are allowed except that LEF and MTX may not be given together.
  - One joint may be injected at or after the Week 16, Week 24, and Week 36 Visit; however, the same joint should not be injected more than once during the study.
- A decrease in dose or dosing frequency of any agent for the treatment of PsA is permitted for reasons of intolerance/AEs/side-effects at any time.
- If, in the judgment of the Investigator, the options outlined above are not considered appropriate for the subject, or the subject does not achieve sufficient response to these options, biologics may be considered. Subjects must discontinue treatment with bimekizumab prior to use of another biologic therapy and follow the withdrawal criteria and follow-up as outlined in Section 6.3.
- Rescue therapy will be determined by the Investigator taking into account the half-life of bimekizumab (27.8 days).

No other medication changes or additions are permitted for rescue therapy.

Subjects may be withdrawn from the study or from study medication at any time and continue treatment per the Investigator's discretion, as described in the Withdrawal Section (Section 6.3).

5.1.5 Safety Follow-Up Visit

All subjects who complete the study and do not enter the extension study or who discontinue early, including those withdrawn from study treatment, will have a SFU Visit 20 weeks after their last dose of study medication.

The assessments for the SFU Visit are presented in Table 5–1.

5.1.6 Safety monitoring strategy

An independent Data Monitoring Committee (DMC) will be reviewing study safety data on an ongoing basis. Details will be available in the DMC charter. A cardiovascular adjudication committee will review cardiovascular events. Further details are provided in Section 12.1.11.

5.1.7 Study duration per subject

For each subject, the study will last a maximum of 68weeks, as follows:

- 2 to 4 weeks of Screening
- 12 weeks in the Double-Blind Period
- 36 weeks in the Dose-Blind Period
- A SFU Visit 20 weeks after the last dose of study medication (for subjects not entering the extension study or who discontinue early, including those withdrawn from study treatment)

The end of the study is defined as the date of the last visit of the last subject in the study.

5.1.8 Planned number of subjects and site(s)

The planned number of randomized subjects in PA0008 is 200; there will be 40 subjects per treatment arm. The planned number of study sites is approximately 70.

5.1.9 Anticipated regions and countries

The planned study sites will be located in Europe and North America.

5.2 Schedule of study assessments

The schedule of study assessments in presented in Table 5–1.

Table 5–1: Schedule of assessments

Visit[a]/ Week / Protocol activity	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
PGADA		X	X	X	X	X	X	X	X	X			X			X	X	X
PtAAP		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																	

Table 5–1: Schedule of assessments

Visit[a]/ Week / Protocol activity	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		
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
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																	

Table 5–1: 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 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	
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; 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 NailPsoriasis 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

Table 5–1: 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		

[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 (Section 9.8).
[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.
[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 as defined in Section 5.1.4 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.

Table 5–1: Schedule of assessments

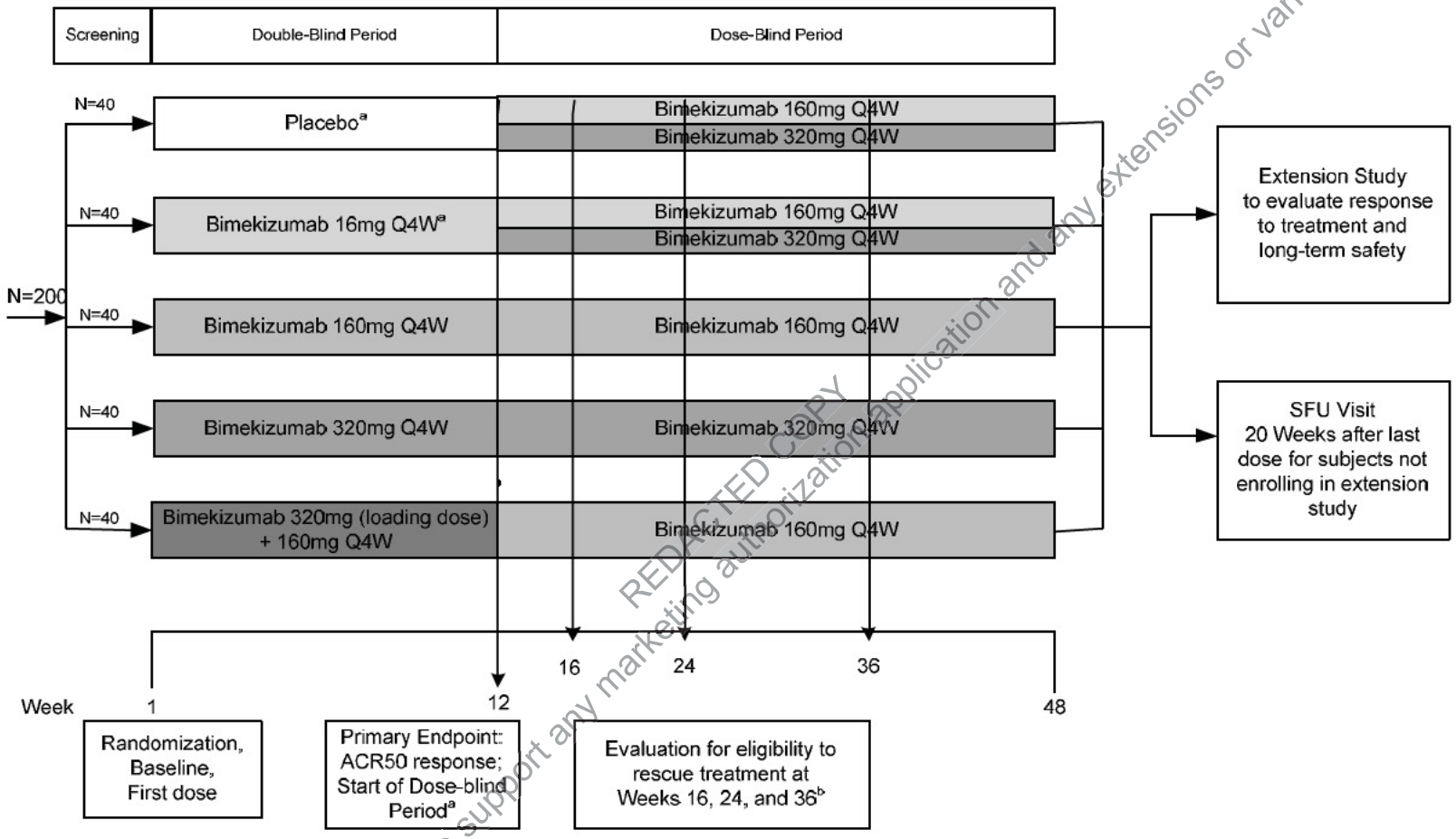
Protocol activity / Visit[a] / Week	Screening (V1) (14-28 days)	Baseline (Day 1, V2) (first dose)	Double-Blind Period (weeks after first dose)					Dose-Blind Period (weeks after first dose)								ET	SFU[b]
			3/ 1	4/ 2	5/ 4	6/ 8	7/ 12	8/ 16	9/ 20	10/ 24	11/ 28	12/ 32	13/ 36	14/ 40	15/ 44	16/ 48		

[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, as detailed in Section 5.1.3.

5.3 Schematic diagram

The study schematic diagram for PA0008 is presented in Figure 5–1.

Figure 5–1: Schematic diagram



ACR50=American College of Rheumatology 50% response criteria; Q4W=every 4 weeks; SFU=Safety Follow-up; SOC=standard of care

[a] After 12 weeks of double-blind treatment, subjects randomized to placebo and bimekizumab 16mg dose will be rerandomized to receive either bimekizumab 160mg or bimekizumab 320mg. Subjects randomized to bimekizumab 160mg or bimekizumab 320mg will continue to receive their originally randomized dose and subjects randomized to the bimekizumab 320mg (loading dose) +160mg treatment arm will continue to receive the bimekizumab 160mg dose (Section 5.1.3).

[b] 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 as defined in Section 5.1.4 will be eligible to receive rescue therapy.

5.4 Rationale for study design and selection of dose

The following doses of bimekizumab are proposed in the Phase 2b study: 16mg, 160mg, and 320mg administered sc Q4W, as well as another dosing arm in which bimekizumab 320mg loading dose will be administered sc at Week 1 followed by bimekizumab 160mg Q4W. The proposed dose range has been selected considering the predicted therapeutic dose range of bimekizumab in PsA based on the available clinical data. The clinical data generated for bimekizumab to date were used to define the exposure:response relationship between the plasma concentration of bimekizumab and ACR and PASI response (REP-1-UCB-4940-PMX-1).

Simulations were performed using the model to predict the dose response of ACR50 and PASI90 responder rates at Week 12 and indicated that increasing doses above 320mg may not provide additional benefit in terms of efficacy in either ACR50 or PASI90 responder rates. Therefore, bimekizumab 320mg has been selected as the maximum dose in the current study. Two dose levels below bimekizumab 320mg were selected to characterize the dose-exposure response curve at the end of current study. The lowest dose level of bimekizumab 16mg Q4W was selected because this dose is expected to provide an ACR50 responder rate close to the placebo, while still delivering some benefit to patients. The bimekizumab 160mg Q4W was selected in order to precisely characterize the dose-exposure response curves.

The rationale for the additional arm with the bimekizumab 320mg loading dose is as follows: the model was used to simulate the effect of loading dose on maximum response or time to maximum response, which indicated that loading dose had minimal benefit on the onset of action or maximum ACR50 response. This inclusion of a fourth arm in which bimekizumab 320mg will be administered at Baseline/Day 1 followed by 160mg Q4W allows a direct comparison with the 160mg unit dose arm to see the effect of loading dose on maximum response as well as time to maximum response.

Doses greater than 320mg have previously been studied in the development of bimekizumab. In the single ascending dose study UP0008, a single dose of bimekizumab 640mg was tested. In the multiple dose study PA0007, a bimekizumab 560mg loading dose followed by 2 subsequent 320mg doses every 3 weeks was tested. At exposure levels achieved at these doses, the compound had no significant safety concerns. In the previous clinical studies, bimekizumab was administered iv and the current study proposes to administer the compound sc. Due to lower bioavailability of sc administration, bimekizumab exposure is expected to be lower with sc administration compared with iv administration , therefore, the dose regimens are expected to be safe.

The proposed doses will provide adequate information to study the dose-exposure response of bimekizumab in PsA. This information will be used to determine the right dose and dosage regimen for future studies of bimekizumab in this indication.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met:

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject or legal representative.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or medication intake according to the judgment of the Investigator.
3. Subject is (male or female), at least 18 years of age.
4. **Female** subjects must be postmenopausal (at least 1 year; to be confirmed hormonally as part of the screening process, if less than 2 years since last menstrual period), permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) or, if of childbearing potential (and engaged in sexual activity that could result in procreation), must be willing to use a highly effective method of contraception up till 20 weeks after last administration of IMP, and have a negative pregnancy test at Visit 1 (Screening) and immediately prior to first dose. The following methods are considered highly effective when used consistently and correctly.
   - combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
   - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomized partner
   - sexual abstinence if it is in accordance with a subject's preferred and common lifestyle. Subjects who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse until 20 weeks after the last dose of IMP. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.

   Male subjects with a partner of childbearing potential must be willing to use a condom when sexually active, up till 20 weeks after the last administration of IMP (anticipated 5 half-lives).
5. Subject has a documented diagnosis of adult-onset PsA classified by CASPAR criteria (Table 19–1), with symptoms for at least 6 months prior to Screening, with active PsA at Baseline/Day 1, 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).
6. Subject must be rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies negative.
8. Subject must have active psoriatic lesion(s) and/or a documented history of PSO.

9. Subjects who are regularly taking NSAIDs/COX-2 inhibitors as part of their PsA therapy are required to be on a stable dose/dose regimen for at least 14 days before Baseline and should remain on a stable dose through the Week 16 visit.
10. Subjects taking corticosteroids must be on an average daily dose of ≤10mg/day prednisone or equivalent for at least 14 days before Baseline and should remain on a stable dose through the Week 16 visit.
11. Subjects taking MTX (≤25mg /week) are allowed to continue their medication if started at least 12 weeks prior to Baseline, with a stable dose for at least 8 weeks before randomization. Dose, dosing schedule and route of administration (oral or sc) should remain stable up to Week 16 visit. It is strongly recommended that subjects taking MTX are also taking folic acid supplementation.
12. Subjects taking LEF (≤20mg/day or an average of 20mg/day if not dosed daily) are allowed to continue their medication if started at least 3 months prior to Baseline, with a stable dose for at least 8 weeks before randomization. Dose and dosing schedule should remain stable up to Week 16.
13. 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

6.2 Exclusion criteria

Subjects are not permitted to enroll in the study if any of the following criteria is met:

1. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 20 weeks following last dose of IMP. Male subjects who are planning a partner pregnancy during the study or within 20 weeks following the last dose.
2. Subjects previously participating in a bimekizumab clinical trial and receiving at least 1 dose of IMP.
3. Subjects participating in another study of a medication or a medical device under investigation within the last 3 months or at least 5 half-lives, whichever is greater.
4. Subjects with a known hypersensitivity to any excipients of bimekizumab.
5. Subjects with use of any medication listed in Table 7-1 and Table 7-2 meeting the exclusionary criteria for the specific medication(s) including wash-out described in the table.
6. Subject has any current sign or symptom that may indicate an active infection (except for the common cold) or has had an infection requiring systemic antibiotics within 2 weeks of Baseline.

7. Subjects with a history of chronic or recurrent infections, or a serious or life-threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster). Subjects with a high risk of infection in the Investigator's opinion (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, subjects who are permanently bedridden or wheelchair assisted, prior prosthetic joint infection at any time, or subjects who are permanently bedridden or wheelchair assisted, etc).
8. Subjects with concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Subjects who have evidence of, or tested positive for hepatitis B or hepatitis C are excluded.

   A positive test for the hepatitis B virus (HBV) is defined as:

   - positive for hepatitis B surface antigen (HbsAg+); or,
   - positive for anti hepatitis B core antibody (HbcAb+)

   A positive test for the hepatitis C virus (HCV) is defined as:

   - positive for hepatitis C antibody (anti-HCV Ab), and
   - positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction)
9. Subjects with known history of or current clinically active infection with Histoplasma, Coccidioides, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus or current active Candidiasis (local or systemic).
10. Subjects receiving any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted). Live vaccines are not allowed during the study or for 20 weeks after the last dose of IMP.

    Live vaccines include, but are not limited to the following:

    – Anthrax vaccine
    – Intranasal influenza vaccine
    – Measles-mumps-rubella (MMR) vaccine
    – Polio live oral vaccine (OPV)
    – Smallpox vaccine
    – Tuberculosis BCG vaccine
    – Typhoid live oral vaccine
    – Varicella vaccine
    – Yellow fever vaccine
11. Subjects receiving Bacillus Calmette-Guerin (BCG) vaccinations within 1 year prior to IMP administration.
12. Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.

13. Subjects with primary immunosuppressive conditions, including subjects who are taking immunosuppressive therapy following organ transplants.
14. Subjects with known TB infection, at high risk of acquiring TB infection, with latent TB infection (LTBI)*, or current or history of NTMB infection (refer to Section 12.6.5 for details on determining full TB exclusion criteria).
    *Subjects with LTBI may enter the study only after they have completed at least 8 weeks of appropriate prophylactic therapy and thereafter, will continue and complete the entire regimen.
15. Subjects who have had a splenectomy.
16. Subjects with concurrent malignancy or a history of malignancy (including surgically resected uterine/cervical carcinoma-in-situ) during the past 5 years will be excluded, with the following exceptions that may be included:
    a) ≤3 excised or ablated, basal cell carcinomas of the skin
    b) One squamous cell carcinoma of the skin (stage T1 maximum) successfully excised, or ablated only (other treatments, ie, chemotherapy, do not apply), with no signs of recurrence or metastases for more than 2 years prior to Screening
    c) Actinic keratosis (-es)
    d) Squamous cell carcinoma-in-situ of the skin successfully excised, or ablated, more than 6 months prior to Screening
17. Subjects having had major surgery (including joint surgery) within the 6 months prior to Screening, or planned surgery within 6 months after entering the study.
18. Subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac (eg, congestive heart failure, New York Heart Association [NYHA] Grade 3 and 4), gastrointestinal (GI) (note: subjects with active peptic ulcer disease are excluded; subjects with a history of peptic ulcer disease are allowed), or neurological disease.
19. Subjects with a history of uncompensated heart failure, fluid overload, or myocardial infarction, or evidence of new-onset ischemic heart disease or in the opinion of the Investigator other serious cardiac disease, within 12 weeks prior to baseline.
20. Subjects with clinically significant laboratory abnormalities (eg, glomerular filtration rate [GFR] <60 ml/min/1.73m^2, neutropenia <1.5x10^9/L, hemoglobin <8.5g/dL, lymphocytes <1.0 x10^9/L, platelets <100 x10^9/L). Individual screening tests for which the results are in error, borderline, or indeterminate for inclusion in the study, can be repeated once for confirmation during the Screening period if they are within 25% of the exclusion limit. Upon retesting, subjects whose results remain outside this threshold should not be randomized.

21. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)*, or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    *An isolated elevation between 2xULN and <3xULN of ALP is acceptable in the absence of an identified exclusionary medical condition.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation during the screening period. Upon retesting, subjects whose ALT, AST, or ALP remain above the thresholds defined above, should not be randomized.

    For randomized subjects with a baseline result >ULN for ALT, AST, ALP, or total bilirubin, a baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the Case Report form (CRF).

    If subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.

22. Subjects with any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.
23. Subjects with erythrodermic, guttate, pustular form of PSO or drug-induced PSO.
24. Subjects with a diagnosis of inflammatory conditions other than psoriasis or psoriatic arthritis, including but not limited to rheumatoid arthritis, sarcoidosis, ankylosing spondylitis, or systemic lupus erythematosus. Subjects with a diagnosis of Crohn's disease or ulcerative colitis are allowed provided they have no active and/or symptomatic disease at Screening and Baseline.
25. Subjects with fibromyalgia or osteoarthritis symptoms that in the Investigator's opinion would have potential to interfere with efficacy assessments.
26. Subjects with a diagnosis of arthritis mutilans.
27. Subjects taking PsA medications other than MTX, LEF, NSAIDs/COX-2 inhibitors, and corticosteroids as outlined in the Inclusion criteria (Section 6.1). Stable doses/regimens of analgesics are also permitted.
28. Subject has a history of chronic alcohol or drug abuse within the previous year.
29. Subject has 12-lead ECG with changes considered to be clinically significant upon medical review by the Investigator or designee.

30. Subject has presence of significant uncontrolled neuropsychiatric disorder, active suicidal ideation, or positive suicide behavior using the "Baseline" version of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) and the Hospital Anxiety and Depression Scale (HADS) with either of the following criteria:
    - Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening/Baseline" version of the eC-SSRS at screening.
    - HADS Depression (HADS-D) Score >10 or Anxiety (HADS-A) score ≥15.
31. Subject is Investigator site personnel directly affiliated with this study and/or immediate families of Investigator site personnel. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
32. Subject is a UCB employee or is an employee of third-party organizations involved in the study.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care.

Subjects should be withdrawn from the study if any of the following events occur:

1. Subject withdraws his/her consent.
2. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
3. The Sponsor or a regulatory agency requests withdrawal of the subject.

Subjects withdrawn from study treatment:

Subjects should be withdrawn from all study treatment if any of the following events occur:

4. Subject develops an illness that in the opinion of the Investigator would interfere with his/her continued participation, if the risk of continuing participation outweighs the potential benefit.
5. Subject considered as having either a suspected new LTBI or who develop active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by interferon-gamma release assay [IGRA] or other diagnostic means) must be immediately discontinued from study medication, and an unscheduled visit must be conducted as soon as possible, but not later than the next regular visit.

    The subject must be permanently withdrawn if further examinations result in a diagnosis of active TB, or if the subject is diagnosed with LTBI with no initiation of prophylactic treatment, prematurely discontinues prophylactic treatment, or, in the opinion of the Investigator or Sponsor, is noncompliant with prophylactic TB therapy.

    Confirmed active TB is a SAE and must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves. Additional information on TB policies is provided in Section 12.6.5.

6. Subject is noncompliant with the study procedures or medications, which may present a risk to the safety of the subject, in the opinion of the Investigator.
7. Subject uses prohibited concomitant medications, as defined in this protocol (Section 7.8.2), that may present a risk to the safety of the subject in the opinion of the Investigator and the Medical Monitor. This includes subjects who start a biologic other than bimekizumab as described in Section 5.1.4.
8. Subject develops laboratory abnormalities (with or without clinical symptoms) of ALT or AST as defined in Section 6.3.1; neutropenia $<0.5x10^9$/L; or lymphopenia $<0.5x10^9$/L. Any laboratory value or change judged to be clinically significant by the Investigator should prompt consideration of whether the subject should continue on IMP. For clarification, laboratory values that are markedly abnormal as per Table 19-2 and Table 19–3 will be flagged to the Investigator and to the medical monitor but do not trigger mandatory withdrawal unless listed above. (Refer to Section 6.3.1 for withdrawal criteria in relation to potential drug-induced liver injury [PDILI].)
9. Subject has active suicidal ideation as indicated by a positive response ("Yes") to Questions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated eC-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
10. Subjects with a HADS-D score ≥15 must be withdrawn. Any subject who develops a HADS-D score of >10 during the study should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.
11. Subjects with newly diagnosed inflammatory bowel disease (IBD) or with IBD flares during the study must:
    - Be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist
    - Discontinue IMP and be followed-up until resolution of active IBD symptoms

If IBD flares increase in severity or frequency during the study, the Investigator should use clinical judgment in deciding whether the subject should continue in the study and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.

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 (NRC, 2010). If a subject withdraws from study treatment for any of the above criteria (#4 through #10) prior to Week 12, they will be asked to return for the study assessments 12 weeks after the first dose (ie, Week 12 Visit) and for the SFU Visit (20 weeks after last dose administration). These data will be used in a sensitivity analysis which is described in Section 15.7. If any of these criteria occur after Week 12, subjects will complete an ET Visit and the SFU Visit. All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable. All subjects who withdraw from the study due to development of a laboratory abnormality specified in Criterion #8 must be closely monitored, with additional monitoring of hepatic markers every week or every 2 weeks until resolution of the event, the event is considered stable, or they have reached the end of the SFU Period for those who at any time have an ALT and/or AST >5X but <8X ULN.

Investigators should attempt to obtain information on subjects in the case of withdrawal or discontinuation. For subjects considered as lost to follow-up, the Investigator should make an effort (at least 1 phone call and 1 written message to the subject), and document his/her effort (date and summary of the phone call and copy of the written message in the source documents), to complete the final evaluation. All results of these evaluations and observations, together with a narrative description of the reason(s) for removing the subject, must be recorded in the source documents. The electronic Case Report Form (eCRF) must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor, whenever possible, to discuss the withdrawal of a subject in advance.

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with potential drug-induced liver injury (PDILI) must be assessed to determine if IMP must be discontinued. In addition, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued.

The PDILI criteria below require immediate and permanent discontinuation of IMP:

- Subjects with either of the following:
  - ALT or AST ≥5xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN
  - Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

The PDILI criterion below allows for subjects to continue on IMP at the discretion of the Investigator.

- Subjects with ALT or AST ≥3xULN (and ≥2x Baseline) and <5xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 12.5.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on subjects in the case of IMP discontinuation to complete the final evaluation. Subjects with PDILI should not be withdrawn from the study until investigation and monitoring are complete. All results of these evaluations and observations, as well as the reason(s) for IMP discontinuation and subject withdrawal (if applicable), must be recorded in the source documents. The CRF must document the primary reason for IMP discontinuation.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

The IMPs used in this study are bimekizumab and placebo.

Bimekizumab will be supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative‑free solution in 2mL Type I, colorless glass vials (1.0mL extractable volume)

closed with a rubber stopper and sealed with an aluminum cap overseal. [redacted]

Placebo will be supplied as 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (United States Pharmacopoeia/European Pharmacopoeia) quality appropriate for injection.

Further details of the study medications and their specifications are provided in the Investigational Medicinal Product Handling Manual.

7.2 Treatments to be administered

The IMP is to be administered in the clinic by study site staff as 2 sc injections. Suitable areas for sc injections are the lateral abdominal wall and upper outer thigh. During each dosing visit, each of the 2 injections should be administered at a separate injection site. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard.

Study medication (bimekizumab and placebo) will be administered at the times indicated in Table 5–1. 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.

An IMP Handling Manual will be provided to each site containing instructions regarding drug preparation and dosing.

7.3 Packaging

The IMPs are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations. Investigational medicinal products will be suitably packaged in such a way as to protect the IMPs from deterioration during transport and storage.

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP) and Good Manufacturing Practice and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

Investigational Medicinal Product must be stored under refrigerated conditions (2ºC to 8ºC) protected from light. The IMP must not be frozen.

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access.

Appropriate storage conditions must be ensured either by controlled room temperature or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing minimum and maximum temperatures reached over the time interval.

In case an out-of-range temperature is noted, it must be immediately communicated to the Clinical Project Manager (CPM) (or designee) before further use of the IMP.

Investigational medicinal product will be shipped to the study sites in temperature controlled containers. Out-of-range shipping or storage conditions must be brought to the attention of the Sponsor or designee, immediately. Authorization to use any out-of-range IMP must be documented and received prior to dispensing or administering the IMP at the study site.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost (due to breakage or wastage), not used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

In order to maintain the blind, all IMP documentation (eg, shipping receipts, drug accountability logs, interactive voice or web response system (IXRS) randomization materials) must be maintained and accessed by unblinded, trained site personnel only. Designated, unblinded site personnel must be appropriately trained and licensed (per country guidelines) to administer injections.

The packaging identifies each kit by a unique number that does not correlate to the contents and therefore, does not unblind study site staff. Unblinded study staff will be responsible for preparation (breaking tamper proof sticker on kit, etc) of the clinical trial material, including recording the administration information in the source document.

The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

The Investigator may assign some of the Investigator's duties for drug accountability at the study site to an appropriate pharmacist/designee.

The Investigator must ensure that the IMP is used only in accordance with the protocol.

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers) and unused IMP containers must be reconciled and returned to UCB (or designee), preferably in their original package. Onsite destruction of used kits only may be allowed with prior approval from the Sponsor or designee after reconciliation. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

During the Double-Blind and Dose-Blind Periods, IMP will be administered in the clinic and compliance will be determined at the visit by study personnel. Drug accountability must be recorded on the Drug Accountability Form.

7.8 Concomitant medication(s)/treatment(s)

All concomitant medications, including over-the-counter products, herbal, traditional remedies, vitamin/mineral supplements, other dietary supplements, "nutraceuticals," and hormones must be recorded in the subject's source documentation (eg, clinical chart) and in the electronic eCRF. This record should include the name of the drug, the dose, the route and date(s) of administration, and the indication for use.

7.8.1 Permitted concomitant treatments (medications and therapies)

No medication increases or additions are permitted for medications taken for PsA until after the Week 16 visit assessments. However, a decrease in dose or dosing frequency of any agent is permitted for reasons of intolerance/AEs/side-effects at any time.

At Week 16, Week 24, and Week 36 of the Dose-blind Period, subjects will be evaluated for their response to treatment to determine eligibility for rescue therapy.

Subjects who have shown <10% improvement from Baseline in TJC and SJC will be eligible for rescue therapy. Rescue therapy for eligible subjects will be at the Investigator's discretion, with the following options:

- Nonsteroidal anti-inflammatory drugs, DMARDs (MTX, sulfasalazine, LEF, apremilast), and/or joint injections may be given as rescue therapy if deemed appropriate by the Investigator as outlined below. Subjects may receive these add-on therapies while continuing to receive their randomized dose of bimekizumab.
  - For subjects taking NSAID/COX-2 inhibitors at Baseline or at Week 16, Week 24, or Week 36, a change can be made to a different NSAID/COX-2. Changes from an NSAID to a COX-2 or from a COX-2 to an NSAID are permitted up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 may be taken at a given time.
  - For subjects not taking NSAID/COX-2 inhibitors at Baseline, Week 16, Week 24, or Week 36, either a NSAID or COX-2 inhibitor can be initiated, up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 may be taken at a given time.
  - Methotrexate may be added or increased to a maximum dose of 25mg/week, or the maximum tolerated dose, whichever is lower. The route of administration may be changed from oral to sc.
  - Sulfasalazine may be given up to a maximum dose of 3g/day, or the maximum tolerated dose, whichever is lower.
  - Leflunomide may be given at a maximum dose of 20mg/day (or an average of 20mg/day if not dosed daily), or the maximum tolerated dose, whichever is lower.
  - Apremilast may be given at a maximum dose of 30mg twice daily, or the maximum tolerated dose, whichever is lower.
  - Combination DMARDs are allowed except that LEF and MTX may not be given together.
  - One joint may be injected at or after the Week 16, Week 24, and Week 36 Visit; however, the same joint should not be injected more than once during the study.

Subjects are allowed to use acetaminophen/paracetamol and mild opioids as needed.

Subjects who are already receiving an established antidepressant regimen should be on a stable dose of the antidepressant for 12 weeks prior to Baseline.

Psoriasis treatments

For treatment of PSO, subjects may continue to use topical moisturizers, emollients, salicylic acid preparations, bath oils, and oatmeal bath preparations for skin conditions during the study, as needed. Over-the-counter shampoos for the treatment of PSO of the scalp are also permitted. Additionally, mild topical steroids are permitted for use limited to the face, axillae, and/or genitalia, as needed. Subjects who use prohibited topical medications will be allowed to stay in the study but will counseled to not use them further. No other topical preparations are allowed in the 2 weeks prior to randomization or during the study unless medically required to treat an AE. See Table 7-2 for prohibited PSO medications.

After the Week 16 Visit, the addition of topical retinoids, vitamin D analogues, coal tar preparations, and more potent topical steroids may be used as medically required to treat a flare, but are not permitted to be used within 24 hours prior to a study visit. Use of psoralen and ultraviolet A light (PUVA/UVA) therapy for the treatment of PSO is not permitted for the first 16 weeks of the study and is discouraged through the duration of the study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Prohibited and/or restricted medications are summarized in Table 7-1 and Table 7-2.

Table 7-1 Prohibited or restricted medications and required wash-out periods prior to Baseline

Drug class	Dose	Exclusion criteria
Analgesics, including opioid analgesics, acetaminophen/paracetamol, etc	Any dose	Any ad hoc use in the 24 hours prior to any Study Visit. Stable doses of analgesics permitted.
NSAIDs/COX-2 inhibitors	Any dose regimen	Any change in dose/dose regimen in the 14 days prior to the Baseline Visit.
Oral corticosteroids	Any dose regimen	Any change in dose/dose regimen in the 28 days prior to the Baseline Visit.
Intramuscular/intravenous /intra-articular corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit.
Intra-articular hyaluronic acid	Any dose	Use in the 6 months prior to the Baseline Visit.
DMARDs: -hydroxychloroquine, -azathioprine, -cyclosporine, -cyclophosphamide, -mycophenolic acid -mycophenolate mofetil -sulfasalazine (SSZ)[a] -any other small molecule DMARDs (eg, tofacitinib, apremilast[a])	Any dose	Use within 12 weeks prior to the Baseline Visit.
-methotrexate (MTX)	Any dose regimen	Use within 12 weeks prior to the Baseline Visit unless Inclusion Criterion #11 is met.

Table 7-1 Prohibited or restricted medications and required wash-out periods prior to Baseline

Drug class	Dose	Exclusion criteria
-leflunomide (LEF)	Any dose	Use in the 6 months prior to the Baseline Visit, unless (1) a cholestyramine washout has been performed, in which case, use up to 28 days prior to the Baseline Visit is acceptable, or (2) Inclusion Criterion #12 is met.
TNF inhibitor[b]: -infliximab (IFX) -adalimumab (ADA) -etanercept (ETN) -golimumab (GOL) -certolizumab pegol (CZP)	Any dose	For IFX, ADA, GOL, and CZP any use within the 3 months prior to the Baseline Visit. For ETN, use within the 28 days prior to the Baseline Visit. This applies to biosimilar versions of any TNF inhibitor
Any non-TNF biologic medications	Any dose	Any exposure history.

ADA=adalimumab; COX-2=cyclooxygenase-2; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; IFX=infliximab; LEF=leflunomide; MTX=methotrexate; SSZ=sulfasalazine; TNF=tumor necrosis factor

[a] SSZ and apremilast are permitted as per Rescue Therapy (Section 5.1.4)

[b] Subjects must not have been exposed to more than 1 TNF inhibitor prior to the Baseline Visit.

Table 7-2 Additional prohibited psoriasis treatments

Drug class	Dose	Exclusion criteria
Phototherapy	Any dose	Use within the 28 days prior to the Baseline Visit.
Topical corticosteroids for dermatological use except as detailed in Section 7.8.1, vitamin D analogues, topical retinoids, keratolytics, coal tar, and fumaric acid esters	Any dose	Use within 14 days prior to the Baseline Visit.
Systemic retinoids	Any dose	Use within 3 months prior to the Baseline Visit

7.9 Blinding

Due to differences in presentation of the IMPs (bimekizumab and placebo), special precautions will be taken to ensure study blinding and study sites will have blinded and unblinded personnel.

Bimekizumab and placebo injections will be prepared and administered at the investigational sites by unblinded, dedicated study personnel according to Table 7–3. The unblinded personnel will not be involved in the study in any way other than assuring the medication is taken from the correct kit and prepared according to the pharmacy manual instructions and administering the drug to the subjects. Preparation will be made from either vials (bimekizumab) or Ampoule (placebo) and will be in identical syringe and needle for all arms of the study. Provisions will be

made to ensure that volume of injection is not revealed to the subject. The number of injections will be kept identical for all patients by adding placebo injection when the bimekizumab dose requires only 1 injection.

Table 7–3: Preparation of placebo and bimekizumab injections

Treatment Arm	Number/volume Placebo injections	Number/volume bimekizumab injections
Placebo	2 x 1.0mL	0
Bimekizumab 16mg	1 x 0.1mL	1 x 0.1mL
Bimekizumab 160mg	1 x 1.0mL	1 x 1.0mL
Bimekizumab 320mg	0	2 x 1.0mL

Study sites will be required to have a written blinding plan in place, signed by the Principal Investigator, which will detail the site's steps for ensuring that the double-blind nature of the study is maintained.

During the study the Sponsor will provide blinded and unblinded site monitors for the purposes of verifying safety, efficacy and drug administration and documentation records. Blinded study monitors and study site personnel, blinded to treatment assignment, will not discuss or have access to any drug related information.

Bioanalytical staff analyzing blood samples for bimekizumab and anti-bimekizumab antibody detection will be unblinded.

Further details are provided in the study manuals and site blinding plan.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

All subject treatment details (bimekizumab or placebo) will be allocated and maintained by the interactive web response system (IXRS).

7.9.1.2 Breaking the treatment blind in an emergency situation

The integrity of this clinical study must be maintained by observing the treatment blind. In the event of an emergency for which the appropriate treatment for a subject cannot be made without knowing the treatment assignment, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IXRS. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

The CPM will be informed immediately via the IXRS when a code is broken, but will remain blinded to specific treatment information. Any unblinding of the IMP performed by the Investigator must be recorded in the source documents and on the Study Termination eCRF page.

7.10 Randomization and numbering of subjects

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by the Sponsor. The randomization schedule will be produced by an independent biostatistician with the Contract

Research Organization (CRO) who is otherwise not involved in this study. Subject treatment assignment will be stratified by region and prior TNF inhibitor exposure (yes/no). The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Enrollment of TNF inhibitor experienced subjects will be limited to 30% of the total study population.

At Screening, each subject will be assigned a 5 digit number that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IXRS regarding a particular subject.

At the Baseline Visit (Day 1), a subject will be randomized into the study. The Investigator or designee will use the IXRS for randomization. The IXRS will automatically inform the Investigator or designee of the subject's identification number. The IXRS will allocate kit numbers to the subject based on the subject number during the course of the study.

Subject numbers and kit numbers will be tracked via the IXRS.

8 STUDY PROCEDURES BY VISIT

The Schedule of Study Assessments (Table 5–1) provides a general overview of study assessments. A list of procedures to be completed at each visit is described below.

Visit windows are +/-3 days from Baseline (Day1, first dose of IMP) at all visits through the Week 12 Visit and +/-4 days for all visits after Week 12 except the SFU Visit. For the SFU Visit (20 weeks after the last dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days). 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. Changes to the dosing schedule outside of the allowed windows must be discussed with the Medical Monitor and may result in subject withdrawal.

8.1 Screening

The Screening Period will last 14 to 28 days.

Prior to any study specific activities, subjects will be asked to read, sign, and date an ICF that has been approved by the Sponsor and an IEC/IRB, and that complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent procedure, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Subjects will also be given the option to participate in the genomic, genetic/epigenetic, and proteomic substudy. Subjects who decide to participate in the substudy will need to complete a separate ICF following the same procedure and given the same considerations as the main ICF. Their willingness to participate in the substudy will be independent from their consent to participate in the main study.

The following procedures or assessments will be performed at the Screening Visit:

- Obtain written informed consent for main study.
- Determine subject's interest in participation in genomic, genetic/epigenetic, and proteomic substudy. Obtain written informed consent for this, if subject wishes to partipate.

- Collect demographic data.
- Collect PsA history.
- Collect significant past medical history and concomitant diseases.
- Assess inclusion and no exclusion criteria.
- Record prior medications.
- Record concomitant medications.
- eC-SSRS
- HADS
- Administer the tuberculosis questionnaire.
- Measure height.
- Measure temperature, pulse and blood pressure.
- Measure weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB.
- Perform TJC/SJC.
- Perform an ECG.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- Perform a serum pregnancy test if the subject is a woman of childbearing. This requirement 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).
- Collect samples for Hepatitis B and C tests.
- Collect samples for an HIV test.
- Collect sample for rheumatoid factor (RF) test.
- Collect sample for anti-CCP antibody test
- Perform an IGRA tuberculosis test.
- Obtain a chest radiograph, unless one has been obtained 3 months prior to the Screening Visit.
- Obtain radiographs of the hand and/or foot, unless 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.

- Register the subject using IXRS.

8.2 Baseline (Day 1)

The following procedures of assessments will be completed prior to administration of IMP:

- Review significant past medical history and concomitant diseases to ensure there are no significant changes in medical history that would exclude the subject based on the exclusion criteria.
- Confirm that the subject meets all inclusion and no exclusion criteria.
- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Administer the tuberculosis questionnaire.
- Measure temperature, pulse, and BP.
- Measure weight.
- Perform TJC/SJC.
- Determine BSA affected by PSO using the BSA palm method.
- If the BSA affected by PSO is ≥3%, determine the PASI.
- Determine the mNAPSI
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP and CRP.

- Perform a urine pregnancy test if the subject is a woman of childbearing potential. This requirement 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.
- Collect blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect blood samples for cytokines, complement, and biomarker analyses.
- If subject provides consent (separate from the consent for the main study):
  - Collect blood samples for genomic and proteomic/metabolomic analyses.
  - Collect blood samples for genetics/epigenetics analysis.
- For participating centers, collect blood sample for flow cytometry.
- Randomize the subject using the IXRS.
- Administer IMP (bimekizumab or placebo).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP at 30 minutes and 1 hour after dosing.

8.3 Double-Blind Period (Week 1 to Week 12)

8.3.1 Week 1 (+/-3 days)

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- Determine the BASDAI.
- Administer the PGADA.
- Administer the PtAAP.
- Measure temperature, pulse, and BP.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- If there has been a delay in menses, perform a urine pregnancy test.
- Collect blood sample for bimekizumab plasma concentrations.
- Collect blood samples for cytokines, complement, and biomarker analyses.
- For consenting subjects:
  - Collect blood samples for genomic, proteomic/metabolomic analyses.
  - Collect blood sample for genetic/epigenetic analysis.
- For participating centers, collect blood sample for flow cytometry.

- Record visit in the IXRS.

8.3.2 Week 2 (+/-3 days)

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the PGADA.
- Administer the PtAAP.
- Measure temperature, pulse, and BP.
- Perform TJC/SJC.
- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- If there has been a delay in menses, perform a urine pregnancy test.
- Collect blood sample for bimekizumab plasma concentrations.
- Record visit in the IXRS.

8.3.3 Week 4 (+/-3 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.

- Measure temperature, pulse, and BP.
- Perform TJC/SJC.
- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP and CRP.
- If there has been a delay in menses, perform a urine pregnancy test.
- Collect blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect blood samples for cytokines, complement, and biomarker analyses.
- For consenting subjects, collect blood samples for genomic, and proteomic/metabolomic analyses.
- For participating centers, collect blood sample for flow cytometry.
- Record visit in the IXRS.
- Administer IMP (bimekizumab or placebo).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.3.4 Week 8 (+/-3 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Measure temperature, pulse, and BP.
- Perform TJC/SJC.

- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the MASES.
- Administer the LDI.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- If there has been a delay in menses, perform a urine pregnancy test.
- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Record visit in the IXRS.
- Administer IMP (bimekizumab or placebo).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.3.5 Week 12 (+/-3 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Administer the tuberculosis questionnaire.
- Measure temperature, pulse, and BP.
- Measure weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB.
- Perform TJC/SJC.
- Determine BSA affected by PSO using the BSA palm method.

- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the mNAPSI.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Perform an ECG.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP and CRP.
- If there has been a delay in menses, perform a urine pregnancy test.
- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect blood samples for cytokines, complement, and biomarker analyses.
- For consenting subjects:
  - Collect blood samples for genomic and proteomic/metabolomics analyses.
  - Collect blood sample for genetic/epigenetic analysis.
- For participating centers, collect blood sample for flow cytometry.
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4 Dose-Blind Period (Week 16 to Week 48)

8.4.1 Week 16 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.

- Administer the PtAAP.
- Administer the PsAID-9.
- Measure temperature, pulse, and BP.
- Perform TJC/SJC.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- If there has been a delay in menses, perform a urine pregnancy test.
- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Evaluation for rescue treatment eligibility (Section 5.1.4)
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.2 Week 20 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the HAQ-DI.
- Administer the PGADA.
- Administer the PtAAP.
- Measure temperature, pulse, and BP.
- Perform TJC/SJC.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- If there has been a delay in menses, perform a urine pregnancy test.

- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.3 Week 24 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Administer the tuberculosis questionnaire.
- Measure temperature, pulse, and BP.
- Measure weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB.
- Perform TJC/SJC.
- Determine BSA affected by PSO using the BSA palm method.
- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the mNAPSI.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP and CRP.

- If there has been a delay in menses, perform a urine pregnancy test.
- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect blood samples for cytokines, complement, and biomarker analyses.
- For consenting subjects:
  - Collect blood samples for genomic and proteomic/metabolomic analyses.
  - Collect blood sample for genetic/epigenetic analysis.
- For participating centers, collect blood sample for flow cytometry.
- Evaluation for rescue treatment eligibility (Section 5.1.4)
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.4 Week 28 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Measure temperature, pulse, and BP.
- Collect samples for hematology/biochemistry/urinalysis.
- If there has been a delay in menses, perform a urine pregnancy test.
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.5 Week 32 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Measure temperature, pulse, and BP.

- Collect samples for hematology/biochemistry/urinalysis.
- If there has been a delay in menses, perform a urine pregnancy test.
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.6 Week 36 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Administer the tuberculosis questionnaire.
- Measure temperature, pulse, and BP.
- Measure weight.
- Perform TJC/SJC.
- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the mNAPSI.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- If there has been a delay in menses, perform a urine pregnancy test.

- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Evaluation for rescue treatment eligibility (Section 5.1.4)
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.7 Week 40 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Measure temperature, pulse, and BP.
- Collect samples for hematology/biochemistry/urinalysis.
- If there has been a delay in menses, perform a urine pregnancy test.
- Record visit in the IXRS.
- Administer IMP (bimekizumab).

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.8 Week 44 (+/-4 days)

The following procedures of assessments will be completed prior to administration of IMP:

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Measure temperature, pulse, and BP.
- Collect samples for hematology/biochemistry/urinalysis.
- If there has been a delay in menses, perform a urine pregnancy test.
- Perform the IGRA tuberculosis test.
- Record visit in the IXRS.
- Administer IMP (bimekizumab). This is the last dose of IMP.

The following procedures of assessments will be completed following administration of IMP:

- Collect pulse and BP once after dosing.

8.4.9 Week 48 (+/-4 days)

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Administer the tuberculosis questionnaire.
- Measure temperature, pulse, and BP.
- Measure weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB.
- Perform TJC/SJC.
- Determine BSA affected by PSO using the BSA palm method.
- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the mNAPSI.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Perform an ECG.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- Perform a urine pregnancy test if the subject is a woman of childbearing. This requirement 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.

- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect blood samples for cytokines, complement, and biomarker analyses.
- For consenting subjects, collect blood samples for genomic and proteomic/metabolomic analyses.
- For participating centers, collect blood sample for flow cytometry.
- Record visit in the IXRS.

8.5 Early Termination Visit

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Administer the tuberculosis questionnaire.
- Measure temperature, pulse, and BP.
- Measure weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB.
- Perform TJC/SJC.
- Determine BSA affected by PSO using the BSA palm method.
- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the mNAPSI.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Perform an ECG.
- Collect samples for hematology/biochemistry/urinalysis.

- Collect blood sample for hs-CRP.
- Perform a urine pregnancy test if the subject is a woman of childbearing. This requirement 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.
- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect blood samples for cytokines, complement, and biomarker analyses.
- For consenting subjects, collect blood samples for genomic and proteomic/metabolomic analyses.
- For participating centers, collect blood sample for flow cytometry.
- Perform an IGRA tuberculosis test.
- Record visit in the IXRS.
- If subject is a PDILI case that results in immediate, permanent IMP discontinuation, conduct a thorough evaluation as described in Section 12.5.1.

8.6 Safety Follow-Up Visit (20 weeks [-3 days/+7 days] after the final dose)

- Record concomitant medications.
- Record AEs.
- eC-SSRS
- HADS
- Administer the PsAQoL.
- Determine the BASDAI.
- Administer the HAQ-DI.
- Administer the SF-36.
- Administer the PGADA.
- Administer the PtAAP.
- Administer the PsAID-9.
- Administer the tuberculosis questionnaire.
- Measure temperature, pulse, and BP.
- Measure weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB.
- Perform TJC/SJC.

- Determine BSA affected by PSO using the BSA palm method.
- If the BSA affected by PSO was ≥3% at Baseline/Day 1, determine the PASI.
- Determine the MASES.
- Determine the LDI.
- Perform the PhGADA.
- Perform an ECG.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect blood sample for hs-CRP.
- Perform a urine pregnancy test if the subject is a woman of childbearing. This requirement 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.
- Collect a blood sample for bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Perform an IGRA tuberculosis test.
- Record visit in the IXRS.

8.7 Unscheduled Visit

At the Investigator's discretion, an Unscheduled Visit may be completed at any time during the study but prior to the SFU Visit, if deemed necessary for the subject's safety and well-being.

If an Unscheduled Visit is conducted due to safety or efficacy reasons, an eC-SSRS assessment will be performed with the subject during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of a laboratory specimen due to collection or analysis issues), an eC-SSRS will not be required at these visits.

At this visit, any of the following assessments may be performed, depending on the reason for the visit:

- Record concomitant medication
- Record AEs
- eC-SSRS
- Measure temperature, pulse, and BP.
- Physical examination
- Record 12-lead ECG

- If medically indicated, obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology, serum chemistry)
  - The blood sample may also be used for PK/PD assessments, if needed.
- Obtain urine sample for standard safety laboratory tests (including urine pregnancy test)

9 ASSESSMENT OF EFFICACY

The ACR50 response at Week 12 is the primary efficacy variable. In addition the ACR20 and ACR70 responses are secondary or other efficacy variables. Several assessments must be completed in order to determine the ACR response. These include the TJC and SJC based on 78 and 76 joints, respectively, PGADA, PhGADA, PtAAP, HAQ-DI, and CRP. The methods for the component measures will be described first, followed by ACR response and assessments used in secondary and other efficacy variables.

The timing for all assessments is specified in the Schedule of Assessments (Table 5–1).

9.1 TJC and SJC

9.1.1 78/76 joint evaluation for ACR response and verification of Inclusion Criterion 5

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 9-1 summarizes the swelling and tenderness grading criteria.

Table 9-1 Swelling and tenderness grading

[redacted]

9.1.2 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

9.2 Patient's Global Assessment of Disease Activity

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.

9.3 Physician's Global Assessment of Disease Activity

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 VAS 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".

This assessment by the Investigator should be made blind to the PGADA.

9.4 Patient's Assessment of Arthritis Pain

The Patient's Assessment of Arthritis Pain VAS or 'Pain 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".

9.5 Health Assessment Questionnaire-Disability Index score

The HAQ-DI contains 20 items divided into 8 domains that measure: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Subjects are required to indicate [redacted] on a 4-point scale that ranges from 0 (without difficulty) to 3 (unable to do). Any individual score of less than 2 is adjusted to 2 [redacted]. 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.

9.6 CRP levels (hs-CRP/CRP)

C-reactive protein (CRP) levels will be analyzed by the central laboratory.

High sensitivity-CRP is performed at Screening, Baseline, and all other study visits as marked with an X in the Schedule of Study Assessments (Table 5–1). 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.

9.7 ACR20, ACR50, and ACR70 response

The ACR20, ACR50, and ACR70 response rates are based on a 20%, 50%, and 70% or greater improvement relative to Baseline in the following measures:

- TJC based on 78 joints
- SJC based on 76 joints
- 3 of the 5 remaining core set measures:
  - PGADA
  - PhGADA
  - PtAAP
  - HAQ-DI
  - CRP

9.8 BSA-PSO

The BSA palm method will be used for the evaluation of BSA affected by PSO 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%

9.9 Psoriasis Area and Severity Index (PASI)

PASI will be assessed in all subjects with Baseline/Day 1 BSA affected by PSO ≥3% determined by the method described in Section 9.8 (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.

The percent area of involvement (BSA%) is estimated across 4 body areas; head, upper limbs, trunk, and lower limbs and then transferred into a grade (Table 9–2).

The Investigator assesses the average redness, thickness, and scaliness of lesions in each body area (each on a 5-point scale); 0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked.

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

Table 9–2: 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 PASI75, PASI90, and PASI100 responses are based on at least 75%, 90%, and 100% improvement in the PASI score. PASI will be assessed at Screening and at Baseline/Day 1. Thereafter PASI will be assessed for the purposes of determining response only in subjects with psoriasis involving at least 3% of body surface area at Baseline/Day 1.

9.10 MDA

Minimal Disease Activity is a state of disease activity deemed a useful target of treatment by both the patient and physician, given current treatment possibilities and limitations. Criteria shown in Table 9–3 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 9–3 are fulfilled:

Table 9–3: Minimal disease activity (MDA) criteria in psoriatic arthritis

A subject is classified as in MDA when they meet 5 of 7 of the following criteria:
Tender joint count ≤1
Swollen joint count ≤1
PASI ≤1 or BSA ≤3
Patient pain VAS ≤15
Patient global activity VAS ≤20
HAQ ≤0.5
Tender enthesial points ≤1

BSA=body surface area; HAQ=Health Assessment Questionnaire; MDA=minimal disease activity; PASI=Psoriasis Area and Severity Index; VAS=visual analog scale
Data sources: Mease, 2011; Coates et al, 2010

9.11 DAS28(CRP)

The components for DAS28(CRP) include the TJC and SJC based on 28 joints (Section 9.1.2), CRP (Section 9.6) and the PGADA (Section 9.2). DAS28(CRP) is calculated as follows:

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

9.12 BASDAI

The BASDAI is the most common instrument used to measure the disease activity of ankylosing spondylitis from the subject's perspective (Garrett et al, 1994) and is considered useful for evaluating axial involvement in subjects with PsA (Fernandez-Sueiro et al, 2009). The BASDAI is a validated self-reported instrument which consists of six 10 unit horizontal NRSs to measure [redacted] (van Tubergen et al, 2015). The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity.

The BASDAI is calculated as follows:

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

9.13 mNAPSI

Subjects with psoriatic nail disease will have a target nail selected at the Baseline visit for evaluation using the mNAPS). 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.

Data will be entered into the eCRF.

9.14 MASES

The MASES is an index that measures the severity (ie, intensity and extent) of enthesitis through the assessment of 13 entheses (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 or 1 and then summed for a possible score of 0 to 13 ..

9.15 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). This is then multiplied by the tenderness score, using a simple grading system (0=absent, 1=present). The digits involved and the matching contralateral digit will also be recorded at the same visits.

9.16 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. Each domain is assessed with a single question using a 0 to 10 numerical rating scale. Each domain score is multiplied by a weighting factor and the results are then summed to provide the total score. The total score ranges from 0 to 10, with higher scores indicating a worse status. The PsAID-9 demonstrated satisfactory psychometric properties in an international validation study; however, further validation is needed (Gossec et al, 2014). 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.

9.17 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 PsAQoL comprises 20 items so that the score ranges from 0 to 20 with higher scores indicating worse HRQoL.

9.18 SF-36

The SF-36 (Version 2, standard recall) is a 36 item generic HRQoL instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items),Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and 1 item for [redacted]. The concepts represented by these domains contribute to physical, mental, and social aspects of HRQoL.

In addition to domain scores, the Physical Component Summary and Mental Component Summary scores are calculated from the 8 domains (excluding the Health Transition item). Component scores appreciate the impact of each domain on physical and mental health status (Maruish, 2011). Each of the 8 domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status. The 2 component summary scores are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general US population.

9.19 Hospital Anxiety and Depression Scale

The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with chronic plaque psoriasis (Langley et al, 2010; Dauden et al, 2009). The HADS 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).

10 ASSESSMENT OF PHARMACOKINETIC, PHARMACODYNAMIC, PHARMACOGENOMIC, AND PROTEOMIC VARIABLES

Plasma concentrations of bimekizumab, population PK variables (CL/F, V/F) and dose-exposure responses (for ACR and PASI) are the PK variables.

The PD variables are the concentrations of cytokines of relevance to IL-17A/F signaling pathway and PsA biology. 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/epigenetic, proteomic, and metabolite

biomarkers relevant to disease biology, disease progression, response to therapy, and inflammatory and immune response processes

The Investigator or designee will obtain blood samples for these measurements at the time points specified in Table 5–1. When these samples are required at a visit during which the subject is dosed with IMP, the blood samples will be drawn prior to dosing. Samples should be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analysis will be provided in a bioanalytical report.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLES

The immunological variables comprise detection of anti-bimekizumab antibodies related to immunogenicity, serum complement concentrations, mononuclear cell subtypes (analyzed by flow cytometry/fluorescence-activated cell sorting), and other exploratory biomarkers.

The Investigator or designee will obtain blood samples for these measurements at the time points specified in Table 5–1. When these samples are required at a visit during which the subject is dosed with IMP, the blood samples will be drawn prior to dosing. Samples should be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. The presence of antibodies to bimekizumab will be determined using a validated bioanalytical method. Detailed information on sample analysis will be provided in a bioanalytical report.

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definition of adverse event

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.

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent Form), including any pretreatment and posttreatment periods required by the protocol, must be reported in the eCRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

Signs or symptoms of the condition/disease for which the IMP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the subject's history or the Baseline Period.

12.1.2 Adverse events of special interest

An AE of special interest (AESI) is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AESI (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

12.1.3 Adverse events for special monitoring

UCB has identified AEs for special monitoring (AESM). An AESM is an AE or safety topic for which special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB), are considered appropriate. Identified AESM can be of particular concern based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or comorbidities and risk factors prevalent in the study population.

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB, see Section 12.6.5), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the eC-SSRS), depression and anxiety (assessed using the HADS, see Section 9.19), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.5.1), malignancies, and inflammatory bowel diseases.

12.1.4 Procedures for reporting and recording adverse events

The subject will be given the opportunity to report AEs spontaneously. A general prompt will also be given at each study visit to detect AEs. For example:

"Did you notice anything unusual about your health (since your last visit)?"

In addition, the Investigator should review any self-assessment procedures (eg, diary cards) employed in the study.

12.1.5 Description of adverse events

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

When recording the intensity of an AE in the CRF (ie, mild, moderate, or severe), the Investigator should use the following criteria:

- Mild: the subject is aware of the sign or symptom (syndrome), but it does not interfere with his/her usual activities and/or is of no clinical consequence
- Moderate: the AE interferes with the usual activities of the subject or it is of some clinical consequence
- Severe: the subject is unable to work normally or to carry out his/her usual activities, or the AE is of definite clinical consequence

Details for completion of the Adverse Event eCRF (including judgment of intensity and relationship to IMP) are described in the eCRF Completion Guidelines.

12.1.6 Follow-up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and AESMs; further details regarding follow-up of PDILI events is provided in Section 12.5.1.5. Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

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

12.1.7 Rule for repetition of an adverse event

An increase in the intensity of an AE should lead to the repetition of the AE being reported with:

- The outcome date of the first AE that is not related to the natural course of the disease being the same as the start date of the repeated AE, and the outcome of "worsening"
- The AE verbatim term being the same for the first and repeated AE, so that the repeated AE can be easily identified as the worsening of the first one

12.1.8 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately notify UCB's PS department by providing the completed Pregnancy Report and Outcome Form (for contact details see SAE reporting information at the beginning of this protocol). The subject should be withdrawn from the study as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for the ET Visit.
- The subject should immediately stop the intake of the IMP.
- An SFU Visit should be scheduled 20 weeks after the subject has discontinued her IMP.

The Investigator must inform the subject of information currently known about potential risks and about available treatment alternatives.

The pregnancy will be documented on the Pregnancy Report and Outcome Form provided to the Investigator. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the Pregnancy Report and Outcome Form in which the Investigator has to report on the health of the mother and of the child. Every reasonable attempt should be made to follow the health of the child for 30 days after birth for any significant medical issues. In certain circumstances, UCB may request that follow-up is continued for a period longer than 30 days. If the subject is lost to follow-up and/or refuses to give information, written documentation of attempts to contact the subject needs to be provided by the Investigator and filed at the site. UCB's Drug Safety department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow-up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent Form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/ CRO contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome Form and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent Form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow-up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, elective abortion when medically indicated (eg, when pregnancy is endangering life or health of woman or when fetus will be born with severe abnormalities), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

12.1.9 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the CRF, and followed as any other SAE. Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

12.1.10 Overdose of investigational medicinal product

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the eCRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

12.1.11 Safety signal detection

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP so that Investigators, clinical study subjects, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the PS representative.

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

In addition, an independent DMC will periodically review and monitor the safety data from this study and advise UCB. The DMC membership includes clinicians knowledgeable about the disease or the treatment. All members have experience and expertise in clinical trials. Board members may not participate in the study as principal or co-Investigators, or as study subject care physicians. The duration of membership for the DMC will be inclusive of planned analyses for PA0008. The DMC may also be asked to provide a review of final study results, as deemed appropriate. The DMC procedures will ensure that data remain blind to the study team and Investigators at all times throughout the conduct of the study. The detailed role, scope, responsibilities, and complete procedures, as well as the identity of the DMC members, will be described in a separate charter document. A cardiovascular adjudication committee will be in place for this study. Specific procedures will be outlined in the charter, which will be developed by the committee members.

12.2 Serious adverse events

12.2.1 Definition of serious adverse event

Once it is determined that a subject experienced an AE, the seriousness of the AE must be determined. An SAE must meet 1 or more of the following criteria:

- Death
- Life-threatening

  (Life-threatening does not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 12.1.2] allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

(A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

Hospitalizations for reasons not associated with the occurrence of an AE [eg, preplanned surgery or elective surgery for a pre-existing condition that has not worsened or manifested in an unusual or uncharacteristic manner] do not qualify for reporting. For example, if a subject has a condition recorded on his/her medical history and later has a preplanned surgery for this condition, it is not appropriate to record the surgery or hospitalization as an SAE, since there is no AE upon which to assess the serious criteria. Please note that if the pre-existing condition has worsened or manifested in an unusual or uncharacteristic manner, this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.

Note: Confirmed active TB is always to be considered as an SAE and must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements.

12.2.2 Procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the SAE Reporting section at the front of the protocol). The Investigator must forward to UCB (or its representative) a duly completed "Investigator SAE Report Form for Development Drug" (SAE Report Form) provided by UCB, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. Information recorded on this form will be entered into the global PS database.

An Investigator SAE Report Form will be provided to the Investigator. The Investigator SAE Report form must be completed in English.

It is important for the Investigator, when completing the SAE Report Form, to include the assessment as to a causal relationship between the SAE and the IMP administration. This insight from the Investigator is very important for UCB to consider in assessing the safety of the IMP and in determining whether the SAE requires reporting to the regulatory authorities in an expedited manner.

Additional information (eg, autopsy or laboratory reports) received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English, or the relevant information included in the same document must be summarized in the Investigator SAE Report Form.

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 30 days from the end of the study for each subject, and to also inform participating subjects of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

Upon receipt of the SAE Report Form, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the IB.

12.2.3 Follow-up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and AESMs; further details regarding follow-up of PDILI events is provided in Section 12.5.1.5. Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

12.3 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AEs of special interest as defined in Section 12.1.2

12.4 Anticipated serious adverse events

The following list of Anticipated SAEs (Table 12–1) has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol. Note that listed events will not be regarded as anticipated SAEs if they are life threatening or if they result in the death of the study subject.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.2.2.

Table 12–1: Anticipated serious adverse events for the population of subjects with psoriatic arthritis

MedDRA system organ class	MedDRA preferred term
Eye disorders	Uveitis
Cardiac disorders	Myocardial infarction Atrial fibrillation
Gastrointestinal disorders	Crohn's disease
Hepatobiliary disorders	Non-alcoholic steatohepatitis
Metabolism and Nutrition disorders	Metabolic syndrome Diabetes mellitus
Musculoskeletal and connective tissue disorders	Psoriatic arthropathy
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma Squamous cell carcinoma
Nervous system disorders	Embolic Stroke Ischaemic Stroke

MedDRA system organ class	MedDRA preferred term
Psychiatric disorders	Anxiety Depression
Skin and subcutaneous tissue disorders	Psoriasis

MedDRA=Medical Dictionary for Regulatory Activities

Note: Exception: Listed events will not be regarded as anticipated SAEs if they are life threatening or if they result in the death of the study subject.

12.5 Laboratory measurements

Clinical laboratory assessments consist of serum chemistry, hematology, and urinalysis, and pregnancy tests (serum or urine) (Table 12–2). A centralized laboratory will be used to supply all laboratory test supplies and analyze all blood and urine samples for hematology, biochemistry and urinalysis measurements. Any unscheduled laboratory testing should also be collected using the central laboratory. Testing to rule out hepatitis B, hepatitis C, and HIV (see Exclusion Criterion #8, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12–2.

Specific details regarding the handling and processing of serum chemistry, hematology, and urinalysis samples are provided in the study laboratory manuals.

Table 12–2: Laboratory measurements

Hematology	Chemistry	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	
WBC count	Total bilirubin	
	LDH	
	Total cholesterol	
	Uric acid	
	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-CRP; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; SFU=Safety Follow-up; RBC=red blood cell; WBC=white blood cell

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

12.5.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 12.1.2), and, if applicable, also reported as an SAE (see Section 12.2.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.5.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 12.5.1.5).

The results of all monitoring, including laboratory testing and other testing, should be made available to the study site and sponsor.

All initial tests resulting in abnormal hepatic laboratory values need to be repeated, but appropriate medical action must not be delayed waiting for the repeat result.

If tests are done locally for more rapid results, a concurrent sample should also be sent to the central laboratory whenever possible. Medical care decisions are to be made initially using the most rapidly available results and a conservative approach must be taken if the results from the 2 laboratory tests are significantly different. Data from the local and central laboratory are to be recorded on the applicable CRF pages.

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.

Table 12–3 summarizes the approach to investigate PDILI.

Table 12–3: Required investigations and follow-up for PDILI

Laboratory value			Immediate		Follow-up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.5.1.4); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values[d]
≥3xULN	NA	Yes				
≥5xULN	NA	NA	Need for hepatology consult to be discussed.(required if ALT or AST ≥8xULN) Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation		
≥3xULN (and ≥2x baseline) and <5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see	Further investigation – immediate IMP discontinuation not required (see Section 12.5.1.2). IMP discontinuation required if any of the	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver

Table 12–3: Required investigations and follow-up for PDILI

Laboratory value			Immediate		Follow-up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
			Follow-up requirements).[c]	following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥3xULN (and ≥2x baseline) after 2 weeks of monitoring without evidence of resolution	with HCP (see Section 12.5.1.4).	chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • Discontinue IMP if levels remain ≥3xULN (and ≥2x baseline) without evidence of resolution[d] Continue to monitor until values normalize, stabilize, or return to within baseline values.[d]

ALP=alkaline phosphatase; ALT=alanine aminotransferase; ASAP=as soon as possible; AST=aspartate aminotransferase; HCP=healthcare practitioner; IMP=investigational medicinal product; NA=not applicable; PDILI=potential drug induced liver injury; ULN=upper limit of normal

[a] 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).

[b] If the subject also has ≥2xULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.

[c] Details provided in Section 12.5.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Unless an alternative monitoring schedule is agreed by the Investigator and UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.5.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 12.5.1.4) and SAE report (if applicable).

12.5.1.2 Immediate action: determination of IMP discontinuation

All PDILI events require immediate action, testing, and monitoring.

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 12–3 for details).

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. The Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

12.5.1.3 IMP restart/rechallenge

Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, maybe fatal, and must not occur.

12.5.1.4 Testing: identification/exclusion of alternative etiology

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 12–4 (laboratory measurements) and Table 12–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding CRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

All blood samples should be stored, if possible. If tests are done locally for more rapid results, a concurrent sample must also be sent to the central laboratory.

The following measurements are to be assessed (Table 12–4):

Table 12–4: 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

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).

The following additional information is to be collected (Table 12–5):

Table 12–5: PDILI information to be collected

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

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

12.5.1.5 Follow-up evaluation

- Potential drug-induced liver injury events require follow-up monitoring as described in Table 12–3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

12.6 Other safety measurements

12.6.1 Vital signs

The Investigator or designee should measure all vital signs (systolic and diastolic BP, temperature [oral, axillary, or otic], pulse rate) after the subject has been sitting for at least 5 minutes, and the subject should remain seated during the measurements. Body temperature should be obtained prior to dosing with IMP at study visits when IMP is administered. At Baseline/Day 1 and Week 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 (any time).

12.6.2 Body weight and height

Height is collected at Screening only. The Investigator or designee will measure the height of the subject with shoes removed in meters and the weight of the subject in kilograms. The same scale should be utilized throughout the study where possible.

12.6.3 Physical examination

The physical examination should be conducted by the Investigator or designee at the time points listed in Table 5–1, and will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; GI; musculoskeletal; hepatic; neurological (including limb reflexes); and mental status. Findings considered clinically significant changes since the physical examination at the Screening Visit will be recorded as AEs.

12.6.4 12-lead electrocardiogram

The Investigator or designee will perform the ECG. The ECGs will be read locally.

12.6.5 Tuberculosis and TB risk factor assessment and management

All subjects will be assessed for TB at screening and at the time points specified in the Schedule of Assessments (Table 5–1) through physical examination for signs and symptoms of TB, chest x-ray (Section 12.6.5.2), laboratory testing (Section 12.6.5.1), and subject questionnaire (Section 12.6.5.3).

At Screening, all subjects will have an IGRA test (QuantiFERON TB GOLD is recommended), a chest x-ray (unless already performed within 3 months of screening) and examination for signs and symptoms of TB. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB.

Exclusion criteria at screening

Subjects with known TB infection, at high risk of acquiring TB infection, with LTBI*, or current or history of NTMB infection.
*Subjects with LTBI may enter the study only after they have completed at least 8 weeks of appropriate prophylactic therapy and thereafter, will continue and complete the entire regimen.

a. Known TB infection whether present or past is defined as:
   - Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)
   - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection, unless adequately treated and proven to be fully recovered upon consult with a TB specialist.
   - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history

b. High risk of acquiring TB infection is defined as:

   – Known exposure to another person with active TB infection within the 3 months prior to Screening

   – Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high

c. Latent TB infection (unless appropriate prophylaxis is initiated at least 8 weeks prior to study treatment and continued to completion of prophylaxis) is defined as:

   – The absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study medication without further evaluation, treatment and discussion with Study Physician, if Latent TB infection is identified. The retest must be done during the protocol-defined Screening window.

     Note: If available, respiratory or other specimens must also be smear and culture negative for TB (Centers for Disease Control [CDC] diagnosis of LTB infection) http://www.cdc.gov/TB/topic /testing/default.htm)

d. Current or history of NTMB infection despite prior or current therapy.

Signs and Symptoms

The Investigator should consider all potential sites of infection when assessing for TB during the physical examination, and other evaluations, and based on the subject's medical or social history.

The most common primary focus of TB is the lung. Other sites may include gastrointestinal system, bone/joints, lymph glands and meninges etc. However, in immune compromised patients and/or patients treated with TNF inhibitors, extra-pulmonary manifestations of TB are common compared to normal population.

Some common symptoms that the subject may present are dependent on the primary focus of infection and may include cough, blood in sputum, night sweats, lymphadenitis, joint pain/swelling, spinal deformity, headache/confusion, abdominal pain (mimicking inflammatory bowel disease), etc. Unusual presentations should always be considered.

Latent tuberculosis infection is defined in the "Exclusion Criteria" above. If the result of the IGRA is indeterminate, the particular IGRA previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study medication without further evaluation by a TB specialist. If LTBI or active TB is identified, subject must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening window. Laboratory diagnosis should be undertaken via mycobacteria culture media (or if available by preferred nucleic acid amplification test such as the Xpert mycobacterium tuberculosis [MTB] rifampin [RIF] test) and result must be negative for TB inducing pathogens.

Test Conversion

Tuberculosis test conversion is defined as a positive IGRA result for the current test, when previous IGRA test results were negative. All subjects with TB test conversion must immediately stop IMP administration. In case of a TB test conversion, the subject must be considered as having either a suspected new latent or an active TB infection and be promptly referred to an appropriate specialist (eg, pulmonologist, infectious disease specialist) for further evaluation. If test conversion indicates LTBI, active TB, or NTMB then, per UCB TB working instructions, TB test conversion (confirmed) should be classified adequately, either as due to LTBI, active TB infection, or NTMB, respectively. Additional assessments (eg, blood tests or IGRA, chest x-rays, or other imaging) should be performed where medically relevant and documented. Such conversions should be reported to the UCB PS function.

Latent TB

In case the evaluation by the appropriate specialist indicates a new LTBI during the study, a prophylactic TB treatment should be initiated and study medication can be continued no sooner than 4 weeks after start of prophylactic TB treatment, if it is deemed likely by the Investigator that prophylactic TB treatment is continued to completion.

If prophylaxis is not initiated, the subject must be withdrawn.

Every related action should be discussed in advance with the Medical Monitor.

Once withdrawn from study treatment, subjects should return for the Week 48/ET Visit, complete all Early Termination Visit assessments, and complete a SFU Visit (20 weeks after the last dose of study medication).

Active TB or NTMB infection

Subjects who develop active TB or NTMB infection during the study must be withdrawn from the study. The subject must be immediately discontinued from study medication and an ET Visit must be scheduled as soon as possible, but no later than the next scheduled visit. The subject should be encouraged to keep the SFU Visit as specified by the protocol. Treatment should be started immediately.

Note that subjects with history of NTMB or active NTMB infection are excluded from the study regardless of prior or current therapy for this condition.

12.6.5.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD is recommended) will be performed at Screening and should be repeated at Week 44, ET and SFU Visits for all subjects. The test results will be reported as positive, negative, or indeterminate. UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, subject must undergo appropriate study-specified withdrawal procedures. The retest during Screening must be done during the protocol-defined Screening window.

12.6.5.2 Chest x-ray for tuberculosis

A plain posteroanterior chest x-ray must be performed in the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The chest x-ray (or, if done, Computed Axial Tomography of the Chest) must be clear of signs of TB infection (previous or

current) before first study medication administration. All chest imaging (particularly x-rays) should be available for review by the Investigator before randomization of the subject. The chest x-ray should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential lung TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The chest imaging must be negative for any old or recent TB infection as determined by a qualified radiologist and/or pulmonary physician. Any new clinically significant findings post Baseline on chest x-ray must be documented in the source documents and the eCRF as an AE.

12.6.5.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed at Screening, Baseline, and at the Week 12, Week 24, Week 36, Week 48, ET, and SFU visits. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has LTB or active TB (see Exclusion Criterion 15, Section 6.2). A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection.

Subjects with a latent or active TB infection must be withdrawn from the study.

12.6.5.4 Tuberculosis management

LTB infection and active TB identified during study

During the study, subjects who develop evidence of LTB infection or active TB must immediately stop further administration of study medication and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Evidence of LTB infection is defined as subject's IGRA test converts to positive or indeterminate (and confirmed indeterminate on repeat), or the subject's questionnaire or history and physical indicates that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the subject should be carefully assessed by a TB specialist for active TB. Subjects diagnosed with active TB or LTB infection should be withdrawn from the study and receive appropriate TB or prophylaxis therapy.

If a TB specialist excludes an active TB infection the subject can proceed with the IMP no earlier than 4 weeks after the start of an appropriate prophylactic therapy.

Any presumptive diagnosis or diagnosis of a TB infection is a reportable event. Confirmed active TB must be reported as an SAE. The Investigator is to complete and submit the TB follow-up form provided.

The subject should be transferred to the care of his/her physician and managed according to the best available standard of care. Subjects identified as having converted to active TB during the

study must be withdrawn and scheduled to return for the ET Visit as soon as possible but no later than the next scheduled study visit and complete all ET Visit assessments.

The subject should be encouraged to complete a SFU Visit (20 weeks after the last dose of study medication).

If infection with NTMB is identified during the study, the same procedure as for active TB acquired during the study must be followed.

12.6.6 Pregnancy testing

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 (serum and urine) must be negative prior to administering IMP.

12.6.7 Assessment of suicidal ideation and behavior

Suicidal ideation and behavior will be assessed by trained study personnel using the eC-SSRS. This scale will be used to assess suicidal ideation and behavior that may occur during the study. The visits at which the eC-SSRS assessments will be performed are specified in the schedule of study assessments (Section 5.2).

The eC-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Posner et al, 2011; Mundt et al, 2010). Subjects respond to standardized clinical questions that are presented in a uniform fashion. The eC-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS takes approximately 3 to 10 minutes to complete.

Refer to Section 6.3 for eC-SSRS-related withdrawal criteria.

13 OTHER STUDY MEASUREMENTS

13.1 Medical history

The Investigator or designee will obtain a complete medical history as part of the screening assessment and include all clinically relevant past or coexisting medical conditions, responses to PsA treatment as available, and surgeries. Findings will be recorded in the eCRF.

13.2 Psoriatic arthritis history

The Investigator or designee will obtain a detailed history of PsA, including the date of onset and past treatments for PsA and PsA subtype. Specific information related to PsA history, including family history, will be recorded in the eCRF.

13.3 Demography

The Investigator or designee will collect demographic information for all subjects according to local rules and regulations. This will include age, gender, race and ethnicity. Information on demographics will be collected according to local rules and regulations. Demographic information will be recorded in the eCRF.

13.4 Prior and concomitant medications

As part of the medical history, the Investigator or designee will obtain the prior and concomitant medications and record these in the eCRF.

14 STUDY MANAGEMENT AND ADMINISTRATION

14.1 Adherence to protocol

The Investigator should not deviate from the protocol. However, the Investigator should take any measure necessary in deviation from or not defined by the protocol in order to protect clinical study subjects from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or sponsor.

After implementation of such measure, the Investigator must notify the CPM of the sponsor within 24 hours and follow any local regulatory requirements.

14.2 Monitoring

UCB (or designee) will monitor the study to meet the CRO's monitoring Standard Operating Procedures (SOPs), ICH-GCP guideline, and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate. Monitoring of the study may be delegated by UCB to a CRO or a contract monitor.

The Investigator and his/her staff are expected to cooperate with UCB (or designee) and to be available during the monitoring visits to answer questions sufficiently and to provide any missing information. The Investigator(s)/institution(s) will permit direct access to source data/documents for study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s).

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of CRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

14.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of CRFs are not considered acceptable source documents. Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of

life questionnaires, for example. Source documents should be kept in a secure, limited access area.

Sponsor or designee will review to ensure that computerized source documents produced by the site are compliant with Food and Drug Administration (FDA) Part 11 requirements and document appropriately. Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

Electronic data records must be saved and stored as instructed by UCB (or designee).

14.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 14.2.1.

14.3 Data handling

14.3.1 Case Report Form completion

This study will use electronic data capture (EDC); the Investigator is responsible for prompt reporting of accurate, complete, and legible data in the eCRF and in all required reports.

This study will also use an electronic device (Site Tablet) to capture patient reported outcomes (see Section 14.2.1).

Serious AE reporting will be done using the SAE Report Form (see Section 12.2.2) while also entering the event in the appropriate eCRF section. The safety database and the clinical database will be reconciled during the study and discrepancies will be corrected as needed.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF. Access to the EDC will be given after training has been received. A training certificate will be provided and filed.

Detailed instructions on the use of the EDC will be provided in the eCRF Completion Guidelines.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be re-approved by the Investigator. Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

14.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. This study is performed using EDC. The data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained within the CDMS to track all data changes in the database once the data have been saved initially into the system or electronically loaded. Regular backups of the electronic data will be performed.

14.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

14.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

14.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including CRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's study master file.

14.6 Audit and inspection

The Investigator will permit study-related audits mandated by UCB, after reasonable notice, and inspections by domestic or foreign regulatory authorities.

The main purposes of an audit or inspection are to confirm that the rights and well-being of the subjects enrolled have been protected, that enrolled subjects (ie, signing consent and undergoing study procedures) are appropriate for the study, and that all data relevant for the evaluation of the IMP have been processed and reported in compliance with the planned arrangements, the protocol, investigational site, and IRB/IEC SOPs, ICH GCP, and applicable regulatory requirements.

The Investigator will provide direct access to all study documents, source records, and source data. If an inspection by a regulatory authority is announced, the Investigator will immediately inform UCB (or designee).

14.7 Good Clinical Practice

Noncompliance with the protocol, ICH-GCP, or local regulatory requirements by the Investigator, institution, institution staff, or designees of the sponsor will lead to prompt action by UCB to secure compliance. Continued noncompliance may result in the termination of the site's involvement in the study.

15 STATISTICS

A description of statistical methods follows and will be described in more detail in the Statistical Analysis Plan (SAP).

15.1 Definition of analysis sets

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

The Randomized Set (RS) consists of all randomized subjects.

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

The Full Analysis Set (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.

The Per-Protocol Set (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.

The Pharmacokinetic Per Protocol Set (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.

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.

The Dose-Blind Set (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.

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.

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. Subjects who are eligible for the ESS but do not receive rescue medication, remain in the DBRS.

15.2 General statistical considerations

Summary statistics will consist of frequency tables for categorical variables. For continuous variables, summary statistics will consist of number of available observations, arithmetic mean, SD, median, minimum, and maximum unless stated otherwise.

All statistical tests will be performed 2-sided at a 5% level of significance unless stated otherwise.

15.3 Planned efficacy analyses

15.3.1 Analysis of the primary efficacy variable

The primary efficacy variable 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 with the corresponding p-value. The analysis will include 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 region as a stratification factor is intended to combine study centers in similar geographic regions. The geographic regions to be used will be defined in the IXRS and in the SAP. The correlation between dose and ACR50 response will be evaluated at a significance level of α=0.05. This evaluation of dose-response will constitute the primary efficacy analysis.

As a supportive 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, region, and prior TNF inhibitor exposure (yes/no). If the logistic regression model is unable to converge, then region may be dropped from the model to facilitate convergence. Comparisons will be made for each dose versus placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio versus placebo, the 95% confidence interval, and the corresponding p-value will be calculated. 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. Each test will only be conducted if the previous test reaches significance at a 2-sided significance level of α=0.05. This procedure will control the overall Type I error rate. If the dose-response

relationship fails to reach significance at a significance level of α=0.05, then no further testing will be conducted and the pairwise comparisons are seen as nonsignificant.

Nonresponder imputation (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 nonresponders for the primary analysis.

15.3.1.1 Supportive analyses

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 intent-to-treat (ITT) principle. Subjects with no valid measurement of the primary efficacy variable at Baseline will be included as nonresponders.

(3) The primary dose response analysis and pairwise comparisons will also be repeated for all individual components of the ACR50 response to explore the effect of the signs and symptoms of the individual components on the composite endpoint. Since all ACR components are continuous variables (eg, change from Baseline in TJC), an analysis of covariance (ANCOVA) with treatment, region, and prior TNF inhibitor exposure as fixed effects and the Baseline values as covariate will be used for the analysis.

Additional sensitivity analyses to evaluate the assumptions related to the handling of missing data for the primary efficacy variable will be performed and are described in Section 15.7.

15.3.2 Other efficacy analyses

15.3.2.1 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 Section 15.3.1. Pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose as described in Section 15.3.1.

Dose- and exposure-response will be assessed using a nonlinear mixed effects modeling to characterize the relationship between dose, exposure, and ACR and PASI responses. The model will be partitioned into structural and stochastic models. The structural model describes the main trends and dependencies in the data, for example how drug concentrations depend on dose and time, or how ACR and PASI depend on drug exposure. The stochastic part of the model is further divided into the interindividual variability (IIV) and the residual unexplained variability (RUV). The IIV describes how individual specific parameters differ from the typical individual. The RUV describes the differences between the observations and the predictions from the model. Further details will be given in a separate data analysis plan and reported in a separate document.

15.3.2.2 Analysis of the other efficacy variables

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

All categorical variables will be summarized using frequency tables by each visit.

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

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 days from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 visit without achieving a response will be censored at the date of the Week 12 visit.

The median time to response including the two-sided 95% confidence interval (CI) will be calculated for each treatment. Between group differences (each bimekizumab dose versus placebo will be analyzed with the log-rank statistic.

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 (see Section 15.7).

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.

15.4 Subgroup analyses

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

- Age
- Gender
- Region
- BASDAI >4
- TNF inhibitor exposure
- Anti-bimekizumab antibody status
- Extent of PSO involvement >3%
- CRP level

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

15.5 Planned safety and other analyses

15.5.1 Safety analyses

Safety variables will be analyzed for all subjects in the SS. In addition, safety analyses during the Dose-Blind Period will be analyzed for all subjects in the DBS.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®). Adverse events will be summarized descriptively by treatment group, primary system organ class, high level term, and preferred term. Additional tables will summarize AEs by intensity and relationship to IMP, AEs leading to withdrawal from the study, SAEs, and deaths.

Laboratory values, urinary values, ECGs, vital signs and extent of exposure will be presented descriptively by treatment group.

15.5.2 Other analyses

Pharmacokinetic variables will be analyzed for all subjects in the PK-PPS. Pharmadynamic variables will be analyzed for all subjects in the PD-PPS.

Pharmacokinetic and PD analyses will be detailed in a separate data analysis plan and reported in a separate document. Plasma concentration time data of bimekizumab and ACR or PASI responder rates will be used as the PK and PD response. If data merits, further PK/PD analysis on other PD variables may be performed

Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit.

Anti-bimekizumab antibody status will be summarized for each treatment at each scheduled visit.

The biomarker data including IL-17A, IL-17F, IL-6, and IL-23 concentrations will be summarized for each treatment at each scheduled visit.

In addition to the PD variables, whole blood will be stored to isolate deoxyribonucleic acid (DNA) which may be used to examine genetic and epigenetic changes.

15.6 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the primary efficacy, key safety, or PK/PD outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important 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 analysis sets.

15.7 Handling of dropouts or missing data

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

Two sensitivity analyses will be performed for the primary dose-response analysis and for supportive analysis (3) (Section 15.3.1.1):

1. An analysis will be performed in which all available data at Week 12 will be considered. This analysis will be based on the ordered categorical analysis to evaluate dose-response as specified in the primary analysis. However, 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. Even though efforts will be made to collect the primary outcome data for all subjects at Week 12, there may still be some subjects for whom Week 12 efficacy data cannot be obtained. In this case, the subjects will be assumed to be nonresponders. The estimand here is the difference in outcome improvement at the planned endpoint for all randomized participants (Mallinckrodt, 2012). This is an estimand of effectiveness to evaluate the de facto hypothesis. 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. Therefore, the results of this analysis should be interpreted in the appropriate context.
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.

Sensitivity analyses will also be performed for the pairwise comparisons of bimekizumab doses versus placebo based on ACR50 response at Week 12. The following sensitivity analyses will be conducted:

1. Missing data will be imputed using multiple imputation (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 Markov-Chain Monte Carlo [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, 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 missing at random (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).
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 dose-response efficacy analysis.

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 dose-response efficacy analysis.

For dose/exposure response model, missing data will not be imputed. If a subject drops out, this will be used as a covariate in the model.

Other binary efficacy variables will be imputed using NRI.

All continuous efficacy variables will be imputed using MI as described above assuming that missingness is MAR.

15.8 Planned interim analysis and data monitoring

There is 1 interim analysis planned for this study. The interim analysis will be performed after all enrolled subjects have completed the 12 weeks Double-Blind Period.

The objectives of this interim analysis are (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.

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

Safety data will be provided to an independent DMC. The DMC will review those safety data periodically. It is not planned for the DMC to review efficacy data, and no formal stopping rules will be applied.

15.9 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 Weeks 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.

16 ETHICS AND REGULATORY REQUIREMENTS

16.1 Informed consent

Subject's informed consent must be obtained and documented in accordance with local regulations, ICH-GCP requirements, and the ethical principles that have their origin in the principles of the Declaration of Helsinki.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the subject in both oral and written form by the Investigator (or designee). Each subject will have the opportunity to discuss the study and its alternatives with the Investigator.

Prior to participation in the study, the written Informed Consent form should be signed and personally dated by the subject, or his/her legal representative, and by the person who conducted the informed consent discussion (Investigator or designee). The subject or his/her legal representative must receive a copy of the signed and dated Informed Consent form. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/IEC review, and regulatory inspection.

If the Informed Consent form is amended during the study, the Investigator (or the sponsor, if applicable) must follow all applicable regulatory requirements pertaining to the approval of the amended Informed Consent form by the IRB/IEC and use of the amended form.

All studies conducted at centers in the United States must include the use of a Health Insurance Portability and Accountability Act Authorization form.

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent form. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

16.2 Subject identification cards

Upon signing the Informed Consent the subject or legal representative will be provided with a subject identification card in the language of the subject. The Investigator will fill in the subject identifying information and medical emergency contact information. The Investigator will instruct the subject to keep the card with him/her at all times.

16.3 Institutional Review Boards and Independent Ethics Committees

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, ICH-GCP, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will

be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

Before initiating a study, the Investigator will have written and dated full approval from the responsible IRB/IEC for the protocol.

The Investigator will also promptly report to the IRB/IEC all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

The Investigator will not make any changes in the study or study conduct without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the Investigator to obtain an expedited review by the IRB/IEC as allowed.

As part of the IRB/IEC requirements for continuing review of approved studies, the Investigator will be responsible for submitting periodic progress reports to the IRB/IEC (based on IRB/IEC requirements), at intervals appropriate to the degree of subject risk involved, but no less than once per year. The Investigator should provide a final report to the IRB/IEC following study completion.

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements. The appropriate IRB/IEC will also be informed by the Investigator or the sponsor, as specified by the applicable regulatory requirements in each concerned country. Where applicable, Investigators are to provide the sponsor (or its representative) with evidence of such IRB/IEC notification.

16.4 Subject privacy

UCB staff (or designee) will affirm and uphold the subject's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the subject number assigned at Screening.

The Investigator agrees that representatives of UCB, its designee, representatives of the relevant IRB/IEC, or representatives of regulatory authorities will be allowed to review that portion of the subject's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, ECG reports, admission/discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports for deaths occurring during the study).

16.5 Protocol amendments

Protocol changes may affect the legal and ethical status of the study and may also affect the statistical evaluations of sample size and the likelihood of the study fulfilling its primary objective.

Significant changes to the protocol will only be made as an amendment to the protocol and must be approved by UCB, the IRB/IEC, and the regulatory authorities (if required), prior to being implemented.

17 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

Finance, insurance, and publication rights are addressed in the Investigator and/or CRO agreements, as applicable.

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19 APPENDICES

19.1 CASPAR criteria

Inflammatory articular disease (joint, spine, or entheseal) AND at least 3 points of the following 5 categories:

Table 19–1: CASPAR Criteria

Category	Definition	Points
1) Evidence of psoriasis: (Score for 1 of the following[a])		
Current psoriasis	Psoriatic skin or scalp disease present today as judged by a dermatologist or rheumatologist	2 points
Personal history of psoriasis	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: (Score for 1 of the following)		
Current dactylitis	Swelling of an entire digit	1 point
History of dactylitis	A history of dactylitis recorded by a rheumatologist	1 point
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

[a] "Score for 1 of the following" means that only 1 of the 3 criteria is applicable (either current psoriasis [scores 2 points], personal history [scores 1 point], or family history [scores 1 point]).

19.2 Markedly abnormal laboratory values

Table 19-2 Definitions of markedly abnormal hematology values

Parameter (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[a]	N/A
Platelets (x 1000)	<50	N/A

LLN=lower limit of normal; N/A = Not Applicable; RCTC= Rheumatology Common Toxicity Criteria
Data source: modified from Appendix Rheumatology Common Toxicity Criteria v.2.0 presented in Woodworth et al, 2007
[a] Withdrawal criteria for neutrophils is <0.5 (Section 6.3).

Table 19–3: Definitions of markedly abnormal biochemistry values

Parameter (RCTC units)	Markedly Abnormal Definition	
	Low	High
Alkaline Phosphatase	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

ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/A=Not applicable; RCTC= Rheumatology Common Toxicity Criteria; ULN=upper limit of normal
Data source: modified from Appendix Rheumatology Common Toxicity Criteria v.2.0 presented in Woodworth et al, 2007

19.3 Protocol Amendment 1

Rationale for the amendment

The purpose of this protocol amendment is the following:

- The SAE reporting fax number was updated.
- The extra-articular manifestations variable was removed from the other efficacy variables, as these will be assessed as AEs. In addition, the other objective regarding extra-articular manifestations was updated to be specific to enthesitis and dactylitis.
- The inclusion criterion #7 that permitted inclusion of subjects with an hs-CRP ≥ULN and one retesting during the Screening Period, was removed to allow subject enrollment independent of the hs-CRP level.
- Since the inclusion criterion on CRP was removed from the protocol, a subgroup analysis on CRP was added to study the impact of CRP levels on the efficacy of bimekizumab.
- Criteria for the definition of AE intensity were added in response to a regulatory agency request.

In addition, minor typographical errors were corrected.

Modifications and changes

Global changes

a. The following global change was made for all visits from Week 4 (Section 8.3.3) through Week 44 (Section 8.4.8).

   - Collect pulse and BP once after dosing (any time).

   Has been changed to:

   - Collect pulse and BP once after dosing.

b. The following appendices and respective references have been removed from the protocol.

   - Section 19.3: Health Assessment Questionnaire Disability Index
   - Section 19.4: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
   - Section 19.5: PsAID-9
   - Section 19.6: Psoriatic Arthritis Quality of Life
   - Section 19.7: Short-Form (SF36) Questionnaire
   - Section 19.8: Tuberculosis Questionnaire

Specific changes

Change #1

Serious adverse event reporting

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 2421 **USA:** +1 800 880 6949 or +1 866 890 3175 **Canada:** +1 877 582 8842
Email	**Global:** DS_ICT@ucb.com

Has been changed to:

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 2421 **USA and Canada: +1 800 880 6949 or +1 866 890 3175**
Email	**Global:** DS_ICT@ucb.com

Change #2

List of abbreviations

Original text:

BASDAI	Bath Ankylosing Spondylitis Disease Index

Has been changed to:

BASDAI	Bath Ankylosing Spondylitis Disease **Activity** Index

Change #3

Section 1 Summary

Original text:

The study population will consist of adult subjects (≥18 years of age) fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR) 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, have a high sensitivity (hs)-C-reactive protein (CRP) ≥upper limit of normal (ULN) (with no other reason for elevated CRP such as infection), and have active psoriatic lesion(s) and/or a documented history of PSO. 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:

Has been changed to:

The study population will consist of adult subjects (≥18 years of age) fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR) 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~~, have a high sensitivity (hs) C-reactive protein (CRP) ≥upper limit of normal (ULN) (with no other reason for elevated CRP such as infection),~~ and have active psoriatic lesion(s) and/or a documented history of PSO. 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:

Change #4

Section 3.3 Other objectives

Original text:

To assess the impact of bimekizumab on extra-articular disease manifestations (dactylitis, enthesitis, uveitis, inflammatory bowel disease, and psoriasis)

Has been changed to:

To assess the impact of bimekizumab on ~~extra-articular disease manifestations (dactylitis, enthesitis, uveitis, inflammatory bowel disease, and psoriasis)~~ **dactylitis and enthesitis**

Change #5

Section 4.1.3 Other efficacy variables

Original text:

- Occurrence of extra-articular manifestations
  - Uveitis flares (as determined by an ophthalmologist or other eye specialist, as appropriate)
  - Inflammatory bowel disease flares (as determined by a gastroenterologist, as appropriate)
  - Psoriasis disease activity

Has been deleted.

Change #6

Section 4.1.3 Other efficacy variables

Original text:

- Change from Baseline in the Bath Ankylosing Spondylitis Disease Index (BASDAI)

Has been changed to:

- Change from Baseline in the Bath Ankylosing Spondylitis Disease **Activity** Index (BASDAI)

Change #7

Section 5.1 Study description

Original text:

This is a multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy and safety of bimekizumab in subjects with active PsA. 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-cyclic citrullinated peptide (CCP) antibodies negative.
- Subject must have an hs-CRP ≥ULN (with no other reason for elevated CRP such as infection) One retesting of CRP during the Screening Period is permitted.

Has been changed to:

This is a multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy and safety of bimekizumab in subjects with active PsA. 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-cyclic citrullinated peptide (CCP) antibodies negative.
- ~~Subject must have an hs-CRP ≥ULN (with no other reason for elevated CRP such as infection) One retesting of CRP during the Screening Period is permitted.~~

Change #8

Table 5-1 Schedule of assessments (footnotes)

Original text:

BASDAI=Bath Ankylosing Spondylitis Index

Has been changed to:

BASDAI=Bath Ankylosing Spondylitis **Disease Activity** Index

Change #9

Table 5-1 Schedule of assessments (footnotes)

Original text:

[d] At Baseline/Day 1, and Week 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 (any time). All other procedures are done prior to dosing.

Has been changed to:

[d] At Baseline/Day 1 ~~and Week 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 ~~(any time)~~. All other procedures are done prior to dosing.

Change #10

Section 6.1, Inclusion criteria

Original text:

7. Subject must have an hs-CRP ≥ULN (with no other reason for elevated CRP such as infection) One retesting of CRP during the Screening Period is permitted.

Has been deleted.

Change #11

Section 6.2, Exclusion criteria

Original text:

10. Subjects with known history of or current clinically active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus or current active Candidiasis (local or systemic).

Has been changed to:

10. Subjects with known history of or current clinically active infection with Histoplasma, Coccidioides, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus or current active Candidiasis (local or systemic).

Change #12

Section 6.3 Withdrawal criteria

Original text:

8. Subject develops laboratory abnormalities (with or without clinical symptoms) of ALT or AST as defined in Section 6.3.1; neutropenia <0.5x109/mL; or lymphopenia <0.5x10^9/mL. Any laboratory value or change judged to be clinically significant by the Investigator, and/or any lab values meeting the Rheumatology Common Toxicity Criteria (RCTC) Grade 4 criteria (with the exception of neutrophils, which will be permitted with the above withdraw criterion [neutropenia <0.5x10^9/mL]; Table 19-2 and Table 19–3) must be discussed with the medical monitor before the subject is dosed again. (Refer to Section 6.3.1 for withdrawal criteria in relation to potential drug-induced liver injury [PDILI].)

Has been changed to:

8. Subject develops laboratory abnormalities (with or without clinical symptoms) of ALT or AST as defined in Section 6.3.1; neutropenia <0.5x109/~~m~~L; or lymphopenia <0.5x10^9/~~m~~L. Any laboratory value or change judged to be clinically significant by the Investigator **should prompt consideration of whether the subject should continue on IMP. For clarification, laboratory values that are markedly abnormal as per Table 19-2 and Table 19-3 will be flagged to the Investigator and to the medical monitor but do not trigger mandatory withdrawal unless listed above**~~, and/or any lab values meeting the Rheumatology Common Toxicity Criteria (RCTC) Grade 4 criteria (with the exception of neutrophils, which will be permitted with the above withdraw criterion [neutropenia <0.5x10^9/mL]; Table 19-2 and Table 19-3) must be discussed with the medical monitor before the subject is dosed again~~. (Refer to Section 6.3.1 for withdrawal criteria in relation to potential drug-induced liver injury [PDILI].)

Change #13

Section 7.8.2 Prohibited concomitant treatments (medications and therapies), Table 7-2

Original table:

Drug class	Dose	Exclusion criteria
Phototherapy	Any dose	Use within the 28 days prior to the Baseline Visit.
Topical corticosteroids for dermatological use except as detailed in Section 7.8.1, vitamin D analogues, topical retinoids, keratolytics, coal tar	Any dose	Use within 14 days prior to the Baseline Visit.
Systemic retinoids	Any dose	Use within 3 months prior to the Baseline Visit

Has been changed to:

Drug class	Dose	Exclusion criteria
Phototherapy	Any dose	Use within the 28 days prior to the Baseline Visit.
Topical corticosteroids for dermatological use except as detailed in Section 7.8.1, vitamin D analogues, topical retinoids, keratolytics, coal tar, **and fumaric acid esters**	Any dose	Use within 14 days prior to the Baseline Visit.
Systemic retinoids	Any dose	Use within 3 months prior to the Baseline Visit

Change #14

Original section and text:

Section 9.19 Extra-articular manifestations

Information regarding uveitis, enthesitis, dactylitis, inflammatory bowel disease, and psoriasis disease activity will be captured. Enthesitis is assessed via MASES. Dactylitis is assessed via LDI.

Has been removed.

Change #15

Section 12.1.5 Description of adverse events

Original text:

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

Has been changed to:

When recording an AE, the Investigator should use the overall diagnosis or syndrome using standard medical terminology, rather than recording individual symptoms or signs. The eCRF and source documents should be consistent. Any discrepancies between the subject's own words on his/her own records (eg, diary card) and the corresponding medical terminology should be clarified in the source documentation.

When recording the intensity of an AE in the CRF (ie, mild, moderate, or severe), the Investigator should use the following criteria:

- **Mild: the subject is aware of the sign or symptom (syndrome), but it does not interfere with his/her usual activities and/or is of no clinical consequence**
- **Moderate: the AE interferes with the usual activities of the subject or it is of some clinical consequence**
- **Severe: the subject is unable to work normally or to carry out his/her usual activities, or the AE is of definite clinical consequence**

Details for completion of the Adverse Event eCRF (including judgment of **intensity and** relationship to IMP) are described in the eCRF Completion Guidelines.

Change #16

Section 12.5 Laboratory measurements, Table 12-2

Original table:

Hematology	Chemistry	Urinalysis
Basophils	Calcium	Albumin
Eosinophils	Chloride	Bacteria
Lymphocytes	Magnesium	Crystals
Atypical lymphocytes	Potassium	Glucose
Monocytes	Sodium	pH
Neutrophils	Glucose	RBC
Hematocrit	BUN	WBC
Hemoglobin	Creatinine	Urine dipstick for pregnancy testing[a]
MCH	hs-CRP/CRP[a]	
MCHC	AST	
MCV	ALT	
Platelet count	GGT	
RBC count	ALP	
WBC count	Total bilirubin	
	LDH	
	Total cholesterol	
	Serum pregnancy testing[b]	

Has been changed to:

Hematology	Chemistry	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	
WBC count	Total bilirubin	
	LDH	
	Total cholesterol	
	Uric acid	
	Serum pregnancy testing[b]	

Change #17

Section 13.1 Demography

13.1 Demography

The Investigator or designee will collect demographic information for all subjects according to local rules and regulations. This will include age, gender, race and ethnicity. Information on demographics will be collected according to local rules and regulations. Demographic information will be recorded in the eCRF.

Has been moved.

13.3 Demography

The Investigator or designee will collect demographic information for all subjects according to local rules and regulations. This will include age, gender, race and ethnicity. Information on demographics will be collected according to local rules and regulations. Demographic information will be recorded in the eCRF.

Change #18

Section 15.1 Definition of analysis sets

Original text:

The PK-PPS consists of all randomized subjects who took at least one dose of the IMP and provided at least 1 quantifiable plasma concentration post-dose.

Has been changed.

The Pharmacokinetic Per Protocol Set (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.

Change #19

Section 15.4 Subgroup analyses

Original text

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

- Age
- Gender
- Region
- BASDAI >4
- TNF inhibitor exposure
- Anti-bimekizumab antibody status
- Extent of PSO involvement ≥3%

Has been changed to:

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

- Age
- Gender
- Region
- BASDAI >4
- TNF inhibitor exposure
- Anti-bimekizumab antibody status
- Extent of PSO involvement >3%
- **CRP level**

19.4 Protocol Amendment 2

The purpose of this substantial protocol amendment is as follows:

- To update the study contact details for the sponsor study physician and clinical trial biostatistician.
- To revise the withdrawal criteria section to provide instructions for the management of subjects with newly diagnosed IBD or with IBD flares during the study.
- Amend the time window between doses during the Double-Blind Period of the study.
- Add new details for the IMP packaging.
- To revise and clarify the SAE criteria for pregnancy for consistency.
- Amend the table for identification/exclusion of alternative etiology to include AST and ALT.

Modifications and changes

Global changes

No global changes have been made. Specific changes are listed below.

Specific changes

Change #1

LIST OF ABBREVIATIONS

The following abbreviations and definitions were added:

IBD **Inflammatory bowel disease**

Change #2

STUDY CONTACT INFORMATION

Original table:

Sponsor Study Physician

Name:	[redacted], MD
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted] (office) [redacted] (mobile)

Has been changed to:

Sponsor Study Physician

Name:	[redacted], MBBS; PhD [redacted] ~~, MD~~
Address:	**UCB Celltech** ~~UCB BIOSCIENCES Inc.~~ **208 Bath Road** ~~8010 Arco Corporate Drive~~ **Slough, SL1 3WE** ~~Raleigh, NC 27617~~ **UNITED KINGDOM** ~~UNITED STATES~~
Phone:	[redacted] **(mobile)** [redacted] ~~(office)~~ [redacted] **(office** [redacted] ~~(mobile)~~

Change #3

Study contact information

Original table:

Clinical Trial Biostatistician

Name:	Dr. rer. nat. habil [redacted], Senior Biostatistician
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Str.10 40789 Monheim am Rhein GERMANY
Phone:	[redacted]

Has been changed to:

Clinical Trial Biostatistician

Name:	[redacted] ~~Dr. rer. nat. habil~~ [redacted] ~~, Senior Biostatistician~~
Address:	**UCB BIOSCIENCES Inc.** ~~UCB BIOSCIENCES~~ ~~GmbH~~ **8010 Arco Corporate Drive** ~~Alfred-Nobel-Str.10~~ **Raleigh, NC 27617**~~40789 Monheim am Rhein~~ **UNITED STATES**~~GERMANY~~
Phone:	[redacted]

Change #4

Section 5.2 Schedule of study assessments, Table 5-1

Original text:

Table footer:

[p] The minimum time between doses during the Double-Blind Period should be no less than 26 days and no more than 30 days and during the Dose-Blind Period should be no less than 24 days and no more than 32 days.

Has been changed to:

[p] The minimum time between doses during the Double-Blind Period should be no less than 2~~5~~6 days and no more than 3~~1~~0 days and during the Dose-Blind Period should be no less than 24 days and no more than 32 days.

Change #5

Section 6.3 Withdrawal Criteria

The following was added to the withdrawal criteria:

11. Subjects with newly diagnosed inflammatory bowel disease (IBD) or with IBD flares during the study must:

- **Be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist**
- **Discontinue IMP and be followed-up until resolution of active IBD symptoms**

If IBD flares increase in severity or frequency during the study, the Investigator should use clinical judgment in deciding whether the subject should continue in the study and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.

Change #6

Section 7.2 Treatments to be administered, paragraph 2

Original text:

Study medication (bimekizumab and placebo) will be administered at the times indicated in Table 5–1. The minimum time between doses during the Double-Blind Period should be no less than 26 days and no more than 30 days and during the Dose-Blind Period should be no less than 24 days and no more than 32 days.

Has been changed to:

Study medication (bimekizumab and placebo) will be administered at the times indicated in Table 5–1. The minimum time between doses during the Double-Blind Period should be no less than 2~~5~~6 days and no more than 3~~1~~0 days and during the Dose-Blind Period should be no less than 24 days and no more than 32 days.

Change #7

Section 7.3 Packaging

The following was added:

The IMPs are manufactured, packaged, and labeled according to Good Manufacturing Practice guidelines and applicable laws or regulations. Investigational medicinal products will be suitably packaged in such a way as to protect the IMPs from deterioration during transport and storage.

Change #8

Section 8 STUDY PROCEDURES BY VISIT

Original text:

Visit windows are +/-3 days from Baseline (Day1, first dose of IMP) at all visits through the Week 12 Visit and +/-4 days for all visits after Week 12 except the SFU Visit. For the SFU Visit (20 weeks after the last dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (3 days/+7 days). The minimum time between doses during the Double-Blind Period should be no less than 26 days and no more than 30 days and during the Dose-Blind Period should be no less than 24 days and no more than 32 days. Changes to the dosing schedule outside of the allowed windows must be discussed with the Medical Monitor and may result in subject withdrawal.

Has been changed to:

Visit windows are +/-3 days from Baseline (Day1, first dose of IMP) at all visits through the Week 12 Visit and +/-4 days for all visits after Week 12 except the SFU Visit. For the SFU Visit (20 weeks after the last dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (3 days/+7 days). The minimum time between doses during the Double-Blind Period should be no less than 2~~5~~6 days and no more than 3~~1~~0 days and during the Dose-Blind Period should be no less than 24 days and no more than 32 days. Changes to the dosing schedule outside of the allowed windows must be discussed with the Medical Monitor and may result in subject withdrawal.

Change #9

Section 12.1.8 Pregnancy

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective for a medical condition or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any

congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report Form.

Has been changed to:

A pregnancy becomes an SAE in the following circumstances: miscarriage, elective abortion when medically indicated (e.g. when pregnancy is endangering life or health of woman or when fetus will be born with severe abnormalities), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

Change #10

Section 12.5.1.4 Testing: identification/exclusion of alternative etiology, Table 12-4

Original table:

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
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[b]
	Serum pregnancy test

	PK sample

ALT=alanine aminotransferase; 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).

Has been changed to:

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

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).

Change #11

Section 19.2 Markedly abnormal laboratory values, Tables 19-1 (Definitions of markedly abnormal hematology values) and 19-2 (Definitions of markedly abnormal biochemistry values)

Amended units in both table headers:

Parameter (SI units)	Markedly Abnormal Definition	
	Low	High

Has been changed to:

Parameter **(RCTC~~SI~~** units)	Markedly Abnormal Definition	
	Low	High

Change #12

Section 19.2 Markedly abnormal laboratory values, Table 19-1 (Definitions of markedly abnormal hematology values), abbreviations in table footer:

LLN=lower limit of normal; N/A = Not Applicable; SI = standard international

Has been changed to:

LLN=lower limit of normal; N/A = Not Applicable; ~~SI = standard international~~ **RCTC=**

Rheumatology Common Toxicity Criteria

Change #13

Section 19.2 Markedly abnormal laboratory values, Table 19-2 (Definitions of markedly abnormal biochemistry values)

ALT=alanine aminotransferase; AST=aspartate aminotransferase; N/A=Not applicable; SI=standard international; ULN=upper limit of normal

Has been changed to:

LLN=lower limit of normal; N/A = Not Applicable; ~~SI=standard international~~ **RCTC=**

Rheumatology Common Toxicity Criteria

20 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subInvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

21 SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.