PROTOCOL AS0011 AMENDMENT 4

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN SUBJECTS WITH ACTIVE ANKYLOSING SPONDYLITIS

PHASE 3

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Confidential Material

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h) All SAEs will be reported and transmitted to Patient Safety through the eCRF system. The numbers below are to be used to send ancillary documentation only (discharge summaries, death certificates, etc) or in the event that the electronic reporting (eCRF) is not available.	
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	Anterior Posterior
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40, 5/6	Assessment of SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria
ASAS-PR	Assessment of SpondyloArthritis International Society partial remission
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score-C-reactive protein
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score major improvement
ASspiMRI-a	Ankylosing Spondylitis spine Magnetic Resonance Imagine-activity
ASQoL	Ankylosing Spondylitis Quality of Life
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BP	blood pressure
CAT	Computed Axial Tomography
CDC	Centers for Disease Control
CDMS	clinical data management system
CHO	Chinese Hamster Ovarian
CI	confidence interval
CMV	cytomegaly virus
COVID-19	coronavirus disease 2019
COX-2 inhibitor	cyclooxygenase 2 inhibitor
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization

CRP	C-reactive protein
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
DVU	disco-vertebral unit
EAM	extra-articular manifestation
ECG	electrocardiogram
eCRF	electronic Case Report Form
ePRO	electronic Patient-Reported Outcomes
EDC	electronic data capture
EQ-5D-3L	European Qol-5 Dimensions 3-Level
ES	Enrolled Set
ET	Early Termination
EULAR	European League Against Rheumatism
FACIT	Functional assessment of chronic illness therapy
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing practice
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HD	high disease
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRQoL	health-related quality of life
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Council for Harmonisation

ID	inactive disease
IEC	Independent Ethics Committee
IGRA	Interferon-Gamma Release Assay
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
LEF	leflunomide
LD	low disease
LTB	latent tuberculosis
LTBI	latent tuberculosis infection
MAR	missing at random
MASES	Maastricht Ankylosing Spondylitis Enthesitis Index
MCID	minimal clinically important difference
MCMC	Markov-Chain Monte Carlo
MCP	metacarpophalangeals
MCS	mental component summary
MedDRA®	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MNAR	missing not at random
mNY	Modified New York (criteria)
MOS	Medical Outcomes Study
MRI	magnetic resonance imaging
MTX	methotrexate
nr-axSpA	nonradiographic axial spondyloarthritis
NRI	nonresponder imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria

OC	observed cases
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PASI	Psoriasis Area and Severity Index
PCS	physical component summary
PD	pharmacodynamics
PDILI	potential drug-induced liver injury
PFS	prefilled syringe
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PHQ-9	Patient Health Questionnaire 9
PIP	proximal interphalangeal
PK	pharmacokinetics
PK-PPS	Pharmacokinetic Per-Protocol Set
PPS	Per-Protocol Set
PRN	as needed
PS	Patient Safety
PsA	psoriatic arthritis
PSO	psoriasis
Q4W	every 4 weeks
r-axSpA	radiographic axSpA
RA	rheumatoid arthritis
RNA	ribonucleic acid
RS	Randomized Set
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
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SPARTAN	Spondyloarthritis Research and Treatment Network
SS	Safety Set

SSZ	sulfasalazine
STIR	short-tau-inversion recovery
$t_{½}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
VAS	visual analog scale
vHD	very high disease
WHO	World Health Organization
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire-specific health problem

1 SUMMARY

This is a multicenter, Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active ankylosing spondylitis (AS), a subtype of axial spondyloarthritis (axSpA) with radiographic evidence of disease (also known as radiographic axSpA [r-axSpA]). To be eligible to participate in this study, subjects must be adults with a diagnosis of active AS, determined by documented radiologic evidence (x-ray) fulfilling the Modified New York (mNY) criteria for AS (1984) (Section 19.2), including at least 3 months of symptoms and age at symptom onset <45 years, and moderate-to-severe active disease at Baseline as defined by both of the following:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 **AND** spinal pain ≥4 on a 0 to 10 numeric rating scale (NRS) (from BASDAI Item 2).

As bimekizumab will be evaluated in axSpA, UCB will also perform a randomized, double-blind, placebo-controlled Phase 3 study (AS0010) in subjects with nonradiographic axial spondyloarthritis (nr-axSpA) in parallel to the present study in AS (AS0011).

The primary objective of AS0011 is to demonstrate the efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) compared with placebo in the treatment of subjects with active AS. The secondary objectives of the study are listed in Section 3.2, and other objectives are listed in Section 3.3.

The primary efficacy variable for this study is the Assessment of SpondyloArthritis International Society 40% response criteria (ASAS 40) response at Week 16. The secondary and other efficacy variables are listed in Section 4.2.1 and Section 4.3.1, respectively.

Safety variables are listed in Section 4.2.2 (secondary safety variables) and Section 4.3.2 (other safety variables). The pharmacokinetic (PK), pharmacogenomic, and immunological variables are listed in Section 4.3.3, Section 4.3.4, and Section 4.3.5 respectively.

AS0011 will evaluate the efficacy, safety, and PK of bimekizumab in adult subjects with active AS at a dose level of bimekizumab 160mg Q4W administered by sc injection.

The overall study design consists of a Screening Period (minimum of approximately 14 days [unless a screenfailed subject from AS0010 will be screened in AS0011] to ≤35 days), a 52-week Treatment Period consisting of a 16-week Double-Blind Treatment Period, a 36-week Maintenance Period, and a Safety Follow-Up (SFU) Visit 20 weeks after the final dose of the investigational medicinal product (IMP) (ie, Week 48 for subjects who completed AS0011; for subjects not entering the extension study or who discontinue early, including those withdrawn from study treatment). The maximum study duration per subject will be 73 weeks.

Approximately 300 subjects will be randomly assigned in a 2:1 ratio to the following treatment groups: bimekizumab 160mg sc Q4W (200 subjects) or placebo (100 subjects). Subjects receiving placebo during the Double-Blind Treatment Period will be re-allocated to bimekizumab treatment at Week 16 after all study assessments have been completed. These subjects will receive bimekizumab 160mg sc at Week 16 and Q4W thereafter (Section 7.2).

A detailed schedule of study assessments is presented in Table 5-2 and a study schematic diagram is presented in Figure 5–1.

Nonbiologic rescue therapy will be at the Investigator's discretion as add-on therapy to bimekizumab at any time from Week 20 or later. Details are provided in Table 7–2.

Subjects completing Week 52 who meet the eligibility criteria may be enrolled in an extension study to continue to receive bimekizumab treatment.

2 INTRODUCTION

2.1 Axial spondyloarthritis

Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases (including axial spondyloarthritis [axSpA], psoriatic arthritis [PsA], reactive arthritis, the arthritis of inflammatory bowel disease [IBD], and undifferentiated SpA) that have features in common with each other and distinct from other inflammatory arthritides, particularly rheumatoid arthritis (RA).

The ASAS working group established classification criteria to distinguish 2 broad categories of SpA: peripheral SpA and axSpA (Rudwaleit et al, 2011; Rudwaleit, 2010; Rudwaleit et al, 2009b). This division is based on the body part predominantly involved in the inflammatory process. Therefore, peripheral SpA includes diseases affecting mainly peripheral joints, such as reactive arthritis and PsA, whereas axSpA comprises those diseases with mainly axial involvement (sacroiliac joints and spine), including AS (also known as r-axSpA) diagnosed with definite radiographic changes of the sacroiliac joint and nr-axSpA.

Patients with axSpA have inflammatory back pain. The disease typically originates in the sacroiliac joints, then progresses to the spine. In the sacroiliac joints and the spine, active inflammation results in erosions, sclerosis, and fatty lesions seen on magnetic resonance imaging (MRI). However, the most characteristic feature is new bone formation leading to ankylosis of the sacroiliac joints and syndesmophytes attached to the vertebral bodies. As a result of extended syndesmophyte formation, over time the spine may become fused (bamboo spine). Objective signs of inflammation (such as enthesitis, dactylitis, peripheral arthritis, or uveitis), genetic features (such as the presence of human leukocyte antigen [HLA] B27), and laboratory parameters (such as elevated C-reactive protein [CRP]) may also be present (Braun, 2012; Rudwaleit et al, 2009a; Braun and Sieper, 2007). Disability in axSpA is related to both the degree of inflammatory activity, causing pain, stiffness, fatigue, and poor quality of sleep, and to the degree of bony ankylosis, causing loss of spinal mobility. Patients with AS show radiographic progression of disease with x-ray identified sacroiliitis, while "bamboo spine" may develop when the outer fibers of the fibrous ring of the intervertebral discs ossify, which results in the formation of marginal syndesmophytes between adjoining vertebrae.

2.1.1 axSpA epidemiology

Axial SpA is a chronic inflammatory disease that impacts a substantial proportion of the population. Limited evidence exists regarding the global occurrence of axSpA with a prevalence of 0.20 to 0.25% in Europe and North America, and a wider range in Asia (0.06 to 0.20%) (Stolwijk et al, 2016); however, recent data suggest that the prevalence is similar to that of RA in the US (axSpA: 0.7% to 1.4%; RA: 0.5% to 1.0%) (Reveille et al, 2012; Myasoedova et al, 2010; Helmick et al, 2008). Axial SpA comprises those diseases with mainly axial involvement (sacroiliac joints and spine), including AS and nr-axSpA.

2.1.2 Current treatments for axSpA

Nonsteroidal anti-inflammatory drugs are used as first-line treatment and are effective for the symptoms (pain and stiffness) of axSpA (van der Heijde et al, 2017; Ward et al, 2015; Poddubnyy, 2013; Poddubnyy et al, 2012), but many patients lose or never have clinically meaningful response and structural damage often progresses despite their use. Conventional disease-modifying antirheumatic drugs (DMARDs, eg, methotrexate [MTX] and sulfasalazine [SSZ]) have no proven efficacy in axial disease, but may benefit patients with peripheral joint disease (Haibel et al, 2007; Braun et al, 2006; Haibel et al, 2005). Therefore, DMARDs are recommended only in patients with predominantly peripheral manifestations (Braun et al, 2011). Patients who are intolerant of or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have approved treatment options such as tumor necrosis factor alpha (TNFα) inhibitors (van der Heijde, 2017; Ward et al, 2015).

Recently, the interleukin (IL)-17 cytokine family has been identified as a therapeutic target in axSpA and secukinumab, an IL-17A monoclonal antibody, has recently been approved as a treatment option in active AS.

2.2 Bimekizumab

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. Interleukin-17A and IL-17F are key proinflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases. Therefore, bimekizumab 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. Bimekizumab is being developed for the treatment of patients with inflammatory diseases such as PsA, psoriasis (PSO), axSpA and hidradenitis suppurativa.

2.2.1 Nonclinical

There is increasing evidence of the role of IL-17F in various inflammatory diseases. Simultaneous inhibition of IL-17A and IL-17F has been shown to be more efficacious than inhibition of IL-17A alone in in vitro models. Intravenously or sc administered bimekizumab was well tolerated in repeat-dose toxicology studies in Cynomolgus monkeys with dosing up to 200mg/kg/week for up to 26 weeks. The findings of note varied from study to study, but were all compatible with decreased muco-epidermal immunity induced by the inhibition of IL-17A and F signaling. They consisted in diarrhea related to infectious enteritis, asymptomatic proliferation of a protozoan commonly found in the cynomolgus monkey, *Balantidium coli*, superficial dermatitis associated with increased bacterial load on the skin (mainly Gram positive cocci, including *Staphylococcus aureus*), and abscesses.

Infection-related safety findings in a nonhuman primate can be highly variable from study to study and have limited ability to accurately predict the incidence and type of infection that can be expected in humans, especially because nonhuman primates bear different commensal flora and show different sensitivity to different pathogens. Immunomodulators can increase the susceptibility of monkeys to potential pathogens that are endemic in nonhuman primate populations and usually remain clinically undetectable or are mild and self-limiting in

immunocompetent animals. Moreover, infections associated with the gastrointestinal (GI) tract that result in chronic enterocolitis are a persistent and widespread colony problem in nonhuman primates, often multifactorial in origin.

The nonclinical studies have highlighted the already known risk of infection linked to decreased muco-epidermal immunity that needs to be carefully monitored in the clinic, but are unlikely to predict the risk of infection in humans based on dose and exposure for the aforementioned reasons. To date, similar findings have not been seen in studies in humans.

Preliminary results from the embryofetal and postnatal study conducted in the Cynomolgus monkey indicate no effects of bimekizumab on the gestation, gestation duration, or the parturition of pregnant females. No bimekizumab-related effects were noted in infants at birth, during postnatal development, or on infant survival rate. Toxicokinetic data confirmed dose-related exposure of maternal animals during the pregnancy and the lactation phase, and of infants at birth and during the postnatal phase.

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

2.2.2 Clinical

2.2.2.1 Completed studies

Twenty clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild-to-moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, UP0031 in 12 healthy volunteers, UP0033 in 189 healthy volunteers, UP0034 in 56 healthy volunteers, UP0042 in 48 Japanese and Caucasian healthy volunteers, UP0074 in 37 healthy volunteers, RA0123 in 159 subjects with moderate-to-severe RA, PS0010 in 250 subjects with moderate-to-severe chronic plaque PSO and the corresponding extension study (PS0011), PS0016 in 49 subjects with moderate-to-severe chronic plaque PSO and the corresponding extension study (PS0018), UC0011 in 23 subjects with moderate-to-severe active ulcerative colitis, HS0001 in 90 subjects with moderate to severe hidradenitis suppurativa, AS0008 in 303 subjects with AS, PA0008 in 206 subjects with PsA, PS0008 in 478 subjects with moderate to severe chronic plaque PSO, PS0009 in 567 subjects with moderate to severe chronic plaque PSO and PS0013 in 435 subjects with moderate to severe chronic plaque PSO.

Information on the clinical data for bimekizumab from completed studies is available in the current version of the IB.

2.2.2.2 Ongoing studies

Several additional studies of bimekizumab in subjects with axSpA are ongoing:

- AS0009 is an open-label extension study for AS0008.
- AS0013 is a Phase 2a Investigator- and subject-blind parallel-group study to evaluate the efficacy and safety of bimekizumab and certolizumab pegol (CZP) in subjects with active AS.
- AS0010 is a Phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active nr-axSpA.
- AS0014 is a Phase 3, open-label extension study for AS0010 and AS0011.

Bimekizumab is also being evaluated in the treatment of other indications (eg, PsA, PSO, hidradenitis suppurativa).

Additional information on the ongoing studies for bimekizumab is available in the current version of the IB.

3 STUDY OBJECTIVE(S)

3.1 Primary objective

The primary objective is to demonstrate the efficacy of bimekizumab administered sc Q4W compared to placebo in the treatment of subjects with active AS.

3.2 Secondary objectives

The secondary objectives of the study are as follows:

- To assess the efficacy of bimekizumab compared to placebo
- To assess the safety and tolerability of bimekizumab
- To assess the impact of bimekizumab on patient-reported quality of life
- To assess the impact of bimekizumab on spinal mobility
- To assess the impact of bimekizumab on enthesitis and on peripheral arthritis

3.3 Other objectives

The other objectives are as follows:

- To assess the immunogenicity of bimekizumab
- To assess the pharmacokinetics of bimekizumab
- To assess the maintenance of efficacy of bimekizumab
- To assess the relationship between exploratory biomarkers, drug treatment, and AS disease biology
- To assess the impact of bimekizumab on work productivity
- To assess the impact of bimekizumab on inflammatory changes using MRI

4 STUDY VARIABLES

4.1 Primary variable

4.1.1 Primary efficacy variable

The primary efficacy variable for this study is:

- ASAS40 response at Week 16.

4.2 Secondary variables

4.2.1 Secondary efficacy variables

The secondary efficacy variables for this study are as follows:

- ASAS40 response at Week 16 in TNFα inhibitor-naïve subjects

- ASAS20 response at Week 16
- Change from Baseline in BASDAI total score at Week 16
- ASAS partial remission (ASAS-PR) at Week 16
- Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) at Week 16
- ASAS5/6 response at Week 16
- Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16
- Change from Baseline in nocturnal spinal pain score (NRS) at Week 16
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) total score at Week 16
- Change from Baseline in the Short Form 36-Item Health Survey (SF-36) physical component summary (PCS) score at Week 16
- Change from Baseline in Bath Ankylosing Spondylitis Disease Metrology Index (BASMI) at Week 16
- Change from Baseline in the Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index in the subgroup of subjects with enthesitis at Baseline at Week 16
- Enthesitis-free state based on the MASES Index in the subgroup of subjects with enthesitis at Baseline at Week 16

4.2.2 Secondary safety variables

Assessment time points for safety variables are specified in Table 5-2. Variables are as follows:

- Incidence of treatment-emergent adverse events (TEAEs)
- Incidence of treatment-emergent serious adverse events (SAEs)
- TEAEs leading to withdrawal from IMP

4.3 Other variables

4.3.1 Other efficacy variables

Other efficacy variables will be assessed as specified in Table 5-2. All time points not specified in Section 4.1.1 or Section 4.2.1 are exploratory:

- ASAS40 response
- Time to ASAS40 response
- ASAS20 response
- Time to ASAS20 response
- ASAS5/6 response
- ASAS-PR

- Change from Baseline in Ankylosing Spondylitis Disease Activity Score C-reactive protein (ASDAS-CRP)
- ASDAS status (eg, inactive disease [ID], low disease [LD], high disease [HD], and very high disease [vHD])
- ASDAS-MI
- Change from Baseline in BASDAI total score
- BASDAI50 response
- Change from Baseline in BASFI
- Change from Baseline in the MASES Index in the subgroup of subjects with enthesitis at Baseline
- Enthesitis-free state based on the MASES in the subgroup of subjects with enthesitis at Baseline
- Change from Baseline in BASMI
- Change from Baseline in Physician's Global Assessment of Disease Activity (PhGADA)
- Change from Baseline in Patient's Global Assessment of Disease Activity (PGADA)
- Change from Baseline in total and nocturnal spinal pain score (NRS)
- Change from Baseline in the average score of Questions 5 and 6 of the BASDAI concerning morning stiffness
- Change from Baseline in CRP
- Responses to the European Qol-5 Dimensions 3-Level (EQ-5D-3L)
- Change from Baseline in EQ-5D-3L visual analog scale (VAS) scores
- Change from Baseline in the EQ-5D utility score
- Change from Baseline in the SF-36 PCS score
- Change from Baseline in the SF-36 mental component summary (MCS) score
- Change from Baseline in sleep quality score (Medical Outcomes Study [MOS 12-item] scale)
- Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale score
- Change from Baseline in ASQoL total score
- Change from Baseline in the Work Productivity and Activity Impairment Questionnaire- specific health problem (WPAI-SHP)
- Change from Baseline in (44/44) tender joint count (TJC) and swollen joint count (SJC)
- Change from Baseline in Ankylosing Spondylitis spine MRI-activity (ASspiMRI-a) in the Berlin modification score

- Change from Baseline in sacroiliac joint Spondyloarthritis Research Consortium of Canada (SPARCC) score

4.3.2 Other safety variables

Other safety variables to be assessed as specified in Table 5-2 are as follows:

- Change from Baseline in vital signs (blood pressure [BP], temperature, and pulse rate)
- Standard 12-lead electrocardiogram (ECG) results
- Change from Baseline in clinical laboratory values (hematology, biochemistry, and urinalysis)
- Change from Baseline in Patient Health Questionnaire-9 (PHQ-9)

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

4.3.3 Pharmacokinetic variable

The PK variable is the plasma concentration of bimekizumab.

4.3.4 Pharmacogenomic variables

Additional blood and stool samples will be collected from subjects who consent to participate in the substudy at specific time points specified in Table 5-2.

Genomic, genetic, epigenetic, proteins, and metabolite biomarkers may be measured to evaluate the relationship with response to treatment with bimekizumab, axSpA disease biology, bone metabolism, and inflammatory and immune response processes. The nature and format of these tentative substudy analyses will be determined at a later time.

Additional candidate serum exploratory variables may include, but are not limited to the blood concentrations of cytokines and chemokines of relevance to the IL-17A/F signaling pathway and axSpA biology, and serum complement concentrations. Stool samples will be collected from subjects who consent to participate in the pharmacogenomics substudy at specific time points specified in Table 5-2. These samples may be used to assess biomarkers of gut inflammation including but not limited to calprotectin and microbiome testing.

4.3.5 Immunological variables

The immunological variables are the anti-bimekizumab antibody status and the treatment-emergent antibody positivity derived from anti-drug antibody assays.

5 STUDY DESIGN

5.1 Study description

This is a multicenter, Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active AS. To be eligible to participate in this study, subjects must meet the following key inclusion criteria:

- Adult subjects with active AS, determined by documented radiologic evidence (x-ray) fulfilling the Modified New York criteria for AS (1984) (Section 19.2), including at least 3 months of symptoms.
- Age at symptom onset <45 years
- Subject must have moderate-to-severe active disease as defined by BOTH of the following at Screening AND Baseline.
  - BASDAI ≥4 AND spinal pain ≥4 on a 0 to 10 NRS (from BASDAI Item 2)

Detailed eligibility criteria are presented in Section 6.1 and Section 6.2.

The study will include the following 3 periods: a Screening Period (minimum of approximately 14 days [unless a screenfailed subject from AS0010 will be screened in AS0011] to ≤35 days), a Treatment Period (52 weeks) consisting of a 16-week Double-Blind Treatment Period and a 36-week Maintenance Period, and a SFU Period (20 weeks after the final dose of IMP).

Eligible subjects will be randomized 2:1 to receive 1 of 2 treatments (bimekizumab 160mg sc Q4W or placebo sc Q4W), and will remain on their allowable background medication. Details of the Treatment Period are provided in Section 5.1.2. At the end of the 16-week Double-Blind Treatment Period subjects receiving placebo will be re-allocated to bimekizumab treatment at Week 16 after all assessments have been completed. These subjects will receive bimekizumab 160mg sc at Week 16 and 160mg sc Q4W thereafter. Starting at Week 20, nonbiologic rescue therapy for axial SpA may be adjusted or added, while continuing bimekizumab as outlined in Table 7–2.

Subjects completing Week 52 who are not withdrawn from IMP, may be eligible for enrollment in an extension study with bimekizumab. Subjects who are ineligible for or elect not to participate in the extension study at Week 52 will undergo a SFU Visit.

Interim analyses of all available data (including efficacy, safety, and PK) will be conducted after the planned number of randomized subjects have completed 24 weeks and 52 weeks of treatment or have withdrawn from IMP or the study. Details of the interim analyses are given in Section 15.8.1. The final analysis of all available data will be performed after all randomized subjects have completed the SFU Visit or have withdrawn from the IMP and/or study.

A detailed schedule of study assessments is presented in Table 5-2 and a study schematic diagram is presented in Figure 5–1.

5.1.1 Screening Period/Baseline

Assessments of eligibility as described in Section 6 will be initiated during the Screening Period with a minimum duration of approximately 14 days (unless a screenfailed subject from AS0010 will be screened in AS0011) and a maximum duration of up to 35 days. The Screening Period

will also enable the washout of medications not permitted for use during the study, allow initiation of latent TB treatment where necessary, and allow completion of imaging assessments required to determine eligibility including time for central reading.

All subjects will have an anterior posterior (AP) pelvis or sacroiliac joint x-ray (read centrally) to determine eligibility as per mNY criteria. Subjects who are mNY-negative may be eligible for Screening in AS0010, a double-blind, randomized, placebo-controlled Phase 3 study in subjects with active nr-axSpA. It is recommended to perform the sacroiliac joint x-ray prior to any other screening assessment to avoid repetition of screening assessments (applicable at sites participating in both Phase 3 studies).

5.1.1.1 Within-study rescreening/retesting requirements

Rules for rescreening or repetition of screening tests within the study are listed below:

- Subjects who fail to meet the eligibility criteria for BASDAI, spinal pain, PHQ-9, eC-SSRS, or the TB questionnaire **are not allowed** to be rescreened.

The Medical Monitor must be contacted for confirmation of rescreening/retesting in all other cases.

- Subjects who initially fail to meet selected eligibility criteria (eg, documented completion of latent tuberculosis infection [LTBI] prophylactic therapy) may be rescreened.
- Subjects for whom eligibility assessments could not be completed as planned (eg, for technical reasons) within the defined Screening Period of 35 days may be rescreened.
- Subjects with individual laboratory screening tests for which the results are exclusionary, can be retested.

Of note, repetition of laboratory screening tests within the Screening Period is permitted for technical reasons (eg, frozen sample, expired laboratory kit) without contacting the Medical Monitor.

5.1.1.2 Cross-study screening requirements

Screening assessments for subjects previously screened for AS0010, who were not eligible for AS0010 based on mNY criteria and therefore entered AS0011 Screening for eligibility, must be repeated during the Screening Period unless defined in Table 5–1. The Medical Monitor must be contacted for confirmation of the rescreening requirements in all cases.

Table 5–1: Cross-study screening requirements

Assessment	Screening requirements
Cross-study screening is not permitted in the following cases:	
BASDAI and spinal pain	Screening of a subject not eligible for AS0010 who will be screened for AS0011, and who did not meet the related Inclusion Criteria in AS0010.
PHQ-9, eC-SSRS, TB questionnaire (Q1)	Screening of a subject not eligible for AS0010 who will be screened for AS0011, and who did meet the related Exclusion Criteria in AS0010.
Cross-study screening is permitted in the following cases:	
CRP	If a subject not eligible for AS0010 will be screened for AS0011, the Screening CRP testing must be repeated during Screening for AS0011 only if the result is older than 35 days at time of randomization at Baseline (Section 12.6).
All safety laboratory assessments	If a subject not eligible for AS0010 will be screened for AS0011, the Screening safety laboratory testing (hematology, biochemistry, urinalysis, urine drug screen, pregnancy testing as applicable, HIV, Hepatitis B and C, and IGRA TB testing), and HLA-B27 testing must be repeated during Screening for AS0011 only if the results are older than 35 days at time of randomization at Baseline (Section 12.6).
Anterior posterior pelvis x-ray	The following will be accepted to qualify subjects with AS for this study: Anterior posterior pelvis x-ray centrally read for AS0010 and determined to be modified New York Criteria positive (+mNY); neither the x-ray nor the reading will be repeated (Section 9.20). The central imaging reader needs to be informed by the site about screening activities in order to transfer and confirm eligibility for the switch from AS0010 to AS0011.

AS=ankylosing spondylitis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; CRP=C-reactive protein; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; IGRA=Interferon-Gamma Release Assay; mNY=modified New York; PHQ-9=Patient Health Questionnaire 9; Q=question; TB=tuberculosis

Assessments at the Screening Visit are presented in Table 5-2.

5.1.2 Treatment Period

5.1.2.1 Double-Blind Treatment Period

During the Double-Blind Treatment Period, subjects will be randomized in a 2:1 fashion (stratified by region and prior TNFα inhibitor experience) to 1 of 2 treatment arms to receive blinded IMP regimens of bimekizumab 160mg sc Q4W or placebo sc Q4W. The enrollment of TNFα inhibitor-experienced subjects will be limited to 30% of the total study population.

Investigational medicinal product treatment details are provided in Section 7.2.

Visit windows of ±3 days are allowed from the first dose at all visits through Week 16. The visit window is relative to the Baseline Visit, not the previous study visit. The time between doses should be ≥25 days and ≤31 days. When applying the allowed visit windows, it must be ensured that the time between these 2 visits does not exceed the allowed time between doses.

Bimekizumab or placebo will be administered sc by unblinded study personnel at the study site.

The Double-Blind Treatment Period ends after Week 16 assessments. At Week 16, subjects will transition from the double-blind, placebo-controlled treatment into the 36-week Maintenance Period with bimekizumab treatment, as discussed in Section 5.1.2.2.

Subjects discontinuing IMP during the Double-Blind Treatment Period will be encouraged to return for all scheduled visits through Week 52 and the SFU Visit (20 weeks after the final dose of IMP), as applicable (Section 5.1.4). Subjects withdrawing from the study will have an ET Visit and a SFU Visit 20 weeks after the final dose of IMP, as applicable.

5.1.2.2 Maintenance Period

The 36-week Maintenance Period starts with the Week 16 IMP administration. All subjects will receive bimekizumab 160mg sc Q4W during the Maintenance Period.

- Subjects who received bimekizumab 160mg sc Q4W during the 16-week Double-Blind Treatment Period will continue to receive bimekizumab 160mg sc Q4W.
- Subjects who received placebo during the 16-week Double-Blind Treatment Period will be re-allocated to bimekizumab treatment. After the Week 16 assessments are performed, all subjects will receive bimekizumab 160mg sc Q4W.

Bimekizumab will be administered by the blinded or unblinded study personnel at the study site, according to the site-specific blinding plan.

Visit windows of ±4 days are allowed for all visits after Week 16. The time between doses during the Maintenance Period should be ≥24 days and ≤32 days. When applying the allowed visit windows, it must be ensured that the time between these 2 visits does not exceed the allowed time between doses.

All subjects will be eligible for nonbiologic rescue therapy from Week 20 onwards, as defined in Table 7–2.

Prior to completion of the Maintenance Period, Investigators should discuss treatment options with the subject. Subjects who complete AS0011 and meet the eligibility criteria may enroll in an extension study to continue to receive bimekizumab.

Subjects discontinuing IMP during the Maintenance Period after Week 16 will be encouraged to return for all scheduled visits through Week 52 and the SFU Visit (20 weeks after the final dose of IMP), as applicable. The SFU Visit is not required if the Week 52 Visit is ≥20 weeks after the final dose of IMP (Section 5.1.4). Subjects withdrawing from the study will have an ET Visit and a SFU Visit 20 weeks after the final dose of IMP.

5.1.3 Early Termination Visit

Subjects withdrawing consent and withdrawn early from the study will undergo the ET Visit assessments (see Section 8.5) and will enter the SFU Period.

Subjects withdrawing from IMP who are not continuing for all scheduled visits through Week 52, will undergo the ET Visit, and will enter the SFU Period.

5.1.4 Safety Follow-Up Visit

All subjects who complete the study and do not enter the extension study will undergo the SFU Visit 20 weeks after their final dose of IMP (see Section 8.6).

Subjects withdrawing from the IMP during the study, will be encouraged by the Investigator to return for all scheduled visits through Week 52 and the SFU Visit (unless the Week 52 Visit occurs ≥20 weeks after the final dose of IMP).

Subjects withdrawing from IMP who are not continuing for all scheduled visits, will undergo the ET Visit and the SFU Visit 20 weeks after their final dose of IMP.

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

5.1.5 Study duration per subject

For each subject, the study will last up to 73 weeks, as follows:

- Screening Period: minimum duration of approximately 14 days (unless a screenfailed subject from AS0010 will be screened in AS0011) to ≤35 days
- 16-week Double-Blind Treatment Period
- 36-week Maintenance Period
- A SFU Visit for subjects who complete the study and who do not enter the extension study or who discontinue from the study early, including those withdrawn from IMP, will be conducted 20 weeks after the final dose of the IMP as applicable (ie, Week 48 for subjects who completed AS0011).

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

5.1.6 Planned number of subjects and site(s)

Approximately 300 subjects will be randomly assigned in a 2:1 ratio to the following treatment groups: bimekizumab 160mg sc Q4W (200 subjects) or placebo sc Q4W (100 subjects). The planned number of study sites is approximately 95.

Enrollment requirements will be applied and controlled by the IXRS system.

The minimum proportion of TNFα inhibitor-naïve subjects will be approximately 70% and the maximum proportion of subjects with prior use of TNFα inhibitor will be approximately 30%.

5.1.7 Anticipated regions and countries

This will be a multicenter, international study conducted in approximately 14 countries in the US, Eastern and Western Europe, and Asia. Enrollment will be competitive among study sites and may be capped in regions or at sites.

5.2 Schedule of study assessments

Table 5-2: Schedule of study assessments

Protocol activity	SC	BL (D1)	Double-Blind Treatment Period (16 weeks)						Maintenance Period (36 weeks)									ET	SFU[b]
Week[a]			1	2	4	8	12	16	20	24	28	32	36	40	44	48	52		
Visit[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
Written informed consent	X																		
Demographic data including lifestyle and infection history	X																		
AS history including EAMs	X																		
Significant past medical history and concomitant diseases	X	X[c]																	
Incl./excl. 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	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
eC-SSRS[d]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-9	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ASQoL		X			X	X	X	X		X			X				X	X	
BASDAI	X	X	X	X	X	X	X	X		X			X				X	X	
BASFI		X	X	X	X	X	X	X		X			X				X	X	
SF-36 PCS and MCS		X				X		X		X			X				X	X	
MOS Short Sleep Scale (12 items)		X				X		X		X			X				X	X	
PGADA		X	X	X	X	X	X	X		X			X				X	X	
Total and nocturnal spinal pain (NRS)		X	X	X	X	X	X	X		X			X				X	X	
Tuberculosis questionnaire	X	X					X			X			X			X		X	X

Table 5-2: Schedule of study assessments

Protocol activity	SC	BL (D1)	Double-Blind Treatment Period (16 weeks)						Maintenance Period (36 weeks)									ET	SFU[b]
Week[a]			1	2	4	8	12	16	20	24	28	32	36	40	44	48	52		
Visit[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
FACIT-Fatigue subscale		X			X			X		X			X				X	X	
EQ-5D-3L		X			X			X		X			X				X	X	
WPAI-SHP		X						X		X			X				X	X	
Vital signs (BP, pulse, temperature)[e]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and body weight[f]	X	X				X		X		X			X				X	X	X
Physical examination[g]	X	X				X		X		X			X				X	X	X
TJC/SJC (44/44)		X				X		X		X							X		
MASES		X			X	X		X		X							X	X	
BASMI		X				X		X		X							X	X	
PhGADA		X			X	X		X		X			X				X	X	
ECG[h]	X							X		X							X	X	X
Hematology/ biochemistry	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X							X					X				X	X	X
Urine drug screen	X																		
CRP	X	X		X	X	X	X	X		X			X				X	X	X
Pregnancy testing[i]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing[j,k]	X																		
HIV testing[j]	X																		
HLA-B27 analysis	X																		

Table 5-2: Schedule of study assessments

Protocol activity	SC	BL (D1)	Double-Blind Treatment Period (16 weeks)						Maintenance Period (36 weeks)									ET	SFU[b]
Week[a]			1	2	4	8	12	16	20	24	28	32	36	40	44	48	52		
Visit[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		
BKZ plasma concentration[j]		X		X	X	X	X	X	X	X			X				X	X	X
Anti-BKZ antibody detection[j]		X			X	X	X	X	X	X			X				X	X	X
Serum and plasma samples for exploratory biomarkers[j,l]		X						X									X		
RNA blood samples for exploratory biomarkers[j,l]		X						X									X		
Blood sample for genetic/ epigenetic analysis[j,l]		X						X									X		
Stool samples[l]		X															X		
IGRA TB test[j,m]	X														X				
Chest x-ray[n]	X																		
Sacroiliac joint x-ray[o]	X																		
Spine x-ray[p]		X																	
Sacroiliac and spine MRI[q]		X						X									X		
Enter IXRS[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration[s]		X			X	X	X	X	X	X	X	X	X	X	X	X			

AS=ankylosing spondylitis; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; BL=Baseline; BKZ=bimekizumab; BP=blood pressure; CRP=C-reactive protein; D=day; EAM=extra-articular manifestation; eC-SSRS=electronic Columbia-Suicide Severity Scale; ECG=electrocardiogram; EQ-5D-3L=EuroQol 5 Dimensions 3 Level; ET=Early Termination; excl.=excluding; FACIT=Functional Assessment of Chronic Illness Therapy; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; IGRA=interferon gamma release assay; IMP=investigational medicinal product; incl.=including; IXRS=interactive voice or web response system; MASES=Maastricht Ankylosing Spondylitis Enthesitis; MCS=mental component score; MOS=Medical Outcomes Study; MRI=magnetic resonance imaging; NRS=numeric rating scale; mNY=modified New York; PCS=physical component score; PGADA=Patient's Global Assessment of Disease Activity; PhGADA=Physician's Global Assessment of Disease Activity; PHQ-9=Patient's Health

Table 5-2: Schedule of study assessments

Protocol activity	SC	BL (D1)	Double-Blind Treatment Period (16 weeks)						Maintenance Period (36 weeks)									ET	SFU[b]
Week[a]			1	2	4	8	12	16	20	24	28	32	36	40	44	48	52		
Visit[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		

Questionnaire 9; RNA=ribonucleic acid; SC=Screening; SF-36=Short Form-36 Health Survey; SFU=Safety Follow-Up; SJC=swollen joint count; TB=tuberculosis; TJC=tender joint count; WPAI-SHP=Work Productivity and Activity Impairment Questionnaire-specific health problem

[a] Visit windows of ±3 days are allowed for all visits through Week 16. The visit window is relative to the Baseline Visit, not the previous week's visit. During the Maintenance Period, visit windows of ±4 days are permitted for all visits after Week 16.

[b] The SFU Visit occurs 20 weeks after the final 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. The visit window for the SFU Visit is -3/+7 days.

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

[d] 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.

[e] Collect vital signs (pulse, BP, and temperature) prior to IMP administration and then at 30 minutes after administration and 1 hour after administration at Baseline and Week 16 only. At all other applicable visits, vital signs will be collected once prior to IMP administration. All other procedures are done prior to dosing.

[f] The Investigator or designee will measure the height of the subject with shoes removed in meters once at Screening and the weight of the subject in kilograms.

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

[h] ECGs will be read centrally.

[i] Pregnancy testing will consist of serum testing at Screening for all women of childbearing potential. A urine dipstick will be used for pregnancy testing at all other visits (Section 12.7.6).

[j] At dosing visits, all blood samples are taken prior to dosing. Blood samples for bimekizumab and anti-bimekizumab antibody detection as well as pharmacogenetics/genomics will be processed as per instructions in the lab manual.

[k] Subjects who have evidence of or test positive for hepatitis B or hepatitis C are excluded. Positive test criteria are defined in Section 6.2.

[l] A separate Informed Consent Form will be required for subjects who decide to participate in the pharmacogenomic substudy. The Informed Consent Form must be signed prior to collecting any samples for the substudy. Blood and/or stool samples are collected for exploratory purposes and participation in either blood or stool sampling (or both) is optional.

[m] An IGRA TB test will be performed at the central laboratory. Details will be specified in the Laboratory Manual.

[n] If a subject has had a recent x-ray of the chest within 3 months prior to the Screening Visit, it may be used as the Screening chest x-ray. Any findings suggestive of active TB are exclusionary.

[o] The following will be accepted to qualify AS subjects for this study: a) sacroiliac joint x-ray centrally read for the Phase 3 study AS0010 determined to be modified New York Criteria positive (+mNY); neither the reading nor the x-ray will be repeated; b) prior sacroiliac joint x-ray (performed at any time prior to the study) was submitted and centrally read for the purposes of this study and determined to be modified New York Criteria positive (+mNY). If the prior x-ray is not meeting central reading criteria for randomization, another x-ray may be performed if prior x-ray is more than 1 year old and if permitted by local guidelines, or c) if no prior x-ray is available, one must be performed at Screening.

Table 5-2: Schedule of study assessments

Protocol activity	SC	BL (D1)	Double-Blind Treatment Period (16 weeks)						Maintenance Period (36 weeks)									ET	SFU[b]
Week[a]			1	2	4	8	12	16	20	24	28	32	36	40	44	48	52		
Visit[a]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17		

[p] The spine x-ray at Baseline for subjects with confirmed eligibility can be performed prior to or after the Baseline Visit, and must be performed prior to or no later than on the day of the second administration of IMP. The spine x-ray will be centrally read and will be used to assess disease progression in the spine in the extension study, given the subject is willing to enter this subsequent study. If the subject has a spine x-ray available from the past 6 months prior to Screening, this x-ray may be used and submitted for central reading.

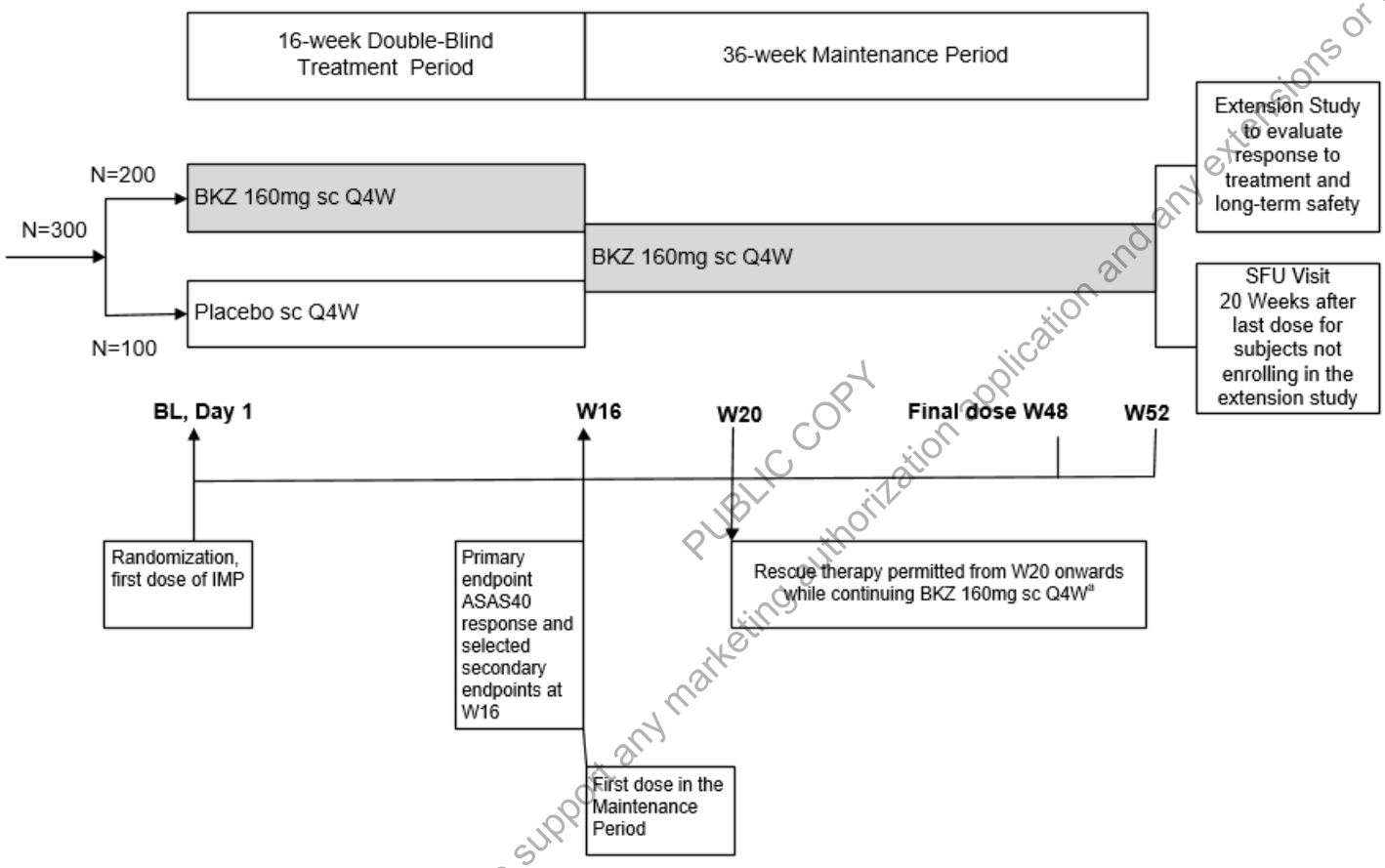
[q] Sacroiliac joint and spine MRIs will be performed for subjects participating in the MRI substudy. Baseline sacroiliac joint and spine MRIs should be performed after confirmation of eligibility based on screening assessments for the study and before the first dose of IMP. The sacroiliac joint and spine MRIs can be performed at Baseline or prior to the actual Baseline Visit. Further sacroiliac joint and spine MRIs will be performed at Weeks 16 and 52, within a window of ±5 days for all subjects participating in the substudy.

[r] The IXRS is used to register subjects at Screening, randomize subjects at Baseline/Day 1, rerandomize subjects at Week 16 and to register all visits.

[s] At Week 16, the Maintenance Period dosing will start, as detailed Section 5.1.2.2. At Week 52, IMP administration will only occur for subjects entering the extension study. Dosing details at Week 52 will be provided in the protocol of the extension study.

5.3 Schematic diagram

Figure 5–1: Schematic diagram: study overview



ASAS40=Assessment of SpondyloArthritis International Society 40% response criteria; BKZ=bimekizumab; BL=Baseline; IMP=investigational medicinal product; Q4W=every 4 weeks; sc=subcutaneous; SFU=Safety Follow-Up; W=week

[a] Subjects are eligible for nonbiologic rescue therapy starting at Week 20 with treatment at the discretion of the Investigator while continuing to receive BKZ. Treatment with non-BKZ biologics or prohibited treatment (see Section 7.8.2) will lead to BKZ discontinuation (Table 7–2).

5.4 Rationale for study design and selection of dose

AS0011 will evaluate the efficacy and safety of bimekizumab at a dose level of bimekizumab 160mg sc Q4W in adult subjects with AS.

5.4.1 Study design

A randomized, double-blind, placebo-controlled study design has been selected to evaluate the efficacy and safety of bimekizumab. The study population will include adult subjects with active AS and allow subjects who have received previous biologic treatment (eg, a TNFα inhibitor) as well as those who are biologic treatment-naïve. The primary efficacy outcome measures (ASAS40 response) and other efficacy assessments included in this study are consistent with those used for other axSpA studies and are considered appropriate for establishing efficacy of bimekizumab. An initial double-blind treatment period of 16 weeks will be used to demonstrate the efficacy of bimekizumab over placebo. The study duration extends beyond the initial Double-Blind Treatment Period (ie, Maintenance Period up to 52 weeks) to collect data on the maintenance of efficacy of bimekizumab for exploratory analyses and to allow continued evaluation of safety data.

5.4.2 Dose selection

A bimekizumab dose of 160mg sc Q4W has been selected for AS0011.

Bimekizumab doses of 16mg to 320mg Q4W were evaluated in a multicenter, Phase 2b, double-blind, placebo-controlled, randomized, parallel-group study in subjects with active AS (AS0008). Results from the Week 12 interim analysis indicated bimekizumab doses up to and including 320mg have an acceptable safety profile and PK/PD modelling indicated a plateau in Week 12 ASAS40 response at doses of 160mg and above. This plateau at bimekizumab160mg was further confirmed based on the observed noncontrolled Week 48 data, which demonstrated a similar ASAS40 response between 160mg and 320mg Q4W at Week 48.

There were no dose-related safety concerns or changes in laboratory values in the preliminary data review up to 48 weeks that preclude the use of any of the tested doses in AS0008 for the Phase 3 program in axSpA.

The same dosing regimen was selected for a Phase 3 program evaluating bimekizumab in subjects with active PsA.

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:

1a. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.

2a. Subject 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. Subject has AS as per the Modified New York (mNY) criteria (1984) including documented radiologic evidence (x-ray) based on central reading and at least 3 months of symptoms (Table 19–2) with age at symptom onset <45 years.
5. Subject has moderate-to-severe active disease as defined by **BOTH** of the following at Screening **AND** Baseline:
   - BASDAI ≥4 AND spinal pain ≥4 on a 0 to 10 NRS (from BASDAI Item 2)

6a. Subjects had to have either failed to respond to 2 different NSAIDs given at the maximum tolerated dose for a total of 4 weeks or have a history of intolerance to or a contraindication to NSAID therapy.

7. Subjects who are regularly taking NSAIDs/COX-2 inhibitors or analgesics (including mild potency opioids) are required to be on a stable dose for at least 14 days before Baseline.
8. Subjects taking corticosteroids must be on an average daily dose of ≤10mg/day prednisone or equivalent for at least 14 days before Baseline.
9. Subjects taking MTX (≤25mg/week) or LEF (≤20mg/day or an average of 20mg/day if not dosed daily) are allowed to continue their medication if started at least 12 weeks prior to Baseline, with a stable dose and route of administration (MTX) for at least 8 weeks before randomization. It is strongly recommended that subjects taking MTX are also taking folic acid supplementation.
10. Subjects taking SSZ up to 3g/day (or 4g/day if in accordance with local standard of care), HCQ up to 400mg/day (other anti-malarials may be used if in accordance with local standard of care), or apremilast (up to 60mg/day and dosed as per local label) are allowed to continue their medication if started at least 8 weeks prior to Baseline, with a stable dose for at least 4 weeks before randomization.
11. Subjects who have taken a TNFα inhibitor must have experienced an inadequate response to previous treatment given at an approved dose for at least 12 weeks or have been intolerant to treatment.
12. Female subjects must be:
    - Postmenopausal. Menopause is defined as 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause.
    - 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 throughout the duration of the study until 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)
- Vasectomized partner
- Abstinence as a form of birth control is generally not allowed in the study unless abstinence is in accordance with a subject's preferred and common lifestyle. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study

6.2 Exclusion criteria

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

1. Female subject who is breastfeeding, pregnant, or plans to become pregnant during the study or within 20 weeks following the final dose of IMP.
2. Subject has previously participated in a bimekizumab clinical study who received at least 1 dose of the IMP (including placebo).

3a. Subject previously participated in another study of a medication (systemic) under investigation within the 12 weeks or at least 5 half-lifes prior to the Baseline Visit, whichever is greater, or is currently participating in another study of a medication (systemic) under investigation, with the exception of subjects who were screen failures in AS0010.

4. Subject previously participated in another study of a medical device under investigation within the 4 weeks prior to the Screening Visit, or is currently participating in another study of a medical device under investigation.
5. Subject has a known hypersensitivity to any excipients of bimekizumab.
6. Subjects with a total ankylosis of the spine.
7. Subjects with fibromyalgia or osteoarthritis symptoms that in the Investigator's opinion would have potential to interfere with efficacy assessments.
8. Subject had acute anterior uveitis within 6 weeks of the Baseline Visit.
9. Subjects who have received more than 1 TNFα inhibitor and/or more than 2 additional non-TNFα biological response modifiers, or any IL-17 biological response modifier at any time are excluded (please refer to Table 7–2).
10. Subject is taking or has taken prohibited medications as outlined in Table 7–2 without meeting the mandatory washout period(s) relative to the Baseline visit.

11. Subject has an active infection or history of infections as follows:
    - Any active infection (except common cold) within 14 days prior to Baseline.
    - A serious infection, defined as requiring hospitalization or iv anti-infectives within 2 months prior to Baseline.
    - A history of opportunistic, recurrent or chronic infections that, in the opinion of the Investigator, might cause this study to be detrimental to the subject. Opportunistic infections are infections caused by uncommon pathogens (eg, Pneumocystis jirovicii, Cryptococcosis) or unusually severe infections caused by common pathogens (eg, cytomegalovirus [CMV], herpes zoster).
12. Subject has 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).
13. Subject has received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline Visit (eg, inactivated influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted) or has received Bacillus Calmette-Guerin vaccinations within 1 year prior to the Baseline Visit.
14. Subject has known tuberculosis (TB) infection, at high risk of acquiring TB infection, or current or history of nontuberculous mycobacterium (NTMB) infection. A subject with latent tuberculosis (LTB) (a positive interferon-gammy release assay [IGRA] and diagnosis confirmed by TB specialist) may be rescreened once and enrolled after receiving at least 4 weeks of appropriate LTB infection therapy and if no evidence of therapy-related hepatotoxicity has occurred prior to the first injection (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] remain ≤3 times upper limit of normal [ULN]).

    Subject has a past history of active TB involving any organ system, unless adequately treated according to World Health Organization (WHO)/Center for Disease Control and Prevention (CDC) therapeutic guidance and proven to be fully recovered upon consult with a TB specialist.

    Refer to Section 12.7.5 for details on determining full TB exclusion criteria.
15. Subject has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
16. Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma or in situ cervical cancer.

17a. Subject has a diagnosis of inflammatory conditions other than AS, including but not limited to psoriatic arthritis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and reactive arthritis. Subjects with a diagnosis of Crohn's disease, ulcerative colitis, or other IBD are allowed as long as they have no active symptomatic disease at Screening or Baseline.

18. Subject has had major surgery (including joint surgery) within the 3 months prior to the Baseline, or has planned major surgery within 6 months after entering the study.

19. Subject has any systemic disease (ie, cardiovascular, neurological, renal, hepatic, metabolic, gastrointestinal, hematological, immunological, etc) considered by the Investigator to be uncontrolled, unstable or likely to progress to a clinically significant degree during the course of the study.

20. Subject has had myocardial infarction or stroke within the 6 months prior to the Screening Visit.

21. Subject has laboratory abnormalities at Screening, including any of the following:

    a. ≥3.0 ULN of any of the following: ALT, AST, alkaline phosphatase (ALP); or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome)

    b. White blood cell (WBC) count <3.00 $x10^3/\mu L$

    c. Absolute neutrophil count <1.5 $x10^3/\mu L$

    d. Absolute lymphocyte count <500 cells/μL

    e. Hemoglobin <8.5g/dL

    f. Creatinine >2mg/dL

    g. Any other laboratory abnormality, which, in the opinion of the Investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results

    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. Upon retesting, subjects whose results remain outside this threshold should not be randomized.

22. Subject has any other condition, including medical or psychiatric, which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.

23. Presence of active suicidal ideation, or positive suicide behavior using the "Screening" version of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) with either of the following criteria:

    – History of a suicide attempt within the 5 years prior to the Screening Visit. Subjects with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare practitioner (HCP) before enrolling into the study.

    – Suicidal ideation in the past month prior to the Screening Visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening" version of the eC-SSRS

24. Subject has moderately severe major depression or severe major depression, indicated by a score ≥15 using the Screening PHQ-9. Medication used to treat depression should be stable for 8 weeks prior to Baseline.
25. Subject has a history of chronic alcohol or drug abuse within 6 months prior to Screening as evaluated by the Investigator based on medical history, site interview, and/or results of the specified urine drug screen.
26. Subject is a member of Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
27. Subject is a UCB employee or 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 the subject withdraws his/her consent.

Subjects should be withdrawn from IMP and encouraged by the Investigator to return for all scheduled visits through Week 52, and the SFU Visit (if the Week 52 Visit is ≥20 weeks after the final dose of IMP, the SFU Visit is not required) if any of the following events occur:

1. The Sponsor or a regulatory agency requests withdrawal of the subject.
2. Subject develops an illness that in the opinion of the Investigator would interfere with his/her continued participation if the risk of continuing IMP outweighs the potential benefit.
3. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
4. 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 or the integrity of the study data, in the opinion of the Investigator and/or the Medical Monitor.
5. Subject has a clinical laboratory value meeting any of the following criteria:
   a. Hepatotoxicity as described in Section 6.3.1.
   b. A laboratory value meeting any of the following criteria:
      - Absolute neutrophil count <1.0 x10^3/µL
      - Absolute lymphocyte count <200 cells/µL

   Subjects may remain on IMP if the result is transient. A retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat absolute neutrophil count or absolute lymphocyte count is still below the allowable values, the subject must be withdrawn from the IMP. If the repeat absolute neutrophil count or absolute lymphocyte count is above the allowable values, the subject may continue to receive IMP.
6. The subject experiences a severe AE, an SAE, or a clinically significant change in a laboratory value occurs that, in the opinion of the Investigator, merits the discontinuation of the IMP and appropriate measures being taken.

7. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test (see Section 12.2 for more information regarding pregnancies).
8. A subject considered as having either a suspected new LTB infection or who develops active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by IGRA or other diagnostic means) must be immediately discontinued from IMP, and an ET Visit must be scheduled 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 latent TB infection (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 an SAE and must be captured in the eCRF in the SAE Report Form section. 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 12.7.5.
9. Subjects with newly diagnosed IBD or with IBD flares during the study must:

   – Be referred, as appropriate, to a healthcare 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 judgement in deciding whether the subject should continue on IMP and contact the Medical Monitor and UCB Study Physician to confirm the subject's suitability for continued participation in the study.
10. Subjects must be referred immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk for:

    – Active suicidal ideation as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the eC-SSRS

    – Moderately severe major depression as indicated by a PHQ-9 score of 15 to 19 if this represents an increase of 3 points compared to the last visit

    The mental health consultation must be recorded in the subject's source documentation.

11. Subjects must be referred immediately to a mental healthcare professional and must be withdrawn from the study in case of:
    - Active suicidal ideation as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the eC-SSRS.
    - Any suicidal behavior since last visit.
    - Severe major depression as indicated by a PHQ-9 score ≥20.

    The mental health consultation must be recorded in the subject's source documentation.
12. Any subject who develops a clinically important infection or recurrent infections not responsive to standard therapy during the study must discontinue IMP until resolution of the infection. The Investigator should use clinical judgement in deciding whether the subject should restart IMP and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.

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

Subjects withdrawing from the study who are not continuing for all scheduled visits, will undergo the ET Visit and the SFU Visit 20 weeks after their final dose of IMP, as applicable.

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 discontinuation of IMP for subjects with either of the following:

- ALT or AST ≥8x ULN
- 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%).

  If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in (Section 12.6.1.2.1) are followed.

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

- Subjects with ALT or AST ≥5xULN and <8xULN, 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 12.6.1 with repeat tests performed in 2 weeks. Upon re-test, if ALT or AST values have reduced to <5xULN, the subject can continue with the study. However, if ALT or AST remains ≥5xULN and <8xULN after re-test, IMP should be temporarily withheld and subject should undergo a repeat test in 2 weeks. If ALT or AST values remain ≥5xULN even after the second re-test, then the subject should be immediately discontinued from IMP and should be followed for possible PDILI.

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 eCRF 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.

- [redacted]
- Placebo will be supplied as 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (US Pharmacopoeia/European Pharmacopoeia) quality in a 1mL PFS for sc injection.

Details of the IMPs and their specification will be provided in the IMP Handling Manual.

7.2 Treatment(s) to be administered

Unblinded study personnel will be responsible for recording the administration information on source documents, and administration of the IMP as sc injections. The unblinded personnel will not be involved in any other aspect of the study. During the Maintenance Period, bimekizumab will be administered by unblinded study personnel, unless the site-specific blinding plan allows for the administration by blinded study personnel.

Suitable areas for sc injections are the lateral abdominal wall, upper arm, and upper outer thigh. Injection sites should be rotated and injections should not be given in areas where the skin is tender, bruised, red, or hard.

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

7.2.1 Double-Blind Treatment Period

Subjects will be randomized 2:1 to receive 1 of 2 blinded treatment regimens during the Double-Blind Treatment Period. To keep the blinding, all subjects will receive administrations as per the dosing scheme shown in Table 7–1.

The IMP (bimekizumab and placebo) will be administered at the time points indicated in Table 5-2. The Double-Blind Treatment Period ends with Week 16 assessments and the final dose in the Double-Blind Period will be administered at Week 12.

During the Double-Blind Treatment Period, bimekizumab or placebo will be administered by unblinded study personnel at the study site.

Table 7–1: Overview on dosing during the Double-Blind Treatment Period

Treatment arm	Dosing
BKZ 160mg sc Q4W	Subjects will receive 1 BKZ 160mg injection sc at Week 0 (Baseline) followed by BKZ 160mg sc Q4W at Weeks 4, 8, and 12.
PBO sc Q4W	Subjects will receive 1 PBO injection sc at Week 0 (Baseline) followed by PBO sc Q4W at Weeks 4, 8, and 12.

BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks, sc=subcutaneous

7.2.2 Maintenance Period

The 36-week Maintenance Period starts with the Week 16 IMP administration. All subjects will receive bimekizumab 160mg sc Q4W during the Maintenance Period and will receive treatments as follows:

- Subjects who received bimekizumab 160mg sc Q4W during the 16-week Double-Blind Treatment Period will continue to receive bimekizumab 160mg sc Q4W.
- Subjects who received placebo during the 16-week Double-Blind Treatment Period will be re-allocated to bimekizumab treatment. After the Week 16 assessments are performed, all subjects will receive bimekizumab 160mg sc at the Week 16 Visit.

During the Maintenance Period, all subjects will receive bimekizumab, and the responsibility for recording the administration information and the administration of the IMP can be switched to the blinded team only if the site-specific blinding plan defines a process of maintaining the blind of the documentation of IMP administration of the Double-Blind Treatment Period.

7.3 Packaging

The IMPs are manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) 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 for 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 according to the storage conditions mentioned on the label.

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

In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

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, damaged (due to breakage or wastage), not used, partially 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.

The packaging identifies each kit by a unique number and by the content. Unblinded study staff will be responsible for preparation (eg, breaking tamper proof sticker on kit) of the clinical trial material, including recording the administration information in the source document during the Double-Blind Treatment Period. During the Maintenance Period, bimekizumab will be administered by unblinded study personnel unless the site-specific blinding plan allows the administration by blinded study personnel (Section 7.2.2).

All IMP documentation of the Double-Blind Treatment Period (eg, shipping receipts, drug accountability logs, 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. Each site will be required to have a written site-specific blinding plan in place signed by the Investigator, which will detail the site's steps for ensuring that the double-blind nature of the study is maintained from Week 0 to Week 16/ET, and for defining site-specific responsibilities of the blinded and unblinded team during the course of the study.

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)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB SOPs or returned to UCB (or designee). 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 Treatment Period and the Maintenance Period, bimekizumab and placebo 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 medications/treatments

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

Medications listed in Table 7–2 are prohibited, restricted, or used as nonbiologic rescue therapy.

Table 7–2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
Analgesics • Acetaminophen/ paracetamol	Any change in dose/dose regimen within 14 days prior to BL	Stable dose/regimen permitted Ad hoc/PRN/"as needed use" permitted, but: **No** ad hoc/PRN/"as needed use" in the 24h prior to any study visit	Ad hoc/PRN/"as needed use" permitted, but: **No** ad hoc/PRN/"as needed use" in the 24h prior to any study visit
NSAID/COX-2 inhibitors	Any change in dose/dose regimen within 14 days prior to BL	Stable dose/ regimen permitted No change until Week 20 Visit	Nonbiologic rescue therapy will be at the Investigator's discretion with the following options for symptoms: • For subjects taking an NSAID/COX-2 inhibitor dosing can be optimized; a change can be made to a different NSAID/COX-2 inhibitor; changes from an NSAID to a COX-2 inhibitor or from a COX-2 inhibitor to an NSAID are also permitted up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 inhibitor may be taken at a given time. • For subjects not taking NSAID/COX-2 inhibitors either 1 NSAID, or 1 COX-2 inhibitor can be initiated, up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 inhibitor may be taken at a given time. • For subjects who cannot take NSAIDs/COX-2 inhibitors, topical NSAIDs are also a potential nonbiologic rescue therapy in regions where they are approved, up to the maximum approved or tolerated dose, whichever is lower.
Mild potency opioids permitted only eg,: • Tramadol/any dose up to maximum approved dose • Codeine/only <90mg of codeine per dosage unit	Any change in dose/dose regimen within 14 days prior to BL	Dosing/ schedule should remain stable for the first 20 weeks of the study	**Prohibited** for rescue therapy

Table 7–2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
Oral corticosteroids/average daily dose of ≤10mg/day prednisone or equivalent	Any change in dose/dose regimen within 14 days prior to BL	Permitted, but: • **No** steroid bursts/tapers • **No** increase in steroid dosing • **No** initiation of steroids until the Week 20 Visit	**Prohibited** for rescue therapy
Topical corticosteroids	None	Permitted	Not applicable
Corticosteroids: • Intramuscular • Intravenous • Intra-articular • Bursal	Use within 28 days prior to BL	**Prohibited** unless used as rescue therapy from Week 20 or later	Nonbiologic rescue therapy will be at the Investigator's discretion with the following options for symptoms: • Sacroiliac joint steroid injection(s), either unilateral or bilateral. For non-axial symptoms: • One peripheral joint (or bursa) may be injected with a steroid at or after any visit where nonbiologic rescue therapy eligibility is assessed; however, the same joint may not be injected more than once during the study and should not be injected within 4 weeks of a sacroiliac joint injection(s).
Intra-articular hyaluronic acid	Use within 8 weeks prior to the BL Visit or during the study	**Prohibited**	Not applicable
Any established antidepressant regimen	Any change in dose/dose regimen within 8 weeks prior to BL	Permitted	Not applicable

Table 7–2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
csARDs/formerly known as DMARDs			
• Azathioprine • Cyclosporine • Cyclophosphamide • Mycophenolic acid • Mycophenylate mofetil • Any other small molecule DMARDs	Use within 8 weeks prior to BL	**Prohibited**	**Prohibited** for rescue
• Methotrexate (MTX)	Use within 12 weeks prior to BL unless Inclusion Criterion #9 is met	Permitted MTX (≤25mg/week)	For non-axial symptoms: • MTX may be added or increased to a maximum dose of 25mg/week, or the maximum tolerated dose, whichever is lower, in accordance with local standard of care. The route of administration may be changed from oral to sc or from sc to oral, at any visit at Week 20 or later. It is strongly recommended that subjects taking MTX are also taking folic acid supplementation.
• Leflunomide (LEF)	Use in the 6 months prior to the BL Visit (unless a cholestyramine washout has been performed; in which case, use up to 28 days prior to the BL Visit is acceptable) unless Inclusion Criterion #9 is met	Permitted LEF (≤20mg/day or an average of 20mg/day if not dosed daily)	For non-axial symptoms: • 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.

Table 7–2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
• Hydroxychloroquine (HCQ) (and other anti-malarials) • Sulfasalazine (SSZ) • Apremilast	Use within 8 weeks prior to BL unless Inclusion Criterion #10 is met	Permitted	For non-axial symptoms: • HCQ may be added or increased to a maximum dose of 400mg/day or the maximum tolerated dose, whichever is lower. Other anti-malarials may be used in accordance with local standard of care. • SSZ may be added or increased up to a maximum dose of 3g/day (up to 4g/day if in accordance with local standard of care), or the maximum tolerated dose, whichever is lower. • Apremilast may be given at a maximum dose of 60mg/day and dosed as per Investigator's discretion or local label. Combination DMARDs are allowed except that LEF and MTX may not be given together.
JAK inhibitors			
• Eg, tofacitinib • Upadacitinib	Use within 8 weeks prior to BL	**Prohibited**	Not applicable

Table 7–2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
Biologic DMARDs			
TNFα inhibitors: • Infliximab (IFX) • Golimumab (GOL) • Certolizumab pegol (CZP) • Adalimumab (ADA) • Etanercept (ETN) • Biosimilar versions of any TNFα inhibitor	For IFX, ADA, GOL, and CZP, any use within the 12 weeks prior to the BL Visit For ETN, use within the 28 days prior to the BL Visit Any use of >1 TNFα in the history Subjects not meeting Inclusion Criterion #11.	**Prohibited**	Not applicable
Other biologics: • Abatacept • Alefacept • Efalizumab • Guselkumab • Sarilumab • Sirukumab • Tocilizumab • Others in development targeting IL-6 or IL-6R	Any use within 12 weeks prior to BL	**Prohibited**	Not applicable
• Ustekinumab	Any use within 24 weeks prior to BL	**Prohibited**	Not applicable
• Tildrakizumab	Any use within 4 months prior to BL	**Prohibited**	Not applicable
• Risankizumab	Any use within 5 months prior to BL	**Prohibited**	Not applicable
• Briakinumab	Any use within 6 months prior to BL	**Prohibited**	Not applicable

Table 7–2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
• Rituximab (incl. biosimilars), ocrelizumab	Any use within 12 months prior to BL	**Prohibited**	Not applicable
Anti-IL-17 therapy: • Bimekizumab • Secukinumab • Ixekizumab • Brodalumab • Others in development	Any exposure history	**Prohibited**	Not applicable

BL=Baseline; ADA=adalimumab; COX-2=cyclooxygenase 2; csARD=conventional synthetic antirheumatic drug; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; h=hour; HCQ=hydroxychloroquine; IFX=infliximab; JAK=Janus kinase; LEF=leflunomide; IL=interleukin; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; PRN=as needed; sc=subcutaneous; SSZ=sulfasalazine; TNFα=tumor necrosis factor alpha

[a] Note: any medication not listed here for rescue therapy must be approved by the Medical Monitor prior to starting that medication.

7.8.1 Permitted concomitant treatments (medications and therapies)

No medication increases or additions for AS are permitted until after the Week 20 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. Permitted nonbiologic rescue therapy is described in Table 7–2.

Whenever possible, physical therapy/physiotherapy/non-medication/complementary and alternative treatment(s) (including traditional Chinese medications) of AS should remain stable through the Week 20 Visit.

Subjects are allowed to use any other medications, including biologics, after at least 28 days of their final dose of the IMP. This is applicable for subjects who discontinue from the study early, including those permanently withdrawn from IMP, or subjects who have completed the study treatment without entering the extension study and are in the SFU Period.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Prohibited concomitant treatments are described in Table 7–2.

7.8.3 Nonbiologic rescue therapy

Nonbiologic rescue therapy will be at the Investigator's discretion as add-on therapy to bimekizumab at any time from Week 20 or later as described in Table 7–2.

7.8.4 Vaccines

Administration of live (including attenuated) vaccines is not allowed during the conduct of the study and for 20 weeks after the final dose of IMP. Administration of inactivated vaccines is allowed during the study at the discretion of the Investigator.

7.9 Blinding

Due to differences in presentation between bimekizumab and placebo treatments in the Double-Blind Treatment Period up to Week 16, special precautions will be taken to ensure study blinding and study sites will have blinded and unblinded personnel.

Bimekizumab and placebo injections will be administered at the investigational sites by unblinded, dedicated study personnel according to the site-specific blinding plan (Section 7.2). 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.

A full blinding plan for the Week 24 interim statistical analysis will be written as described in Section 15.8.1.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

All subject treatment details will be allocated and maintained by the interactive response technology (IXRS) system.

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 Clinical Project Manager (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 UCB (or designee). The randomization schedule will be produced by the IXRS vendor. The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subjects treatment assignment will be stratified by region and prior TNFα inhibitor exposure (yes/no). Enrollment of TNFα 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. Subjects who were screen failures in AS0010 and who are rescreened in AS0011, will be assigned a new subject number and will be registered in IXRS.

Eligible subjects will be randomized to treatment groups at the Baseline Visit (Day 1). To randomize a subject, unblinded study personnel will contact the IXRS and provide brief details about the subject to be randomized. The IXRS will automatically inform the unblinded study personnel of the subject's randomization number and the treatment arm assigned. At the end of the 16-week Double-Blind Treatment Period subjects receiving placebo will be re-allocated to the bimekizumab treatment group. 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 Assessments (Table 5-2) 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 (Day 1, first dose of IMP) at all visits through the Week 16 Visit and ±4 days from all visits thereafter. For the SFU Visit (20 weeks after the final dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days). The minimum amount of time between bimekizumab doses should be no less than 25 days and no more than 31 days from Baseline to Week 16 and 24 to 32 days thereafter. When applying the allowed visit windows, it must be ensured that the time between these 2 visits does not exceed the allowed time between doses.

Changes to the dosing schedule outside of the allowed windows should be discussed with the Medical Monitor and may result in subject withdrawal.

8.1 Screening (Visit 1)

The Screening Period will last for a minimum of approximately 14 days (unless a screenfailed subject from AS0010 will be screened in AS0011) and up to a maximum of 35 days.

Prior to any study specific activities, subjects will be asked to read, sign, and date an Informed Consent Form (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 pharmacogenomic and/or MRI substudies. Subjects who decide to participate in the substudies 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 substudies will be independent from their consent to participate in the main study.

Subjects who initially fail to meet selected eligibility criteria (including but not limited to documented completion of LTBI prophylactic therapy) or for whom eligibility assessments could not be completed as planned may be rescreened once after discussion with the Medical Monitor.

An overview on rescreening/retesting requirements is provided in Section 5.1.1.1 and Section 5.1.1.2.

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

- Obtain written informed consent for the main study and for the MRI and/or the pharmacogenomic substudies for participating subjects.
- Collect demographic data including the lifestyle and infection history.
- Collect AS history including extra-articular manifestations (EAMs).
- Collect significant past medical history and concomitant diseases.
- Assess that all inclusion and no exclusion criteria are met.
- Record prior medications.
- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the BASDAI.
- Administer the TB questionnaire.
- Measure BP, pulse, and temperature.
- Measure height and body weight.

- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Perform an ECG.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Serum pregnancy test if the subject is a woman of childbearing potential.
  - Hepatitis B and C tests.
  - HIV test.
  - HLA-B27 status.
  - IGRA TB test.
- Collect urine samples for:
  - Urinalysis.
  - Urine drug screen.
- Obtain a chest x-ray, unless one has been obtained within 3 months prior to the Screening Visit. Any findings suggestive of active TB are exclusionary.
- Obtain an x-ray of the sacroiliac joint unless one has been obtained up to 6 months prior to Screening or as part of screening for AS0010 (see Section 9.20.1 for details).
- Register the subject using the interactive voice or web response system (IXRS).

8.2 Baseline (Visit 2, Day 1, first dose of IMP)

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.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.
- Administer the SF-36 questionnaire.
- Administer the MOS Short Sleep Scale (12 items).

- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the TB questionnaire.
- Administer the FACIT-Fatigue subscale.
- Administer the EQ-5D-3L.
- Administer the WPAI-SHP.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Perform the TJC and SJC assessment.
- Determine the MASES.
- Determine the BASMI.
- Administer the PhGADA.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- For subjects consenting on a separate ICF for participation in the pharmacogenomic substudy:
  - Collect serum and plasma samples for exploratory biomarkers.
  - Collect ribonucleic acid (RNA) blood samples for exploratory biomarkers.
  - Collect blood samples for genetic/epigenetic analysis.
  - Collect stool samples.
- Obtain an x-ray of the spine unless one has been obtained up to 6 months prior to Screening (see Section 9.20.2 for details). The spine x-ray must be performed prior to or no later than on the day of the second administration of IMP.
- Obtain MRIs of the sacroiliac joint and the spine for subjects consenting on a separate ICF for participation in the MRI substudy prior to the first IMP administration (see Section 9.20.3 for details).
- Randomize the subject using the IXRS.
- Administer IMP.

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

- Measure vital signs approximately 30 minutes and 1 hour after dosing.

8.3 Double-Blind Treatment Period

8.3.1 Week 1 (±3 days) (Visit 3)

- Record concomitant medications.
- Record AEs.
- Administer the BASDAI.
- Administer the BASFI.
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Record the visit in the IXRS.

8.3.2 Week 2 (±3 days) (Visit 4)

- Record concomitant medications.
- Record AEs.
- Administer the BASDAI.
- Administer the BASFI.
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Measure BP, pulse, and temperature.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations.
- Record the visit in the IXRS.

8.3.3 Week 4 (±3 days) (Visit 5)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.

- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the FACIT-Fatigue subscale.
- Administer the EQ-5D-3L.
- Measure BP, pulse, and temperature.
- Determine the MASES.
- Administer the PhGADA.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.3.4 Week 8 (±3 days) (Visit 6)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.
- Administer the SF-36 questionnaire.
- Administer the MOS Short Sleep Scale (12 items).
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Perform the TJC and SJC assessment.
- Determine the MASES.
- Determine the BASMI.

- Administer the PhGADA.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.3.5 Week 12 (±3 days) (Visit 7)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the TB questionnaire.
- Measure BP, pulse, and temperature.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.3.6 Week 16 (±3 days) (Visit 8)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.

- Administer the BASDAI.
- Administer the BASFI.
- Administer the SF-36 questionnaire.
- Administer the MOS Short Sleep Scale (12 items).
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the FACIT-Fatigue subscale.
- Administer the EQ-5D-3L.
- Administer the WPAI-SHP.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Perform the TJC and SJC assessment.
- Determine the MASES.
- Determine the BASMI.
- Administer the PhGADA.
- Perform an ECG.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect urine samples for:
  - Urinalysis.
  - Urine pregnancy test if the subject is a woman of childbearing potential.
- For subjects consenting on a separate ICF for participation in the pharmacogenomic substudy:
  - Collect serum and plasma samples for exploratory biomarkers.
  - Collect RNA blood samples for exploratory biomarkers.
  - Collect blood samples for genetic/epigenetic analysis.

- Obtain MRIs of the sacroiliac joint and the spine for subjects consenting on a separate ICF for participation in the MRI substudy. Magnetic resonance imaging at Week 16 should be performed within ±5 days (see Section 9.20.3 for details).
- Record the visit in the IXRS.
- Administer IMP.

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

- Measure vital signs approximately 30 minutes and 1 hour after dosing.

8.4 Maintenance Period

8.4.1 Week 20 (±4 days) (Visit 9)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Measure BP, pulse, and temperature.
- Collect blood samples for:
  - Hematology and biochemistry.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.4.2 Week 24 (±4 days) (Visit 10)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.
- Administer the SF-36 questionnaire.
- Administer the MOS Short Sleep Scale (12 items).
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the TB questionnaire.
- Administer the FACIT-Fatigue subscale.

- Administer the EQ-5D-3L.
- Administer the WPAI-SHP.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Perform the TJC and SJC assessment.
- Determine the MASES.
- Determine the BASMI.
- Administer the PhGADA.
- Perform an ECG.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.4.3 Week 28 (±4 days) (Visit 11)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Measure BP, pulse, and temperature.
- Collect blood samples for hematology and biochemistry.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.4.4 Week 32 (±4 days) (Visit 12)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Measure BP, pulse, and temperature.

- Collect blood samples for hematology and biochemistry.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.4.5 Week 36 (±4 days) (Visit 13)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.
- Administer the SF-36 questionnaire.
- Administer the MOS Short Sleep Scale (12 items).
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the TB questionnaire.
- Administer the FACIT-Fatigue subscale.
- Administer the EQ-5D-3L.
- Administer the WPAI-SHP.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Administer the PhGADA.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect urine samples for:
  - Urinalysis.
  - Urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.

- Administer IMP.

8.4.6 Week 40 (±4 days) (Visit 14)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Measure BP, pulse, and temperature.
- Collect blood samples for hematology and biochemistry.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.4.7 Week 44 (±4 days) (Visit 15)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Measure BP, pulse, and temperature.
- Collect blood samples for:
  - Hematology and biochemistry.
  - IGRA TB test.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.4.8 Week 48 (±4 days) (Visit 16)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the TB questionnaire.
- Measure BP, pulse, and temperature.
- Collect blood samples for hematology and biochemistry.
- Perform a urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.
- Administer IMP.

8.4.9 Week 52 (±4 days) (Visit 17)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.
- Administer the SF-36 questionnaire.
- Administer the MOS Short Sleep Scale (12 items).
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the FACIT-Fatigue subscale.
- Administer the EQ-5D-3L.
- Administer the WPAI-SHP.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Perform the TJC and SJC assessment.
- Determine the MASES.
- Determine the BASMI.
- Administer the PhGADA.
- Perform an ECG.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect urine samples for:
  - Urinalysis.
  - Urine pregnancy test if the subject is a woman of childbearing potential.

- For subjects consenting on a separate ICF for participation in the pharmacogenomic substudy:
  - Collect serum and plasma samples for exploratory biomarkers.
  - Collect RNA blood samples for exploratory biomarkers.
  - Collect blood samples for genetic/epigenetic analysis.
  - Collect stool samples
- Obtain MRIs of the sacroiliac joint and the spine for subjects consenting on a separate ICF for participation in the MRI substudy. Magnetic resonance imaging should be performed within ±5 days of the Week 52 Visit (see Section 9.20.3 for details).
- Record the visit in the IXRS.

8.5 Early Termination Visit (if applicable)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the ASQoL.
- Administer the BASDAI.
- Administer the BASFI.
- Administer the SF-36 questionnaire.
- Administer the MOS Short Sleep Scale (12 items).
- Perform the PGADA.
- Administer the total and nocturnal spinal pain NRS.
- Administer the TB questionnaire.
- Administer the FACIT-Fatigue subscale.
- Administer the EQ-5D-3L.
- Administer the WPAI-SHP.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Determine the MASES.
- Determine the BASMI.
- Administer the PhGADA.

- Perform an ECG.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect urine samples for:
  - Urinalysis.
  - Urine pregnancy test if the subject is a woman of childbearing potential.
- Record the visit in the IXRS.

8.6 Safety Follow-Up Visit (-3 days/+7 days)

- Record concomitant medications.
- Record AEs.
- Administer the eC-SSRS and the PHQ-9.
- Administer the TB questionnaire.
- Measure BP, pulse, and temperature.
- Measure body weight.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB, and risk for exposure to TB.
- Perform an ECG.
- Collect blood samples for:
  - Hematology and biochemistry.
  - CRP.
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
- Collect samples for:
  - Urinalysis.
  - Urine pregnancy test if the subject is a woman of childbearing potential.
- Record the 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, 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, assessments including, but not limited to the following may be performed, depending on the reason for the visit:

- Record concomitant medication.
- Record AEs.
- Administer the eC-SSRS.
- Measure BP, pulse, and temperature.
- Physical examination.
- Record 12-lead ECG.
- If indicated, obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology, serum chemistry).
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection.
  - An IGRA TB test.
- Obtain urine sample for:
  - Urine pregnancy test.
  - Urinalysis.

9 ASSESSMENT OF EFFICACY

9.1 ASAS20, 40, ASAS 5/6 response, and ASAS-PR

The ASAS20 response is defined as an improvement of at least 20% and absolute improvement of at least 1 unit on a 0 to 10 NRS in at least 3 of the 4 following domains:

- PGADA (see Section 9.8)
- Pain assessment (the total spinal pain NRS score; see Section 9.9)
- Physical function (measured by BASFI, Section 9.5)
- Inflammation (the mean of the BASDAI Questions 5 and 6, [see Section 9.3] concerning morning stiffness intensity and duration)

and absence of deterioration in the potential remaining domain (deterioration is defined as a relative worsening of at least 20% and an absolute worsening of at least 1 unit).

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

The ASAS 5/6 response is defined as at least 20% improvement in 5 of 6 domains, including spinal mobility (lateral spinal flexion) and CRP as more objective measures (Brandt et al, 2004).

The ASAS-PR is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains listed above for ASAS20.

The ASAS20, 40, ASAS 5/6 response, and ASAS-PR will be derived from assessments at the visits specified in Table 5-2.

9.2 ASQoL

The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring health-related quality of life (HRQoL) in subjects with AS (Doward et al, 2003). The ASQoL has been used and has shown to be responsive in axSpA (Barkham et al, 2009; Haibel et al, 2008). Each statement on the ASQoL is given a score of 1 = Yes or 0 = No. A score of "1" is given where the item is affirmed, indicating adverse quality of life. All item scores are summed to total score ranging from 0 to 18 with a higher score indicating worse HRQoL.

The ASQoL will be assessed by the subject at the visits specified in Table 5-2.

9.3 Inflammation – BASDAI (mean of Questions 5 and 6)

Question 5 of the BASDAI (described completely in Section 9.4) measures intensity of morning stiffness. The subject considers the previous week and responds to the question, "How would you describe the overall level of morning stiffness you have had from the time you wake up?" The response is indicated on a 10-point NRS in which 0=None and 10=Very severe. Question 6 of the BASDAI measures duration of morning stiffness. The subject considers the previous week and responds to the question, "How long does your morning stiffness last from the time you wake up? The response is indicated on a 10-point NRS in which 0=0 hours, 5=1 hour, and 10=2 or more hours. The ratings for each question are summed and divided by 2 to provide the mean of questions 5 and 6.

The BASDAI Questions 5 and 6 will be assessed by the subject at the visits specified in Table 5-2.

9.4 BASDAI

The most common instrument used to measure the disease activity of AS from the subject's perspective is the BASDAI (Garrett et al, 1994). The BASDAI is a validated self-reported instrument which consists of six 10-unit horizontal NRSs to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week (van Tubergen et al, 2015). The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. [redacted] and the score is used as the "total back pain" factor in the calculation of ASDAS-CRP. [redacted] and the score is used as the "peripheral pain/swelling" factor in the calculation of ASDAS-CRP. Question 6 of the BASDAI asks the subject to describe his/her overall stiffness from the time of awakening in the past week, and the score is used as the "duration of morning stiffness" factor in the calculation of ASDAS-CRP.

The BASDAI total score is calculated as follows:

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

Fatigue item of the BASDAI

Fatigue, as a major symptom of AS, can effectively be measured with single-item questions such as the BASDAI item (van Tubergen et al, 2002b). This item has shown moderate to good reliability and responsiveness (van Tubergen et al, 2002b). The same minimal clinically important difference (MCID) will be used for the fatigue item of the BASDAI as for the total BASDAI score, ie, a change of 1 unit on the NRS.

The BASDAI will be assessed at the visits specified in Table 5-2.

9.5 Physical function – BASFI

The BASFI is a validated disease-specific instrument for assessing physical function (van der Heijde et al, 2005; Calin et al, 1994). The BASFI comprises 10 items relating to the past week. The NRS version will be used for the answering options of each item on a scale of 0 ("Easy") to 10 ("Impossible") (van Tubergen et al, 2015; van Tubergen et al, 2002a). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to 10, with lower scores indicating better physical function. The MCID used to interpret scores is 7mm on a 0 to 100mm VAS or 17.5% of the Baseline score (Pavy et al, 2005); an MCID of 1 unit will be used for the NRS version.

The BASFI will be assessed by the subject at the visits specified in Table 5-2.

9.6 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). One additional item asks respondents about health change (Health Transition) over the past year. 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). The norm-based T-scores for the 2 SF-36 component summary (PCS and MCS) and the 8 domain scores are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general US population (Maruish, 2011). An individual respondent's score that falls outside the T-score range of 45 to 55 should be considered outside the average range for the US general population. When considering group-level data, a score below 47 should be considered indicative of impaired functioning within that health domain or dimension. Similar to individual respondent data, group mean scores of 47 or greater should be considered average or above average as compared to the general US population. Higher scores indicate a better health status.

The SF-36 will be assessed by the subject at the visits specified in Table 5-2.

9.7 MOS-12

The MOS Sleep Scale is a validated generic self-administered scale measuring specific aspects of sleep. The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 5-point scale ranging from "none of the time" to "all of the time," except sleep quantity, which is reported in hours. All scores are transformed linearly to range from 0 to 100, again with the exception of the sleep quantity subscale, which is scored in hours. Higher scores indicate more of the attribute implied by the scale name (eg, more sleep disturbance, more adequate sleep, and greater sleep quantity). The psychometric properties of the MOS Sleep Scale have been found to be satisfactory by Hays and colleagues (Hays et al, 2005). The domains of interest for this study are the Sleep Disturbance and the Sleep Problems Index II domains.

The MOS-12 Sleep Scale will be assessed by the subject at the visits specified in Table 5-2.

9.8 PGADA

Subjects will score the global assessment of their disease activity in response to the question "How active was your spondylitis on average during the last week?" using a NRS where 0 is "not active" and 10 is "very active" (van Tubergen et al, 2015).

The PGADA will be assessed by the subject at the visits specified in Table 5-2.

9.9 Total and nocturnal spinal pain

The pain experienced by AS subjects is adequately measured by 2 separate questions: 1) total pain in the spine due to AS (ie, "How much pain of your spine due to spondylitis do you have?"); and 2) pain in the spine at night due to AS (ie, "How much pain of your spine due to spondylitis do you have at night?") (Sieper et al, 2009; van der Heijde et al, 2005; Committee for Proprietary Medicinal Product [CPMP]/EWP/556/95, 2004). When responding to each question, the subject is to consider the average amount of pain in the preceding week.

Total and nocturnal spinal pain will be assessed by the subject at the visits specified in Table 5-2.

9.10 FACIT-Fatigue subscale

The FACIT-F is a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function over the past 7 days (FACIT.org). The scale consists of 5 subscales (physical well-being, social/family well-being, emotional well-being, functional well-being, and fatigue). The fatigue subscale is the only one used in this study. It is composed of 13 items, all scored from 0 (Not at all) to 4 (Very much). The FACIT-Fatigue subscale score ranges from 0 to 52 with 0 being the worst possible score and 52 being the best possible score. To obtain a score from 0 to 52, all negatively worded questions have to be recoded, so that responses range from worst (0) to the best (4) outcome.

The FACIT-Fatigue subscale will be completed by the subject at the visits specified in Table 5-2.

9.11 EQ-5D-3L

The EQ-5D-3L is comprised of a 5-item health status dimension and a VAS. The response to each of the 5 health status dimensions is divided into 3 levels (no problem, some or moderate problems, or extreme problems) and is scored as 1, 2, and 3, respectively. The EQ-5D-3L VAS

records the respondent's self-rated health status on a vertical 20cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status).

The EQ-5D-3L will be assessed by the subject at the visits specified in Table 5-2.

9.12 TJC and SJC (44/44)

The following 44 joints are to be examined for tenderness and swelling by the 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. Preferably the same assessor should evaluate the subject at each arthritis assessment.

- Upper body (4) – bilateral sternoclavicular, and acromioclavicular joints.
- Upper extremity (26) – bilateral shoulders, elbows, wrists (includes radiocarpal, carpal and carpometacarpal bones considered as a single unit), metacarpophalangeals (MCPs) I, II, III, IV, and V, and thumb interphalangeals (IPs), and proximal IPs (PIPs) II, III, IV, and V.
- Lower extremity (14) – bilateral knees, ankles, and metatarsophalangeals (I, II, III, IV, and V).

The assessment for tenderness and swelling is made on 44 joints from the above list. Artificial and ankylosed joints are excluded from swelling and tenderness assessments. The assessments per visit are described in the schedule of study assessments Table 5-2.

Table 9–1 summarizes the swelling and tenderness grading criteria.

Table 9–1: Tenderness and swelling grading

Grade	Tenderness response (44)	Swelling response (44)
0	Not tender	None
1	Tenderness present	Detectable synovial thickening

9.13 WPAI-SHP v2.0

The WPAI-SHP v2.0 is a patient-reported questionnaire that assesses subject's employment status, work absenteeism, work impairment while working (presenteeism), overall work, and daily activity impairment attributable to a specific health problem (WPAI-SHP) (Reilly et al, 1993). It has been used in several clinical studies of biologic therapy in subjects with plaque PSO (Kimball et al, 2012; Vender et al, 2012).

Five out of 6 items of the WPAI-SHP are regrouped into the 4 dimensions, with scores expressed as percentage, where higher numbers indicate greater impairment and less productivity, ie, worse outcomes, as described in the WPAI-SHP scoring rules.

The WPAI-SHP v2.0 will be assessed by the subject at the visits specified in Table 5-2.

9.14 CRP

Blood will be collected for measurement of CRP (ie, determination of hs-CRP). After Baseline, the CRP data will not be sent to the Investigator to protect the blinded nature of the treatment assignments and response.

9.15 ASDAS

The ASDAS is comprised of a number of assessments which are scored by the subject and Investigator and multiplied by a validated formula (van der Heijde et al, 2009) as listed:

- 0.121 x Total back pain (BASDAI Q2 result, Section 9.4)
- 0.058 x Duration of morning stiffness (BASDAI Q6 result, Section 9.4)
- 0.110 x PGADA (Section 9.8)
- 0.073 x Peripheral pain/swelling (BASDAI Q3 result, Section 9.4)
- 0.579 x (natural logarithm of the CRP [mg/L] + 1)

Back pain, PGADA, duration of morning stiffness, peripheral pain/swelling, and fatigue are all assessed on a numerical scale (0 to 10 units) (Lukas et al, 2009). The results of these calculations are summed to calculate the ASDAS.

The variables related to ASDAS disease activity are defined as follows:

- ASDAS-Inactive Disease (ASDAS-ID): ASDAS <1.3
- ASDAS-Low Disease activity (ASDAS-LD): ASDAS ≥1.3, <2.1
- ASDAS-High Disease activity (ASDAS-HD): ASDAS ≥2.1, ≤3.5
- ASDAS-very High Disease activity (ASDAS-vHD): ASDAS >3.5

The variable related to ASDAS improvement is defined as follows:

- ASDAS-MI: ASDAS reduction (improvement) of ≥2.0 relative to Baseline

The ASDAS variables will be derived from assessments at the visits specified in Table 5-2.

9.16 MASES

Enthesitis is assessed with the 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.

The MASES will be assessed at the visits specified Table 5-2.

9.17 BASMI

The BASMI characterizes the spinal mobility of subjects with AS. The BASMI is a disease-specific measure consisting of 5 clinical measures to reflect subject axial status: cervical rotation; tragus to wall distance; lateral spinal flexion; modified Schober test; intermalleolar distance. Each of the 5 movements is scored according to the linear BASMI definition. The mean of the 5 scores provides the BASMI score. The higher the BASMI score the more severe the subject's limitation of movement due to their AS.

The BASMI will be assessed at the visits specified in Table 5-2.

9.18 PhGADA

The Investigator will assess the overall status of the subject with respect to their AS signs and symptoms and functional capacity using an NRS in which 0=very good, asymptomatic and no limitations of normal activities and 10=very poor, very severe symptoms which are intolerable and inability to carry out normal activities.

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

The PhGADA will be assessed at the visits specified in Table 5-2.

9.19 Occurrence of extra-articular manifestations

Information regarding dactylitis, PSO, uveitis, and IBD events during the study will be captured as AEs. Enthesitis will be assessed regularly via the MASES performed at site visits as specified in Table 5-2.

9.20 Imaging evaluation

Screening imaging evaluations need to be completed during the Screening Period.

Radiographs and MRIs are read by 2 independent, highly trained expert rheumatology imaging specialist physicians. A third person will serve as an adjudicator.

Details for standardized performance and processing of the x-rays and MRIs will be provided in an Imaging Manual.

The MRIs and x-rays in Section 9.20 will be read centrally by readers who are blinded to treatment assignment and chronological order of the imaging according to a charter for independent imaging assessment.

Chest x-rays are discussed in Section 12.7.5.2.

In addition to the analyses mentioned below, x-rays and MRI images may be evaluated using other reading criteria or methods.

9.20.1 Sacroiliac joint x-ray (AP Pelvis Joint Film for modified New York Criteria)

The sacroiliac joint is assessed by radiography with an AP pelvis or sacroiliac joint x-ray that will be assessed by a central reading review during the Screening Period to evaluate for modified New York Criteria status (Table 19–2) as described in Section 6.1. Sacroiliac joint changes will be scored according to the imaging specifications.

The following will be accepted to qualify subjects with AS for this study:

- Anterior posterior pelvis x-ray centrally read for one of the Phase 3 studies AS0010 or AS0011 and determined to be modified New York Criteria positive (+mNY); neither the x-ray nor the reading will be repeated.

- Prior sacroiliac joint or AP pelvis x-ray (performed at any time prior to the study) was submitted and centrally read for the purposes of this study and determined to be modified New York Criteria positive (+mNY). If the prior x-ray does not meet central reading criteria for randomization, another x-ray may be performed if the prior x-ray is more than 1 year old and if permitted by local guidelines.
- If no recent x-ray is available, one must be performed at Screening.

9.20.2 Spine x-ray

Subjects with confirmed eligibility based on screening assessments will have a spine x-ray performed at Baseline. The x-ray can be performed prior to or after the Baseline Visit, and must be performed prior to or no later than on the day of the second administration of IMP.

If the subject has a spine x-ray available from the past 6 months prior to Screening, this x-ray may be used and submitted for central reading. The spine x-ray will be centrally read and will be used to assess disease progression in the spine after 1 year in the extension study, given the subject is willing to enter this subsequent study.

9.20.3 Sacroiliac joint and spine MRI assessment substudy

While radiography can detect chronic bony changes (eg, sclerosis, erosions, bridging, and ankyloses), structural changes generally occur slowly and x-rays are insensitive; therefore, changes are difficult to detect in the relatively short duration of a randomized clinical study. Unlike radiography, MRI can be used to visualize active inflammation in the sacroiliac joints and spine in addition to structural lesions. Inflammation of the sacroiliac joints and spine is a key feature of axSpA that is potentially amenable to treatment with bimekizumab. If bimekizumab is effective, it is expected that reduction in inflammation in the sacroiliac joints and spine can be detected using MRI within the 52-week Treatment Period of this study. Recently, a Danish study demonstrated significant changes in ASspiMRI-a (Berlin modification) and SPARCC MRI-assessed inflammation scores and in MRI-assessed erosion scores within 12 weeks after initiation of adalimumab (see below for further description of these MRI scoring methods). The researchers concluded that MRI-assessed structural lesions change rapidly and may have value for assessing the effects of disease-modifying treatment in clinical trials (Pedersen et al, 2016). In this study, MRI changes will be evaluated in the sacroiliac joint and spine to evaluate the effect of bimekizumab on objective signs of inflammation through the SPARCC and ASspiMRI scores as outlined below. In addition, exploratory evaluation of other chronic MRI features, such as erosions and fatty lesions, will be performed as indicators of disease modification associated with structural disease progression (Baraliakos et al, 2014).

Magnetic resonance imaging of the spine and sacroiliac joints will be performed for consenting subjects in the MRI substudy after confirmation of eligibility based on screening assessments and before the first dose of IMP. If needed, the sacroiliac joint and spine MRIs can be performed at Baseline or prior to the actual Baseline Visit after confirmation of eligibility based on Screening assessments.

A central reader will assess the Baseline MRIs to identify MRI-positive subjects as per the OMERACT criteria. Further MRIs of the spine and sacroiliac joint for MRI-positive and MRI-negative subjects will be performed at Week 16 and Week 52 within a window of ±5 days for subjects participating in the MRI substudy. All MRIs will be centrally read.

Refusal to participate in the substudy will not affect a subject's opportunity to participate in the main study.

The following 2 different scoring systems will be utilized to determine changes from Screening (Lukas et al, 2007):

SPARCC Sacroiliac Joint score

This method is a scoring system for assessing the sacroiliac joint based on short-tau-inversion recovery (STIR) sequences. An abnormal increased signal on the STIR sequence represents bone marrow edema. The sacroiliac joint is divided into 4 quadrants (upper iliac, lower iliac, upper sacral, and lower sacral). The presence of increased signal on STIR in each of these 4 quadrants is scored as either 0=normal signal or 1=increased signal. The maximum score for abnormal signal in the 2 sacroiliac joints of 1 coronal slice is therefore 8. Joints that include a lesion exhibiting intense signal are each given an additional score of 1 per slice (that demonstrate this feature). Each sacroiliac joint that includes a lesion demonstrating continuous increase signal of depth ≥1cm from the articular surface is also given an additional score of 1. The maximum score for a single coronal slice is 12. Scoring is repeated in each of 6 consecutive coronal slices, so that the total sacroiliac joint SPARCC MRI score can range from 0 to 72.

ASspiMRI-a (Berlin modification) score (spine)

This method is a scoring system with a concentration on STIR sequences which quantifies changes in 23 disco-vertebral units (DVU) of the spine. A DVU is defined as the region between 2 virtual lines through the middle of each vertebra. Active inflammation is scored by grading the degree of bone marrow edema from 0 to 3 in 1 dimension on 1 or more consecutive slices that represent the highest level of inflammation in a particular DVU. There is no grading for erosion in the Berlin modification. The total spine ASspiMRI-a score in the Berlin modification can range from 0 to 69.

Additional scoring systems of inflammation may be used as appropriate methodology becomes accepted.

10 ASSESSMENT OF PHARMACOKINETIC AND PHARMACOGENOMIC VARIABLES

10.1 Pharmacokinetic variables

The PK variable is the plasma concentrations of bimekizumab. The Investigator or designee will obtain blood samples for these measurements at the time points specified in Table 5-2. 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. The relationship between PK concentrations and efficacy, PD and safety endpoints may also be assessed. The data from this study may be combined with data from other studies as part of this assessment.

10.2 Pharmacogenomic variables

A separate ICF will be required for those subjects who agree to participate in the genomics, genetics, and proteomics substudy, and must be signed prior to collection of any samples for the substudy. The substudy will only be conducted where ethically accepted and authorized by the regulatory agencies. Refusal to participate in the substudy will not affect a subject's ability to participate in the main study.

These analyses will enable evaluation of biomarkers relative to disease biology and progression, drug treatment and bone metabolism, and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined at a later date.

For individuals consenting to the genomics, genetics, and proteomics substudy, blood samples will be drawn for exploratory genetic/epigenetic, genomic, proteomic, metabolomics analysis, and for candidate biomarker analyses. Candidate biomarker evaluations may include, but are not limited to, IL-17A/IL-17F pathway signaling and axSpA biology (eg, IL-17A, IL-17F, IL-23, IL-6, tumor necrosis factor, dendritic cell-specific transmembrane protein, and circulating osteoclast precursors). These plasma samples may be used for additional analyses of other exploratory biomarkers.

Collection of these samples will occur at the time points specified in the schedule of study assessments (Table 5-2). At dosing visits, blood samples will be drawn prior to dosing, and will 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. The samples will be stored at -80°C at the central biorepository for up to 20 years to allow for future exploratory research.

Stool samples will be collected at time points specified in Table 5-2. These samples may be used to assess biomarkers of gut inflammation including but not limited to calprotectin and microbiome testing.

Blood and/or stool samples for pharmacogenomic and biomarker assessments are collected for exploratory purposes and participation in either blood or stool sampling (or both) is optional.

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

Immunological variables are the anti-bimekizumab antibody status, and the treatment-emergent antibody positivity derived from anti-drug antibody assays.

The Investigator or designee will obtain blood samples for these measurements at the time points specified in Table 5-2. 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.

The presence of anti-bimekizumab antibodies will be determined using a tiered approach of screening, confirmatory, and titer assays. Where applicable, a neutralizing-antibody assay will be performed.

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 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 ICF), including any pretreatment and post-treatment 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.

12.1.1.2 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 12.1.1.3], 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.)

12.1.1.2.1 Anticipated serious adverse events

The following Anticipated SAEs are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 12.1.2.3.

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

MedDRA system organ class	MedDRA preferred term
Skin and subcutaneous tissue disorders	Psoriasis
Eye disorders	Uveitis
Musculoskeletal and connective tissue disorders	Dactylitis Tendonitis Atlantoaxial instability
Gastrointestinal disorders	Colitis ulcerative Crohn's disease
Cardiac disorders	Aortic valve incompetence Atrial tachycardia Atrioventricular block Bundle branch block Cardiomyopathy
Vascular disorders	Aortitis
Respiratory, thoracic and mediastinal disorders	Pulmonary fibrosis
Nervous system disorders	Cauda equina syndrome
Injury, poisoning and procedural complications	Spinal cord injury Spinal fracture Cervical vertebral fracture Lumbar vertebral fracture Thoracic vertebral fracture
Immune system disorders	Amyloidosis
Psychiatric disorders	Depression

AS=ankylosing spondylitis; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event
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.

12.1.1.3 Adverse events of special interest

An AE of special interest (AESI) is any AE that a regulatory authority has mandated to 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.

12.1.1.4 Other safety topics of interest

Pre-specified safety topics of interest for the study are: infections (serious, opportunistic, fungal, and TB), neutropenia, hypersensitivity, suicidal ideation and behavior, major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel diseases (with gastroenterology referral, as appropriate).

This is based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action. There are no specific AE reporting requirements for these topics, however special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB) are in place.

12.1.2 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.

12.1.2.1 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.

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

12.1.2.2 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

12.1.2.3 Additional 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. The Investigator must enter the information regarding the SAE into the appropriate eCRFs and transmit to UCB via the clinical database, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. This information will be received by UCB and entered into the global safety database. Any ancillary documentation (eg, autopsy or other documentation) that is valid for the SAE can be sent to UCB using the contact information (fax/email) for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol.

It is important for the Investigator, when entering the SAE data into the eCRF, 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 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 eCRF and transmitted to UCB via the clinical database.

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 electronic transmission of the SAE, UCB will perform an assessment of expectedness of the reported SAE. The assessment of the expectedness of the SAE is based on the Investigator's Brochure.

12.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has 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, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 12.6.1.4.

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.

Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

12.2 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately (within 24 hours) notify UCB's PS department by entering all pregnancy information into the eCRF. An automatic notification will be sent to UCB's PS department. The subject should be permanently withdrawn from IMP as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should immediately stop the intake of the IMP.
- The subject should return for an early ad-hoc study visit.
- A Safety Follow-Up Visit should be scheduled 20 weeks after the final dose of IMP.

The Investigator should discuss with the subject the possibility to continue the study by attending the scheduled visits for assessments without IMP administration. The tests or assessments, which are considered contraindicated during the pregnancy should not be performed. The early ad-hoc study visit will be considered as the ET Visit if the subject does not wish to pursue the study investigations.

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

The pregnancy will be documented in the eCRF. The progression of the pregnancy and the eventual birth (if applicable) must be followed up using the eCRF. 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 PS 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/contract research organization (CRO) contract monitor for the study. The Investigator will complete the information in the eCRF 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, medically indicated abortion (eg, when the pregnancy is endangering life or health of the woman, or when the 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 eCRF.

12.3 Suspected transmission of an infectious agent

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 eCRF, 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.

12.4 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).

12.5 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 Data Monitoring Committee (DMC) will periodically review and monitor safety data from this study and advise UCB. Details are provided in the DMC Charter. Cardiovascular and Neuropsychiatric Adjudication Committees will also periodically review and monitor safety data from this study and advise UCB. Details are provided in the Adjudication Committee Charters.

12.6 Laboratory measurements

Clinical laboratory assessments consist of biochemistry, hematology, 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 (except the urine pregnancy test). Any unscheduled laboratory testing should also be collected using the central laboratory (with the exception of urgent safety laboratory measurements which should be performed locally and centrally simultaneously). Testing to exclude hepatitis B, hepatitis C, and HIV (see Exclusion Criterion #12, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12–2. A urine dipstick will be used for pregnancy testing.

Rescreening and retesting rules are provided in Section 5.1.1.1 and Section 5.1.1.2.

Specific details regarding the handling and processing of biochemistry and hematology samples are provided in the study laboratory manuals.

For subjects consenting to the pharmacogenomic substudy, blood and/or stool samples will be collected at defined timepoints (Table 5-2) and shipped and stored according to the laboratory manual.

The following laboratory parameters will be measured:

Table 12–2: Laboratory measurements

Hematology	Biochemistry	Urinalysis
Basophils	Calcium	pH
Eosinophils	Chloride	Albumin (protein)
Lymphocytes	Magnesium	Glucose
Monocytes	Potassium	Blood
Neutrophils	Sodium	Leukocyte esterase
Hematocrit	Glucose	Nitrite
Hemoglobin	BUN	Urine dipstick for pregnancy testing[a]
MCH	Creatinine	Urine drug screen[c]
MCHC	AST	
MCV	ALT	
Platelet count	ALP	
RBC count	GGT	
WBC count	Total bilirubin	
	LDH	
	Total cholesterol	
	Serum pregnancy testing[a]	
	CRP[b]	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; ET=Early Termination; GGT=gamma-glutamyltransferase; IMP=investigational medicinal product; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SFU=Safety Follow-Up; WBC=white blood cell

[a] A serum pregnancy test will be performed at Screening for all women of childbearing potential. A urine pregnancy test (urine dipstick analyzed locally) is also required at the Baseline Visit, Q4W from Week 4 to Week 52, ET, and at SFU visits. Pregnancy test results must be negative prior to administering IMP.

[b] CRP will be tested at specified visits (Table 5-2).

[c] Urine drug screen will be performed at the Screening Visit.

12.6.1 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 PDILI events meeting SAE criteria should be reported to the Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported within 24 hours of learning of their occurrence as an AE of special interest (see Section 12.1.1.3), and, if applicable, also reported as an SAE (see Section 12.1.1.2).

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 12.6.1.1). 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 12.6.1.4).

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 eCRF 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.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 12.6.1.2.1 are met, rechallenge with IMP may be appropriate.

The approach to investigate PDILI is summarized in Table 12–3.

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or 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 IMP discontinuation[d].	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.6.1.3); 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.[e]
≥3xULN	NA	Yes				
≥8xULN	NA	NA				

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 12.6.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 4 weeks of monitoring without evidence of resolution	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.6.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[e] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • ALT or AST remains ≥5xULN <8xULN, IMP should be temporarily withheld and subject should undergo repeat test in 2 weeks. Continue IMP if ALT or AST values <5xULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values. If ALT or AST remains ≥5xULN after second re-test, immediate IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[e]

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**

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 12.6.1.1. 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] Details are provided in Section 12.6.1.2.

[e] 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.

12.6.1.1 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 12.6.1.3) and SAE report (if applicable).

12.6.1.2 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 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.

12.6.1.2.1 IMP restart/rechallenge

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 12–3), but for whom an alternative diagnosis is confirmed, ie, drug-induced liver injury is excluded, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met at the time of the rechallenge:

- The results of additional testing and monitoring described in Section 12.6.1.3 and Section 12.6.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan and understands their individual benefit risk for restarting IMP and this is adequately documented.

12.6.1.3 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 detailed 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 eCRF. 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: 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	Urine drug screen[a]
Chemistry	Amylase
	Sodium, potassium, chloride, glucose, BUN, creatinine
	Total bilirubin, ALP, AST, ALT, GGT, total cholesterol, albumin
	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[c]
	PK sample

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CPK=creatine phosphokinase; GGT=gamma-glutamyltransferase; 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] Tests in addition to the specified analytes may be performed based on the Investigator's medical judgment and subject 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).

[c] For women of childbearing potential.

Additional information to be collected is presented in 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

12.6.1.4 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.

12.7 Other safety measurements

12.7.1 Vital signs

The Investigator or designee should measure all vital signs (systolic and diastolic BP, temperature [oral, axillary, or otic], pulse rate) prior to dosing after the subject has been sitting for at least 5 minutes, and the subject should remain seated during the measurements. At Baseline/Day 1 and Week 16, collect vital signs prior to drug administration and then at approximately 30 minutes and 1 hour after dosing.

12.7.2 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 at the time points listed in Table 5-2. The same scale should be utilized throughout the study where possible.

12.7.3 Physical examination

The physical examination should be conducted by the Investigator or designee at the time points listed in Table 5-2 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.

12.7.4 12-lead electrocardiogram

The Investigator or designee will perform the ECG which will be read centrally at the time points listed in Table 5-2. Full details of ECG recording will be provided in the ECG Manual.

12.7.5 Assessment and management of TB and TB risk factors

All subjects will be assessed for TB at Screening and at the time points specified in the schedule of assessments (Table 5-2) through physical examination for signs and symptoms of TB, chest x-ray (Section 12.7.5.2), laboratory testing (Section 12.7.5.1), and TB questionnaire (Section 12.7.5.3).

At Screening, all subjects will have an IGRA test (QuantiFERON TB test 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 directed at potential exposure to TB and symptoms of TB.

For the purposes of this study, TB definitions are as follows:

a. Known TB infection:
   - 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:
   - Known close 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 4 weeks prior to IMP dosing and continued to completion of prophylaxis):

   – The absence of signs, symptoms, 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 IMP without further evaluation by a TB specialist and discussion with the Study Physician, if LTB 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 (CDC diagnosis of LTB infection) http://www.cdc.gov/TB/topic /testing/default.htm).

d. NTMB infection is defined as a clinical infection caused by mycobacterial species other than those belonging to the Mycobacterium tuberculosis complex.

e. Tuberculosis test conversion:

   – 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 and be referred to a TB specialist for further evaluation. Confirmed TB test conversions should be classified as due to LTBI, active TB infection, or NTMB, and reported to the UCB PS function.

Subject eligibility, retesting requirements, and treatment requirements are shown in Figure 12–1.

Figure 12–1: Schematic diagram of TB test results and study eligibility

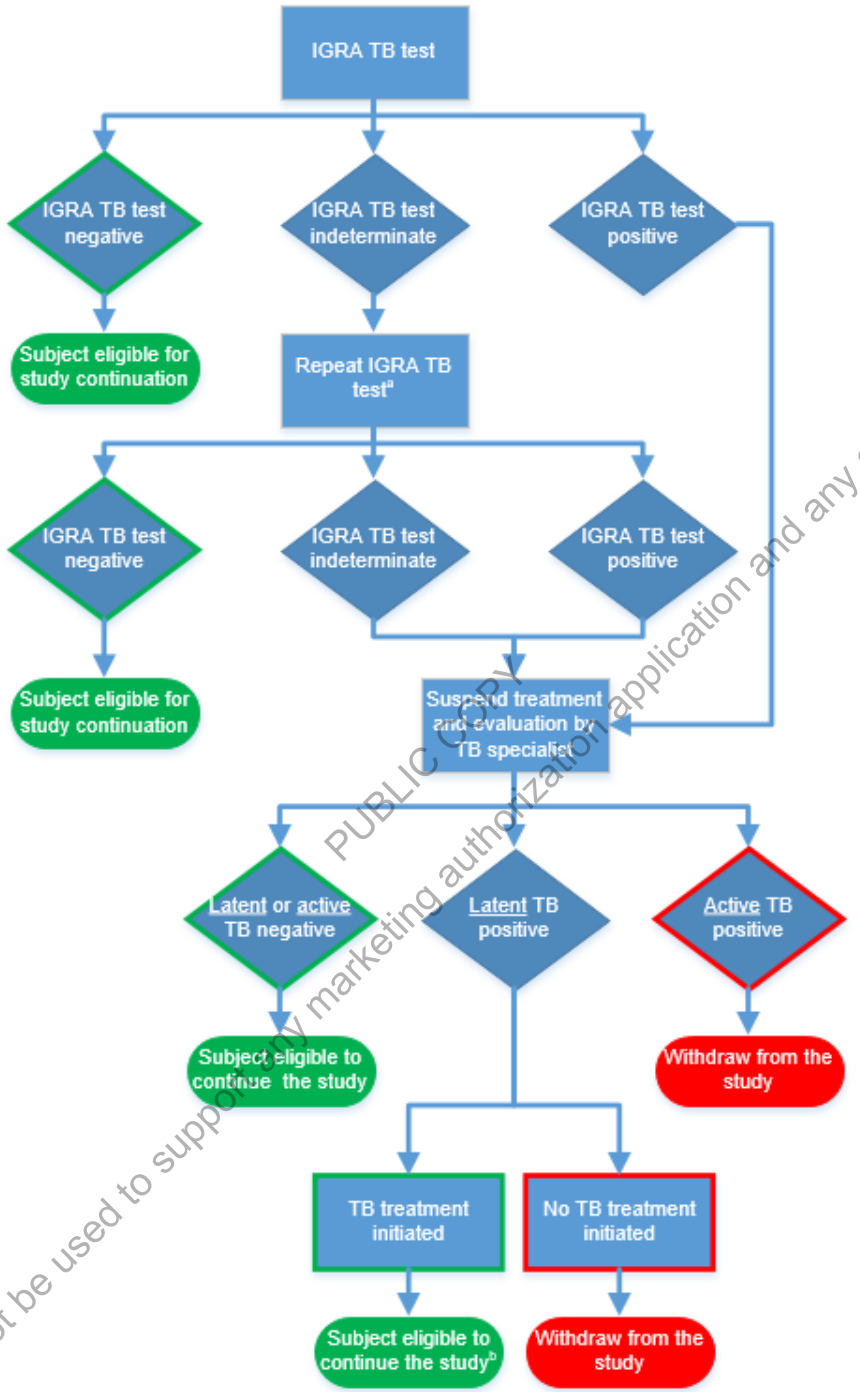
CDC=Center for Disease Control; IGRA=interferon-gamma release assay; LTBI=latent tuberculosis infection; TB=tuberculosis; WHO=World Health Organization

[a] IGRA retest must be done during the protocol-defined Screening window.

[b] Subject has a past history of active TB involving any organ system unless adequately treated according to WHO/CDC therapeutic guidance and proven to be fully recovered upon consult with a TB specialist. Subjects who have recently (no more than 12 months prior to Screening) completed the full treatment course of prophylaxis for LTBI are allowed. Prophylaxis should be in accordance with WHO or CDC guidelines and TB specialist judgment based on the origin of infection.

[c] Subjects with LTBI may enter the study only after they have completed at least 4 weeks of appropriate prophylactic therapy and thereafter, will continue and complete the entire regimen.

Figure 12–2: Schematic diagram of TB test results during the study



ASAP=as soon as possible; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; LTBI=latent tuberculosis infection; TB=tuberculosis

[a] IGRA retest must be done ASAP and prior to the next IMP dose

[b] Subjects with LTBI may continue the study only after they have completed at least 4 weeks of appropriate prophylactic therapy and thereafter, will continue and complete the entire regimen.

12.7.5.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB test is recommended) will be performed as described in Table 5-2 for all subjects. The test results will be reported as positive, negative, or indeterminate. Positive and indeterminate TB test results that occur during the course of the study must be reported as an AE and appropriately updated once the final diagnosis is known (eg, active TB, latent TB, or false positive TB test). 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. For indeterminate test results, the retest during Screening must be done during the protocol-defined Screening window.

12.7.5.2 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 [CAT] of the chest) must be clear of signs of TB infection (previous or current) before first IMP administration. All chest imaging (particularly x-rays) should be available for review by the Investigator before randomization of the subject. The chest x-ray reading should be repeated if the TB test was confirmed positive. If the second read of the pretreatment chest x-ray is confirmed to be clear, the subject may be included in the study 4 weeks after the start of the TB prophylactic treatment. If the pretreatment chest x-ray is not available for a re-read, it should be repeated after notification to the radiologist that this subject is IGRA positive, and confirmed to be clear for signs of TB.

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.

12.7.5.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed as described in Table 5-2. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] 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 #14 in 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.

12.7.5.4 Tuberculosis management

During the study, subjects who develop evidence of LTB infection or active TB must immediately stop further administration of IMP 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 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 final dose of IMP).

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

12.7.6 Pregnancy testing

Pregnancy testing will consist of serum testing at Screening for all women of childbearing potential. A urine dipstick will be used for pregnancy testing at all other visits.

The Screening Visit serum pregnancy test results must be negative, and received and reviewed prior to randomization. A negative urine pregnancy test result should be obtained immediately prior to each administration of IMP and at all visits specified in Table 5-2. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

12.7.7 PHQ-9

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

The PHQ-9 will be completed by the subject at the visits specified in Table 5-2.

Refer to Section 6.3 for PHQ-9-related withdrawal criteria.

12.7.8 Assessment of suicidal ideation and behavior

Suicidal ideation and behavior will be assessed by using the eC-SSRS; the questionnaire will be completed by the subject. 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 (Table 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 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. Demographic information will be recorded in the eCRF.

The Investigator or designee will obtain a complete history of lifestyle (alcohol or drug consumption within 6 months prior to Screening, nicotine consumption at the time of screening) and infections (fungal skin infections within 12 months prior to Screening) as part of the screening assessment. Lifestyle and infection history will be recorded in the eCRF.

13.2 Medical and ankylosing spondylitis history

The Investigator or designee will obtain a complete medical history and a medical history related to AS (including EAMs, the date of diagnosis, and past treatments for AS, and ASAS classification criteria as referenced in Section 19.1) as part of the Screening assessment and include all clinically relevant past or coexisting medical conditions, responses to AS treatment as available, Baseline GI-related symptoms, and surgeries. Findings will be recorded in the eCRF.

13.3 Prior and concomitant medications

As part of the medical history, the Investigator or designee will determine 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 and/or printouts of eCRFs 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, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Electronic Patient-Reported Outcome (ePRO) measures (eg, ASQoL; BASDAI, BASFI, SF-36, MOS-12, PGADA, total and nocturnal spinal pain, FACIT-Fatigue, EQ-5D-3L, WPAI-SHP) will be completed by each subject and will be collected electronically.

The data collection and database management system will be supplied by a vendor and will be compliant with the relevant regulations. The data collected on the ePROs will be uploaded to a central server database and will be sent electronically to UCB (or a designated CRO).

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.

Serious AE reporting will be done using the eCRF in the appropriate SAE Report Form section and transmitted to Patient Safety (see Section 12.1.2.3). 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. Case Report Form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

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 trial 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 following analysis sets were defined:

- The Enrolled Set (ES) will consist of all subjects who have given informed consent.
- The Randomized Set (RS) will consist of all randomized subjects.
- The Safety Set (SS) will consist of all randomized subjects who received at least 1 dose of the IMP.
- The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of the IMP and have a valid measurement of all components of the primary efficacy variable at Baseline.
- The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviation affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will be evaluated during a data evaluation meeting prior to unblinding of the data. Exclusions from the FAS will be considered important protocol deviations that also result in exclusion from the PPS.
- The Pharmacokinetics Per-Protocol Set (PK-PPS) consists of all randomized subjects who received at least 1 dose of the IMP and provided at least 1 quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration.
- The coronavirus disease 2019 (COVID-19) free set will consist of all subjects in the RS who had no COVID-19 impact up to the primary efficacy endpoint. Further details will be defined as part of the SAP.

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 and secondary efficacy variables

A fixed sequence testing procedure will be applied for each of the primary and selected secondary variables. The testing procedure will control the family-wise type-I-error and will account for multiplicity. The family-wise error will be set to α=0.05 (2-sided).

For the testing procedure, the hypotheses are mapped into a set ranging from H_1 to H_{12}.

For each test based on a binary efficacy variable, the null hypothesis is that the conditional odds ratio is equal to 1.

H_0: $OR_{T1/T2} = 1$

The alternative hypothesis is that the conditional odds ratio is not equal to 1.

H_A: $OR_{T1/T2} \neq 1$

For each test on a continuous efficacy variable, the null hypothesis is that there is no difference between treatment groups.

H_0: $T_1 - T_2 = 0$

The alternative hypothesis is that there is a difference between treatment groups.

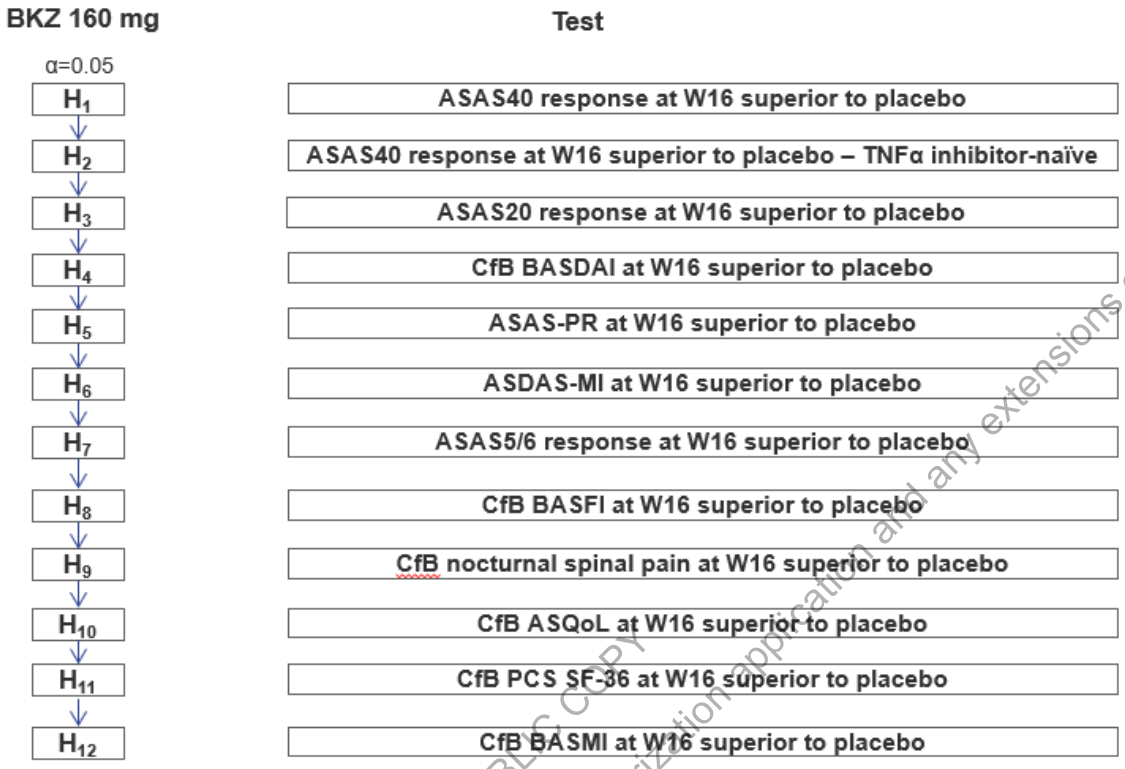
H_A: $T_1 - T_2 \neq 0$

The treatment comparison for each of these hypotheses is between bimekizumab 160mg sc Q4W and placebo. Point estimates and 95% confidence intervals (CI) will be calculated.

The testing starts with H_1. If H_1 can be rejected at α=0.05 (2-sided), the corresponding α will be passed on to the next test in the sequence (ie, H_2) and testing will continue. The hierarchical testing will be stopped if a hypothesis cannot be rejected at α=0.05 (2-sided).

The sequential testing procedure of primary and secondary efficacy endpoints is shown in Figure 15–1.

Figure 15–1: Sequential testing procedure of primary/secondary efficacy endpoints



ASAS40 (20)=Assessment of SpondyloArthritis International Society 40% (20%) response criteria; ASAS5/6=Assessment of SpondyloArthritis International Society 5 out of 6 response criteria; ASAS-PR=Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; BKZ=bimekizumab; CfB=change from Baseline; H=hypothesis; PCS=physical component summary; SF-36=Short Form 36-item Health Survey; TNFα=tumor necrosis factor alpha; W=Week

15.3.1.1 Analysis of the primary efficacy variable

The primary efficacy analysis will be performed based on the RS.

The primary endpoint is the ASAS40 response at Week 16. The primary efficacy analysis will evaluate the composite estimand in the RS. The composite estimand combines the clinically meaningful improvement from Baseline based on the ASAS40 response and not discontinuing treatment early. In practice, this composite estimand is similar to non-responder imputation (NRI), referred to here as modified NRI.

The following 4 attributes describe the estimand that will be used to define the treatment effect of interest for the primary efficacy analysis:

1. Population = Subjects enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
2. Subject-level outcome = ASAS40 at Week 16.
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving ASAS40 at Week 16 and not discontinuing study treatment through Week 16.
4. Population-level summary measure = Conditional odds ratio comparing bimekizumab to placebo.

Missing data at Week 16 that are not preceded by an intercurrent event, and any data after an intercurrent event will be imputed as non-responders.

Any use of prohibited or rescue therapy through Week 16 would constitute an important protocol deviation which would be accounted for when the supportive analysis based on the PPS is performed (see Section 15.3.1.1.1).

The statistical hypothesis for the ASAS40 response at Week 16 is that the conditional odds ratio for the ASAS40 response in the bimekizumab treatment group relative to the placebo group is equal to 1.

A logistic regression model will be used to assess the effect of bimekizumab vs placebo on ASAS40 response. The model will include fixed effects for treatment. The suitability of including the stratification variables of prior TNFα inhibitor exposure (yes/no) and region will be assessed, and will be added to the model if appropriate. Comparisons will be made for bimekizumab vs placebo using the 2-sided Wald test at a significance level of α=0.05 (ie, H_1 in Figure 15–1). The odds ratio versus placebo, p-value, and the 95% CI will be calculated.

15.3.1.1.1 Supportive analyses

Supportive analyses for the primary efficacy variable will be conducted. The analyses will be repeated:

1. Based on the PPS to evaluate the effect of important protocol deviations on the analysis.
2. For all subjects in the FAS to evaluate the consistency between the RS and the more restrictive FAS. This analysis will only be performed if the number of subjects in RS and FAS are different.
3. For all individual components of the ASAS40 response to explore the effect of the signs and symptoms of the individual components on the composite endpoint. Since all ASAS components are continuous variables (eg, change from Baseline in total spinal pain), an analysis of covariance (ANCOVA) with treatment, region, and prior TNFα inhibitor exposure as fixed effects and the Baseline values as covariate will be used for the analysis.
4. Using a modified composite estimand where intercurrent events are defined only as discontinuation due to adverse event or lack of efficacy.

5. Using a treatment policy imputation.
6. Using a tipping point analysis.
7. Using observed cases only (OC).
8. Using the COVID-19-free set.

Further specification of additional supportive analyses to evaluate varying assumptions related to the handling of missing data will also be performed and are described in Section 15.7.

15.3.1.2 Analyses of the secondary efficacy variables

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

Binary variables will be analyzed to evaluate the composite estimand in the RS, as done for the primary efficacy variable. The composite estimand combines (1) achieving the given binary response and (2) not discontinuing treatment prior to Week 16. The statistical hypothesis for the binary variables at Week 16 is that the conditional odds ratio for binary variables in the bimekizumab treatment group compared with the placebo treatment group is equal to 1.

Continuous variables will be analyzed for treatment effects using a similar estimand approach as for the primary efficacy variable, except for the following:

- Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment prior to Week 16. A hypothetical strategy for addressing intercurrent events will be implemented. This estimand targets the treatment difference in a scenario where withdrawal from study treatment does not occur, such that outcomes for subjects without an intercurrent event are as observed, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16. A multiple imputation strategy will be used to impute data following an intercurrent event.
- Population-level summary measure = The difference in adjusted means between bimekizumab and placebo.

Any missing data at Week 16 that is not preceded by an intercurrent event (ie, discontinuation of study medication) will be imputed based on a predefined multiple imputation (MI) model. The missing value will be 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. The statistical model for the comparison of bimekizumab and placebo will be an ANCOVA with treatment, region, and prior TNFα inhibitor exposure as fixed effects and the Baseline value as covariate. The statistical hypothesis for the continuous variables at Week 16 is that the treatment difference between the bimekizumab treatment group and placebo is equal to 0.

All secondary efficacy variables will also be summarized based on observed case data. Binary outcomes will also be summarized using the modified composite estimand.

15.3.2 Analyses of other efficacy variables

All other efficacy variables will be analyzed based on the RS.

Binary variables will be summarized using frequency tables by each visit. Generally, the estimand structure for binary other efficacy variables is as described below. Note that further details will be provided in the SAP.

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria.
2. Subject-level outcome = The given variable and time point being summarized (eg, ASAS-PR at Week 24).
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment prior to the time point being summarized. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving the given variable at the specified time point and not discontinuing study treatment through that time point.
4. Population-level summary measure = Unadjusted proportion of responders.

Any missing data that are not preceded by an intercurrent event as described above will be imputed based on a NRI as described for the primary and secondary efficacy variables.

Continuous variables will be summarized using descriptive statistics by each visit. Generally, the estimand structure for continuous other efficacy variables is as described below. Note that further details will be provided in the SAP.

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria.
2. Subject-level outcome = The given variable and time point being summarized (eg, Change from Baseline in BASFI at Week 36).
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment prior to the time point being summarized. A hypothetical strategy will be implemented in which outcomes for subjects without an intercurrent event are as observed at the given time point, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through the time point being summarized. A multiple imputation strategy will be used to impute data following an intercurrent event.
4. Population-level summary measure = Unadjusted mean.

Any missing data that are not preceded by an intercurrent event as described above will be imputed based on a predefined multiple imputation model as described for continuous secondary efficacy variables.

In some cases, other efficacy variables may also be summarized based on observed case data (ie, subjects with missing data or who have prematurely discontinued study treatment are treated as missing).

Time to ASAS20/40 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. The median time to response, including the 2-sided 95% CI, will be calculated for each treatment. Between-group differences will be analyzed with the log-rank statistic.

15.3.3 Subgroup analyses

Subgroup analyses using descriptive statistics will be performed on the primary efficacy variable. The following variables for subgroup analyses will be defined:

- Age at Baseline (<45 years of age; ≥45 years of age)
- Gender (male; female)
- Disease duration (<5 years; ≥5 years)
- Region (eg, Asia, Eastern Europe, North America, Western Europe)
- Body mass index at Baseline (<18.5kg/m^2; 18.5kg/m^2 to <25kg/m^2; 25kg/m^2 to <30kg/m^2; ≥30kg/m^2)
- Prior TNFα inhibitor exposure (yes; no)
- CRP at Baseline (≤ULN; >ULN)
- ASDAS status at Baseline (<1.3 [inactive disease]; 1.3 to ≤2.1 [low disease activity]; >2.1 to ≤3.5 [high disease activity]; >3.5 [very high disease activity])
- HLA-B27 positivity (yes; no)
- Anti-bimekizumab antibody status (positive, negative)

15.4 Planned safety analyses

15.4.1 Safety analyses

Safety variables will be analyzed for all subjects in the SS.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA® 19.0). Adverse events with an onset date on or after the date of first IMP administration and up to 20 weeks after the last (most recent) dose of IMP will be defined as TEAEs. Treatment-emergent AEs will be summarized descriptively by treatment group, primary system organ class, high level term, and preferred term. Additional tables will summarize TEAEs leading to withdrawal from IMP, TEAEs by intensity and relationship to IMP. Treatment emergent AEs leading to withdrawal from both IMP or the study, serious TEAEs, TEAEs of special interest, TEAE of special monitoring, and deaths will be also be tabulated and listed.

When analyzing categorical data, the number and percentage of subjects in each category will be presented by treatment group. In addition, shift tables may be used to evaluate the number and percentage of subjects having a different post-Baseline status when compared to their Baseline status.

Laboratory values (including markedly abnormal values), urinary values, vital signs, ECGs, eC-SSRS, and extent of exposure will be presented descriptively by treatment group. Definitions for markedly abnormal laboratory values will be provided in the SAP.

15.5 Planned other analyses

15.5.1 Pharmacokinetic analyses

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

Pharmacokinetic analyses will be detailed in a separate data analysis plan and reported in a separate document.

Bimekizumab plasma concentrations will be summarized by treatment arm for subjects who received at least 1 dose of bimekizumab at applicable time points scheduled in Table 5-2.

15.5.2 Immunological analyses

Anti-bimekizumab antibody levels will be determined using a tiered approach applying Screening, Confirmatory, and Titration assays. The details of this approach will be described in a separate Analytical Plan. Anti-bimekizumab antibody levels will be summarized by treatment arm for subjects who received at least 1 dose of bimekizumab at applicable time points scheduled in Table 5-2.

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 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 variable will use a conservative approach to handling missing data that is similar to non-responder imputation. The sensitivity of results to the approach for handling missing data will be evaluated via supportive analyses using different missing data mechanisms.

In instances where MI is used, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by regression for monotone missing data. The planned multiple imputation procedures are based on an assumption of data missing at random (MAR).

The following supportive analyses for the primary efficacy variable will be conducted:

1. Multiple imputation as described above will be performed using the modified composite estimand as specified for the use with the secondary variables. The definition of an intercurrent event is changed from all treatment discontinuation, to discontinuation of treatment due to AE or lack of efficacy.
2. Tipping point analyses will be performed to evaluate missingness assumptions. These tipping point analyses will be performed on the monotone missing data and only if the primary analysis is significant at α=0.05. Various delta adjustments will be made to the assumed responses on the monotone missing data in each treatment group independently with various degrees of plausibility. It will include scenarios where subjects who have missing data and

are randomized to bimekizumab have a lower probability of response compared to subjects who have missing data and were randomized to placebo. For binary variables, this includes the worst case scenario where subjects who have missing data and are randomized to bimekizumab are considered nonresponders, while subjects who have missing data and were randomized to placebo are considered responders. The goal of the tipping point analysis is to systematically vary assumptions until there is no evidence of a treatment effect (if possible). The plausibility of such required delta adjustment will then be assessed. Details will be provided in the Statistical Analysis Plan (SAP).

3. The treatment policy strategy for addressing intercurrent events will be considered. This will be based on an analysis of all available data at Week 16 regardless of the occurrence of intercurrent events. This analysis will use the same models specified for the primary and secondary analyses, where subjects are analyzed according to their randomized treatment, even if they discontinued study treatment for any reason prior to Week 16. Even though efforts will be made to collect the primary outcome data for all subjects at Week 16, there may still be some subjects for whom Week 16 efficacy data cannot be obtained. In this case, missing data will be imputed using MI under the assumption of MAR. Results will be combined into a single inference using Rubin's rule. 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 16 assessment. Therefore, the results of this analysis should be interpreted in the appropriate context.
4. An additional supportive analysis will be based on observed data only for subjects who are still on the initially randomized treatment at Week 16. Subjects with missing data or who have prematurely discontinued study treatment will be treated as missing.

For the secondary and other efficacy variables, the binary endpoints will be analyzed using modified NRI, MI, and OC, and the continuous endpoints will be analyzed using MI and OC.

Additional details on these supportive analyses will be provided in the SAP.

15.8 Planned interim analysis and data monitoring

15.8.1 Interim analyses

Two interim analyses will be performed: one after the planned number of randomized subjects have completed the Double-Blind Treatment Period and the Week 24 assessments, and one after the planned number of subjects have completed Week 52.

The purpose of the Week 24 interim analysis is to perform a comprehensive evaluation of all available double-blind data for the 2 treatment arms and to prepare a regulatory submission for a Marketing Authorization Application based on this analysis.

For the Week 24 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 original randomized IMP dosing regimen until the subject completes the Maintenance Period at Week 52.

The Week 24 interim analysis will evaluate the primary and secondary efficacy variables, as well as all other efficacy, safety, and PK variables up to Week 24 according to the statistical methods

specified in the SAP. No formal alterations to the further study conduct (eg, stopping rules, sample size re-estimation, or changes to eligibility criteria) are planned for this interim analysis.

To ensure blinding of Investigators and subjects, a statistical blinding plan will be written to evaluate the potential bias of the Maintenance Period, define blinded and unblinded teams, and describe the process of interim results generation and dissemination. The plan will be finalized prior to the lock of the database at the Week 24 interim analysis.

The purpose of the Week 52 interim analysis is to perform a comprehensive evaluation of all available data for the study and to supplement the regulatory submission based on the Week 24 interim analysis.

The Week 52 interim analysis will evaluate all efficacy, safety, and PK variables up to Week 52 according to the statistical methods specified in the SAP. Only data from the SFU visits for subjects who discontinued and did not enter the extension study will not be included.

Additional interim analyses and data cuts may be performed for regulatory purposes.

15.8.2 Data monitoring and Adjudication Committees

A DMC will be reviewing safety data on an ongoing basis. The DMC membership includes experienced clinicians and a statistician, all of whom have expertise in clinical studies. Further details are specified in the DMC Charter.

Cardiovascular and Neuropsychiatric Adjudication Committees will also periodically review data from this study. Details are provided in the Cardiovascular Adjudication Committee and Neuropsychiatric Adjudication Committee charters.

Other adjudication committees may be added as necessary.

Both Data Monitoring and Adjudication Committee members may not participate in the study as principal or co-Investigators, or as study subject care physicians and must not be members of the study team at UCB or the conducting CRO. The duration of membership for the committees will be inclusive of planned analyses for AS0011.

15.9 Determination of sample size

Approximately 300 subjects will be randomly assigned in a 2:1 ratio to the following treatment groups: bimekizumab 160mg sc Q4W (200 subjects) or placebo sc Q4W (100 subjects).

The primary efficacy analysis is based on the bimekizumab dose versus placebo for ASAS40 response at Week 16.

All sample size and power calculations were done at a significance level of 0.05.

All sample size and power calculations were performed using the software nQuery Advisor® 7.0.

15.9.1 Power calculation for primary endpoint

The sample size assumptions for bimekizumab versus placebo are based on the ASAS40 response data from the Phase 2b bimekizumab study in subjects with active AS (AS0008).

An ASAS40 response at Week 16 of 40% can be assumed for the bimekizumab treatment group. This assumed treatment response is based on the bimekizumab 160mg dose results of AS0008 at Week 12 (46.7%). It was also assumed that the treatment response at Week 12 and Week 16

would be the same (ie, conservative assumption). In addition, the observed ASAS40 response rates were adjusted to account for a higher number of subjects with prior TNFα inhibitor exposure and for a higher number of subjects with early withdrawal. Placebo ASAS40 response at Week 16 was assumed to be 15% and is more conservative than that of AS0008 at Week 12 (ie, ASAS40 response=13.3%).

The sample size for showing statistical superiority of bimekizumab versus placebo was calculated using a 2-sided 2-sample Chi square test with continuity correction (Fleiss et al, 1980). With 200 subjects in the bimekizumab treatment group and 100 subjects in the placebo group, the test for detecting statistical superiority of bimekizumab versus placebo based on ASAS40 response at Week 16 is powered with >99%.

15.9.2 Power calculations for secondary endpoints in the hierarchical testing

The assumptions for power calculations of the secondary endpoints are based on the Week 12 results of AS0008, unless indicated otherwise. It was assumed that the treatment response at Week 12 and Week 16 would be the same (ie, conservative assumption). In addition, the observed data were adjusted in the same way as the primary endpoint to account for a higher number of subjects with prior TNFα inhibitor exposure and for a higher number of subjects with early withdrawal.

All power calculations for binary endpoints were performed using a 2-sided 2-sample Chi-square test with continuity correction (Fleiss et al, 1980). All power calculations for continuous endpoints were performed using a 2-sided 2-group Satterthwaite t-test (Moser et al, 1989) The power calculations provided below represent independent evaluations for each endpoint and do not account for multiplicity.

For ASAS40 response of the TNFα inhibitor-naïve population at Week 16, an ASAS40 response of 48% for the bimekizumab group was assumed. Placebo ASAS40 response at Week 16 is 18%. It is also assumed that 70% of the subjects in each treatment group are TNFα inhibitor-naïve. With those assumptions, the endpoint is powered with >99% at the planned sample size (ie, 140 and 70 subjects in the bimekizumab and placebo group, respectively).

For ASAS20 response at Week 16, an ASAS20 response of 70% for the bimekizumab group was assumed. Placebo ASAS20 response at Week 16 is 30%. With those assumptions, the endpoint is powered with 99% at the planned sample size.

For change from Baseline in BASDAI total score at Week 16, an adjusted between-treatment difference of - 1.38 with an SD=1.8 for bimekizumab and SD=1.4 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For ASAS-PR at Week 16, an ASAS-PR of 17% for the bimekizumab group was assumed. Placebo ASAS-PR at Week 16 was assumed to be 3.3%. With those assumptions, the endpoint is powered with 94% at the planned sample size.

For ASDAS-MI at Week 16, the ASDAS-MI data of AS0008 at Week 12 and Week 16 were used and the placebo response was extrapolated to Week 16. The assumed ASDAS-MI are 36.0% and 13.8% at Week 16 for the bimekizumab and placebo group, respectively. With those assumptions, the endpoint is powered with 98% at the planned sample size.

For ASAS5/6 response at Week 16, an ASAS5/6 response of 44% for the bimekizumab group was assumed. Placebo ASAS-PR at Week 16 was assumed to be 5%. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in BASFI at Week 16, an adjusted between-treatment difference of - 2.35 with an SD=1.9 for bimekizumab and placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in nocturnal spinal pain score at Week 16, the AS data from the certolizumab pegol study AS001 were used. An adjusted between-treatment difference of -1.88 with an SD=2.9 for bimekizumab and SD=2.4 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in ASQoL total score at Week 16, an adjusted between-treatment difference of - 2.39 with an SD=4.5 for bimekizumab and placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in SF-36 PCS score at Week 16, an adjusted between-treatment difference of 4.56 with an SD=8.1 for bimekizumab and SD=5.8 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in BASMI at Week 16, an adjusted between treatment difference of - 0.55 with an SD=0.8 for bimekizumab and SD=0.7 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

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 Informed Consent Form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (Investigator or designee). The subject 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. A 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 Form, the subject 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, Investigator's Brochure, 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.

18 REFERENCES

Baraliakos X, Heldmann F, Callhoff J, Listing J, Appelboom T, Brandt J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis. 2014;73:1819-25.

Barkham N, Keen HI, Coates LC, O'Connor P, Hensor E, Fraser AD, et al. Clinical and imaging efficacy of infliximab in HLA–B27–Positive patients with magnetic resonance imaging–determined early sacroiliitis. Arthritis Rheum. 2009;60:946-54.

Brandt J, Listing J, Sieper J, Rudwaleit M, van der Heijde D, Braun J. Development and preselection of criteria for short term improvement after anti-TNFalpha treatment in ankylosing spondylitis. Ann Rheum Dis. 2004;63:1438-44.

Braun J. Axial spondyloarthritis: thoughts about nomenclature and treatment targets. Clin Exp Rheumatol. 2012;30:S132-5.

Braun J, Sieper J. Ankylosing spondylitis. Lancet. 2007;369:1379-90.

Braun J, van den Berg R, Baraliakos X, Boehm H, Burgos-Vargas R, Collantes-Estevez E, et al. 2010 update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Ann Rheum Dis. 2011;70:896-904.

Braun J, Zochling J, Baraliakos X, Alten R, Burmester G, Grasedyck K, et al. Efficacy of sulfasalazine in patients with inflammatory back pain due to undifferentiated spondyloarthritis and early ankylosing spondylitis: a multicentre randomised controlled trial. Ann Rheum Dis. 2006;65:1147-53.

Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol. 1994;2:2281-5.

Carpenter JR, Kenward MG. Multiple imputation and its application. Chichester: John Wiley & Sons Ltd; 2013.

CPMP/EWP/556/95. Points to consider on the clinical investigation of medicinal products other than NSAIDS for the treatment of RA. June 2004.

CPMP/ICH/135/95. Note for guidance on good clinical practice. July 2002.

Doward LC, Spoorenberg A, Cook SA, Whalley D, Helliwell PS, Kay LJ, et al. Development of the ASQL: a quality of life instrument specific to ankylosing spondylitis. Ann Rheum Dis. 2003;62:20-6.

FACIT.org. https://www.facit.org/measures/FACIT-F (Accessed on 03 February 2021).

Fleiss JL, Tytun A, Ury HK. A simple approximation for calculating sample sizes for comparing independent proportions. Biometrics. 1980;36:343-6.

Food and Drug Administration. Guidance for Industry. Drug-induced liver injury: premarketing clinical evaluation. US Dept of Health and Human Services, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, 07/2009.

Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol. 1994;21:2286-91.

Haibel H, Brandt HC, Song IH, Brandt A, Listing J, Rudwaleit M, et al. No efficacy of subcutaneous methotrexate in active ankylosing spondylitis: a 16-week open-label trial. Ann Rheum Dis. 2007;66:419-21.

Haibel H, Rudwaleit M, Braun J, Sieper J. Six months open label trial of leflunomide in active ankylosing spondylitis. Ann Rheum Dis. 2005;64:124-6.

Haibel H, Rudwaleit M, Listing J, Heldmann F, Wong RL, Kupper H, et al. Efficacy of adalimumab in the treatment of axial spondyloarthritis without radiographically defined sacroiliitis: results of a twelve-week randomized, double-blind, placebo-controlled trial by an open-label extension up to week fifty-two. Arthritis Rheum. 2008;58:1981-91.

Hays RD, Martin SA, Sesti AM, Spritzer KL. Psychometric properties of the Medical Outcomes study sleep measure. Sleep Med. 2005;6:41-4.

Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh KC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58:15-25.

Heuft-Dorenbosch L, Spoorenberg A, van Tubergen A, Landewé R, van der Tempel H, Mielants H, et al. Assessment of enthesitis in ankylosing spondylitis. Ann Rheum Dis. 2003;62:127-32.

International Menopause Society. Cornwall, UK: Menopause Terminology; c2015. http://www.imsociety.org/menopause_terminology.php. Accessed 25 Jan 2016.

Kimball AB, Yu AP, Signorovitch J, Xie J, Tsaneva M, Gupta SR, et al. The effects of adalimumab treatment and psoriasis severity on self-reported work productivity and activity impairment for patients with moderate to severe psoriasis. J Am Acad Dermatol. 2012;66(2):e67-e75.

Lukas C, Braun J, van der Heijde D, Hermann K-G A, Rudwaleit M, Ostergaard M, et al. Scoring inflammatory activity of the spine by magnetic resonance imaging in ankylosing spondylitis: a multireader experiment. J of Rheum. 2007;34:862-70.

Lukas C, Landewé R, Sieper J, Dougados M, Davis J, Braun J, et al. Development of an ASAS-endorsed disease activity score (ASDAS) in patients with ankylosing spondylitis. Ann Rheum Dis. 2009;68:18-24.

Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharm Stat. 2012;11:456-61.

Mallinckrodt CH. Preventing and Treating Missing Data in Longitudinal Clinical Trials: A Practical Guide. New York, NY: Cambridge University Press; 2013.

Maruish ME, editor. User's manual for the SF-36v2 Health Survey. 3rd ed. Lincoln, RI: QualityMetric Incorporated; 2011.

Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index

(LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res 2011;63 Suppl 11:S64-85.

Moser BK, Stevens GR, Watts CL. The Two-Sample T Test Versus Satterthwaite's Approximate F Test Article. Communication in Statistics-Theory and Methods.1989;18(11):3963-75.

Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and Validation of a Computer-Automated Columbia-Suicide severity Rating Scale Using Interactive Voice Response Technology. J Psychiatr Res. 2010;44(16):1224-8.

Myasoedova E, Crowson CS, Kremers HM, Therneau TM, Gabriel SE. Is the incidence of rheumatoid arthritis rising?: results from Olmsted County, Minnesota, 1955-2007. Arthritis Rheum. 2010;62:1576-82.

Pavy S, Brophy S, Calin A. Establishment of the minimum clinically important difference for the bath ankylosing spondylitis indices: a prospective study. J Rheumatol. 2005;32:80-5.

Pedersen SJ, Poddubmyy D, Sorensen IJ, Loft A-G, Hindrup JS, Thamsborg G, et al. Course of Magnetic Resonance Imaging-Detected Inflammation and Structural Lesions in the Sacroiliac Joints of Patients in the Randomized, Double-Blind, Placebo-Controlled Danish Multicenter Study of Adalimumab in Spondyloarthritis, as Assessed by the Berlin and Spondyloarthritis Research Consortium of Canada Methods. Arthritis and Rheumatology. 2016;68:418-29.

Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? Ther Adv Musculoskelet Dis. 2013;5:45-54.

Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H, et al. Effect of non-steroidal anti-inflammatory drugs on radiographic spinal progression in patients with axial spondyloarthritis: results from the German Spondyloarthritis Inception Cohort. Ann Rheum Dis. 2012;71:1616-22.

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry. 2011;168(12):1266-77.

Reilly MC, Zbronzek AS, Dukes EM. The Validity and Reproducibility of a Work Productivity and Activitiy Impairment Instrument. Pharmacoeconomics. 1993:4(5):353-65.

Reveille JD, Witter JP, Weisman MH. Prevalence of axial spondyloarthritis in the United States: estimates from a cross-sectional survey. Arthritis Care Res (Hoboken). 2012;64:905-10.

Rudwaleit M. New approaches to diagnosis and classification of axial and peripheral spondyloarthritis. Curr Opin Rheumatol. 2010;22:375-80.

Rudwaleit M, Haibel H, Baraliakos X, Listing J, Märker-Hermann E, Zeidler H, et al. The early disease stage in axial spondylarthritis: results from the German Spondyloarthritis Inception Cohort. Arthritis Rheum. 2009a;60:717-27.

Rudwaleit M, van der Heijde D, Landewe R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis International Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis. 2011;70:25-31.

Rudwaleit M, Landewé R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis. 2009b;68:770-6.

Sieper J, Rudwaleit M, Baraliakos X, Brandt J, Braun J, Burgos-Vargas R, et al. The Assessment of SpondyloArthritis International Society (ASAS) handbook: a guide to assess spondyloarthritis. Ann Rheum Dis. 2009;68(Supple 2):ii1-44.

Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. Arthritis Care Res (Hoboken). 2016; 68(9):1320-31.

Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol. 2007;34:1401-14.

van der Heijde D, Dougados M, Davis J, Weisman MH, Maksymowych W, Braun J, et al. Assessment in Ankylosing Spondylitis International Working Group/Spondylitis Association of America recommendations for conducting clinical trials in ankylosing spondylitis. Arthritis Rheum. 2005;52:386-94.

van der Heijde D, Ramiro S, Landewé R, Baraliakos X, van den Bosch F, Sepriano A, et al. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis. 2017;76(6):978-91.

van der Heijde D, Schiff MH, Sieper J, Kivitz AJ, Wong RL, Kupper H, et al. Adalimumab effectiveness for the treatment of ankylosing spondylitis is maintained for up to 2 years: long-term results from the ATLAS trial. Ann Rheum Dis. 2009;68:922-9.

van Tubergen A, Black PM, Coteur G. Are patient-reported outcome instruments for ankylosing spondylitis fit-for-purpose for the axial spondyloarthritis patient? A Qualitative and Psychometric Analysis. Rheum. 2015;54:1842-51.

van Tubergen A, Debats I, Ryser L, Londoño J, Burgos-Vargas R, Cardiel MH, et al. Use of a numerical rating scale as an answer modality in ankylosing spondylitis-specific questionnaires. Arthritis Rheum. 2002a;47:242-8.

van Tubergen A, Coenen J, Landewé R, Spoorenberg A, Chorus A, Boonen A, et al. Assessment of fatigue in patients with ankylosing spondylitis: a psychometric analysis. Arthritis Rheum. 2002b;47:8-16.

Vender R, Lynde C, Ho V, Chau D, Poulin-Costello M. Work productivity and healthcare resource utilization outcomes for patients on etanercept for moderate-to-severe plaque psoriasis: Results from a 1-year, multicentre, open-label, single-arm study in a clinical setting. Appl Health Econ Health Policy. 2012:10(5):343-53.

Ward MM, Deodhar A, Akl EA, Lui A, Ermann J, Gensler LS, et al. American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment

Network 2015 Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Rheum. 2015;2016 Feb;68(2):282-98.

19 APPENDICES

19.1 ASAS classification criteria for axial SpA

Table 19–1: ASAS classification criteria for axial SpA (for subjects with chronic back pain of at least 3 months and age at onset <45 years)

Imaging criteria	**ASAS clinical criteria for axial SpA**
Sacroiliitis (MRI or radiographs[a]) plus ≥1 SpA feature	HLA-B27 plus ≥2 other SpA features
SpA features[b]	
Inflammatory back pain[c]	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	HLA-B27
Uveitis	Elevated CRP
Dactylitis	

ASAS=Assessment of SpondyloArthritis International Society; axSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis

[a] Active inflammatory lesions of sacroiliac joints with definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with spondyloarthritis in MRI or radiographic sacroiliitis Grade 2 to 4 bilaterally or Grade 3 to 4 unilaterally according to modified NY criteria. For this study, only MRI will be permitted for study entry for the imaging criterion.

[b] "Family history for SpA" and "Good response to NSAIDs" are excluded as SpA feature criteria.

[c] Inflammatory back pain according to ASAS criteria for axSpA defined as the presence of 4 out of 5 of the following parameters:

1. age at onset <45 years
2. insidious onset
3. improvement with exercise
4. no improvement with rest
5. pain at night (with improvement upon getting up)

19.2 Modified New York (mNY) Classification Criteria for AS

Table 19–2: Modified New York (mNY) Classification Criteria for AS

Diagnosis
Clinical criteria: a. Low back pain and stiffness for more than 3 months which improves with exercise, but is not relieved by rest b. Limitation of motion of the lumbar spine in both the sagittal and frontal planes. c. Limitation of chest expansion relative to normal values corrected for age and sex.
Radiologic criterion: Sacroiliitis grade ≥2 bilaterally or grade 3 to 4 unilaterally
Grading
Definite ankylosing spondylitis if the radiologic criterion is associated with at least 1 clinical criterion

AS=ankylosing spondylitis; mNY=modified New York Criteria
Note: A second grading of "probable ankylosing spondylitis" is part of the modified NY criteria, but it is not applicable for this study.

19.3 Protocol Amendment 1

Rationale for the amendment

The major purpose of this protocol amendment was to implement changes in response to scientific discussions and feedback provided at meetings with Investigators and advisors or for clarifications. Mainly, imaging assessments were amended with sacroiliac joint and spine MRIs performed at Weeks 16 and 52 for all consenting subjects participating in the MRI substudy regardless of MRI positivity at Baseline. These additional MRIs will allow an exploratory evaluation of any changes in the sacroiliac joint or spine after 16 or 52 weeks in subjects who were MRI-negative at Baseline and on early signals such as the impact on erosions and fatty lesions at Week 16. Additionally, including MRI-positive and MRI-negative subjects in the substudy was considered a more holistic strategy comparable to the approach used for other compounds. At the same time, the number of participating subjects will be expanded to include subjects in the substudy without restriction.

Further key changes are summarized below. The amendment:

- Clarifies that the minimum duration of the Screening Period of 14 days does not apply to screenfailed subjects from AS0010 who are screened for AS0011.
- Changes the categorization of PHQ-9 from an other efficacy variable to an other safety variable for consistency within the program.
- Clarifies that protected adults will not be enrolled in the study.
- Clarifies that subjects with a diagnosis of PsA will be excluded from the study as per the revised Exclusion Criterion 17.
- Adds new sections summarizing all within-study rescreening/retesting and cross-study screening rules in one place and updates corresponding protocol sections.
- Updates the IMP description for consistency within the program.
- Updates for clarification and adds more detail to sections presenting exclusionary, concomitant, or rescue medication.
  - To clarify that permitted acetaminophen/paracetamol serve as examples for the larger group of analgesics and are permitted as rescue therapy except for 24 hours prior to any study visit.
  - To add that topical steroids are permitted.
  - To clarify that any change in dose/dose regimen of oral corticosteroids within 14 days prior to Baseline is exclusionary.
  - To clarify that apremilast used as a rescue medication can be dosed as per Investigator's discretion or local label.
  - To clarify that the use of more than 1 TNFα inhibitor and the inclusion of any subject not meeting the related Inclusion criterion is exclusionary.
- Restructures sections related to exclusionary, concomitant medication, or rescue medication to allow a side by side presentation in one table.

- Clarifies that the 12-item MOS Sleep Scale is rated using the 5-point scale.
- Removes the option for enrollment in a separate observational pregnancy follow-up study sponsored by UCB.
- Updates statistical terminology and replaces "sensitivity analyses" with "supportive analyses".
- Increases the threshold for subgroup analyses by disease duration from 2 to 5 years.
- Updates the section detailing the status of bimekizumab studies.
- Updates the list of references.
- Updates instances of "AS" in the summary and introduction to clarify that "AS" is also known as "radiographic axSpA".
- Updates instances of "ASAS criteria" to "ASAS classification criteria" for consistency where applicable.

In addition, a few minor updates including consistency changes for PDILI-related text, contact details, the list of abbreviations, and minor formatting changes for the purpose of clarity have been made.

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- All instances that referred to "legal representatives" were updated to remove this terminology from the entire protocol. Protected adults will not be enrolled in the study.
- All instances that referred to a minimum of 14 days for the Screening Period have been updated to clarify that this requirement does not apply to screenfailed subjects from AS0010 who are screened for AS0011. The minimum requirement is still applicable to all other subjects.
- All instances of "sensitivity analysis" were replaced with "supportive analysis". The revision corresponds to the structure of study estimands described in the ICH E9 (R1) Addendum.

Specific changes

Change #1

Study contact details

Sponsor study physician

[redacted]

UCB BIOSCIENCES Ltd.
208 Bath Road
Slough SL1 3WE
UNITED KINGDOM

[redacted]

Has been changed to:

[redacted]

UCB BIOSCIENCES GmbH
Alfred-Nobel-Straße 10
40789 Monheim am Rhein
GERMANY

[redacted]

Clinical Trial Biostatistician

[redacted]

UCB BIOSCIENCES Inc.
8010 Arco Corporate Drive
Raleigh, NC 27617
UNITED STATES

[redacted]

Has been changed to:

[redacted]

UCB BIOSCIENCES Ltd.
208 Bath Road
Slough SL1 3WE
UNITED KINGDOM

[redacted]

Change #2

Section 1, Summary, paragraph 1 sentence 1 and paragraph 7

This is a multicenter, Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active ankylosing spondylitis (AS), a subtype of axial spondyloarthritis (axSpA) with radiographic evidence of disease.

...

The overall study design consists of a Screening Period (≥14 days to ≤35 days), a 16-week Double-Blind Treatment Period, a 36-week Maintenance Period, and a Safety Follow-Up (SFU) Visit 20 weeks after the final dose of the investigational medicinal product (IMP) ....

Has been changed to:

This is a multicenter, Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active ankylosing spondylitis (AS), a subtype of axial spondyloarthritis (axSpA) with radiographic evidence of disease **(also known as radiographic axSpA [r-axSpA]).**

...

The overall study design consists of a Screening Period **(**minimum of **approximately** 14 days **[unless a screenfailed subject from AS0010 will be screened in AS0011]** to ≤35 days), **a 52-week Treatment Period consisting of** a 16-week Double-Blind Treatment Period, a 36-week Maintenance Period, and a Safety Follow-Up (SFU) Visit 20 weeks after the final dose of the investigational medicinal product (IMP) ...

Change #3

Section 2.1, Axial spondyloarthritis, paragraph 2, sentence 3

Therefore, peripheral SpA includes diseases affecting mainly peripheral joints, such as reactive arthritis and PsA, whereas axSpA comprises those diseases with mainly axial involvement (sacroiliac joints and spine), including AS diagnosed with definite radiographic changes of the sacroiliac joint and nr-axSpA.

Has been changed to:

Therefore, peripheral SpA includes diseases affecting mainly peripheral joints, such as reactive arthritis and PsA, whereas axSpA comprises those diseases with mainly axial involvement (sacroiliac joints and spine), including AS (**also known as r-axSpA**) diagnosed with definite radiographic changes of the sacroiliac joint and nr-axSpA.

Change #4

Section 2.2.2.1, Completed studies, paragraph 1

Nine clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild-to-moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, UP0031 in 12 healthy volunteers, UP0042 in 48 Japanese and Caucasian healthy

volunteers, RA0123 in 159 subjects with moderate-to-severe RA, PS0010 in 250 subjects with moderate-to-severe chronic plaque PSO, PS0016 in 49 subjects with moderate-to-severe chronic plaque PSO, and UC0011 in 23 subjects with moderate-to-severe active ulcerative colitis.

Has been changed to:

~~Nine~~ **Thirteen** clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild-to-moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, UP0031 in 12 healthy volunteers, UP0042 in 48 Japanese and Caucasian healthy volunteers, RA0123 in 159 subjects with moderate-to-severe RA, PS0010 in 250 subjects with moderate-to-severe chronic plaque PSO **and the corresponding extension study (PS0011),** PS0016 in 49 subjects with moderate-to-severe chronic plaque PSO **and the corresponding extension study (PS0018)**, UC0011 in 23 subjects with moderate-to-severe active ulcerative colitis, **AS0008 in 303 subjects with AS, and PA0008 in 206 subjects with PsA.**

Change #5

Section 2.2.2.2, Ongoing studies

The following bullet has been deleted:

- AS0008 is a Phase 2b, double-blind, randomized, placebo-controlled, multiple-dose study to evaluate the efficacy and safety of bimekizumab in subjects with active AS.

The following bullet has been added:

- **AS0010 is a Phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active nr-axSpA.**

Change #6

Section 4.3.1, Other efficacy variables

The following variable has been removed:

- Change from Baseline in Patient Health Questionnaire-9 (PHQ-9)

Change #7

Section 4.3.2, Other safety variables

The following variable has been added:

- **Change from Baseline in Patient Health Questionnaire-9 (PHQ-9)**

Change #8

Section 5.1, Study description, paragraph 3

The study will include the following 3 periods: a Screening Period (≥14 days to ≤35 days), a Treatment Period (52 weeks) consisting of a 16-week Double-Blind Treatment Period and a 36-week Maintenance Period, and a SFU Period (20 weeks after the final dose of IMP).

Has been changed to:

The study will include the following 3 periods: a Screening Period (minimum of **approximately** 14 days **[unless a screenfailed subject from AS0010 will be screened in AS0011]** to ≤35 days), a Treatment Period (52 weeks) consisting of a 16-week Double-Blind Treatment Period and a 36-week Maintenance Period, and a SFU Period (20 weeks after the final dose of IMP).

Change #9

Section 5.1.1, Screening Period/Baseline, paragraph 1 first sentence

Assessments of eligibility as described in Section 6 will be initiated during the Screening Period with a minimum duration of 14 days and a maximum duration of up to 35 days.

Has been changed to:

Assessments of eligibility as described in Section 6 will be initiated during the Screening Period with a minimum duration of **approximately** 14 days (**unless a screenfailed subject from AS0010 will be screened in AS0011)** and a maximum duration of up to 35 days.

The following paragraph was added:

All subjects will have an anterior posterior (AP) pelvis or sacroiliac joint x-ray (read centrally) to determine eligibility as per mNY criteria. Subjects who are mNY-negative may be eligible for Screening in AS0010, a double-blind, randomized, placebo-controlled Phase 3 study in subjects with active nr-axSpA. It is recommended to perform the sacroiliac joint x-ray prior to any other screening assessment to avoid repetition of screening assessments (applicable at sites participating in both Phase 3 studies).

Change #10

Section 5.1.1, Screening Period/Baseline, last paragraph

Screening assessments for subjects previously screened for AS0010, who were not eligible for AS0010 and therefore entered Screening again for eligibility during the Screening Period of AS0011, must be repeated unless defined otherwise. These cross-study rescreening rules pertaining to laboratory testing are provided in Section 12.6 and imaging is described in Section 9.21.

Has been deleted.

Change #11

Section 5.1.1, Screening Period/Baseline

The following sections have been added.

5.1.1.1 Within-study rescreening/retesting requirements

Rules for rescreening or repetition of screening tests within the study are listed below:

- Subjects who fail to meet the eligibility criteria for BASDAI, spinal pain, PHQ-9, eC-SSRS, or the TB questionnaire **are not allowed** to be rescreened.

The Medical Monitor must be contacted for confirmation of rescreening/retesting in all other cases.

- Subjects who initially fail to meet selected eligibility criteria (eg, documented completion of latent tuberculosis infection [LTBI] prophylactic therapy) may be rescreened.
- Subjects for whom eligibility assessments could not be completed as planned (eg, for technical reasons) within the defined Screening Period of 35 days may be rescreened.
- Subjects with individual laboratory screening tests for which the results are exclusionary, can be retested.

Of note, repetition of laboratory screening tests within the Screening Period is permitted for technical reasons (eg, frozen sample, expired laboratory kit) without contacting the Medical Monitor.

5.1.1.2 Cross-study screening requirements

Screening assessments for subjects previously screened for AS0010, who were not eligible for AS0010 based on mNY criteria and therefore entered AS0011 Screening for eligibility, must be repeated during the Screening Period unless defined in Table 5–1. The Medical Monitor must be contacted for confirmation of the rescreening requirements in all cases.

Table 5-1: Cross-study screening requirements

Assessment	Screening requirements
Cross-study screening is not permitted in the following cases:	
BASDAI and spinal pain	Screening of a subject not eligible for AS0010 who will be screened for AS0011, and who did not meet the related Inclusion Criteria in AS0010.
PHQ-9, eC-SSRS, TB questionnaire (Q1)	Screening of a subject not eligible for AS0010 who will be screened for AS0011, and who did not meet the related Exclusion Criteria in AS0010.
Cross-study screening is permitted in the following cases:	
CRP	If a subject not eligible for AS0010 will be screened for AS0011, the Screening CRP testing must be repeated during Screening for AS0011 only if the result is older than 35 days at time of randomization at Baseline (Section 12.6).

Table 5-1: Cross-study screening requirements

Assessment	Screening requirements
Cross-study screening is not permitted in the following cases:	
All safety laboratory assessments	If a subject not eligible for AS0010 will be screened for AS0011, the Screening safety laboratory testing (hematology, biochemistry, urinalysis, urine drug screen, pregnancy testing as applicable, HIV, Hepatitis B and C, and IGRA TB testing) and HLA-B27 testing must be repeated only during Screening for AS0011 if the results are older than 35 days at time of randomization at Baseline (Section 12.6).
Anterior posterior pelvis x-ray	The following will be accepted to qualify subjects with AS for this study: Anterior posterior pelvis x-ray centrally read for AS0010 and determined to be modified New York Criteria positive (+mNY); neither the x-ray nor the reading will be repeated (Section 9.20). The central imaging reader needs to be informed by the site about screening activities in order to transfer and confirm eligibility for the switch from AS0010 to AS0011.

AS=ankylosing spondylitis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; CRP=C-reactive protein; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; IGRA=Interferon-Gamma Release Assay; mNY=modified New York; PHQ-9=Patient Health Questionnaire 9; Q=question; TB=tuberculosis

Change #12

Section 5.1.2.1, Double-Blind Treatment Period, paragraph 3

Visit windows of ±3 days are allowed from the first dose at all visits through Week 16. The visit window is relative to the Baseline Visit, not the previous study visit. The time between doses should be ≥25 days and ≤31 days.

Has been changed to:

Visit windows of ±3 days are allowed from the first dose at all visits through Week 16. The visit window is relative to the Baseline Visit, not the previous study visit. The time between doses should be ≥25 days and ≤31 days. **When applying the allowed visit windows, it must be ensured that the time between these 2 visits does not exceed the allowed time between doses.**

Change #13

Section 5.1.2.2, Maintenance Period, paragraph 3

Visit windows of ±4 days are allowed for all visits after Week 16. The time between doses during the Maintenance Period should be ≥24 days and ≤32 days.

Has been changed to:

Visit windows of ±4 days are allowed for all visits after Week 16. The time between doses during the Maintenance Period should be ≥24 days and ≤32 days. **When applying the allowed visit windows, it must be ensured that the time between these 2 visits does not exceed the allowed time between doses.**

Change #14

Section 5.1.3, Nonbiologic rescue therapy

The entire section has been deleted from Section 5 and merged with Table 7-2. Subsequent sections have been re-numbered and in-text references were updated.

Change #15

Section 5.1.5, Study duration per subject, bullet #1

- Screening Period: ≥14 days to ≤35 days

Has been changed to:

- Screening Period: **minimum duration of approximately** 14 days **(unless a screenfailed subject from AS0010 will be screened in AS0011)** to ≤35 days

Change #16

Section 5.1.6, Planned number of subjects and site(s)

Approximately 300 subjects will be randomly assigned in a 2:1 ratio to the following treatment groups: bimekizumab 160mg sc Q4W (200 subjects) or placebo sc Q4W (100 subjects). The planned number of study sites is approximately 85.

Has been changed to:

Approximately 300 subjects will be randomly assigned in a 2:1 ratio to the following treatment groups: bimekizumab 160mg sc Q4W (200 subjects) or placebo sc Q4W (100 subjects). The planned number of study sites is approximately ~~85~~ **95**.

Change #17

Section 5.2, Table 5-2, Schedule of assessments, footnotes n and q

[n] If a subject has had a recent x-ray of the chest within 3 months prior to the Screening Visit, it may be used as the Screening chest x-ray. The chest x-ray has to be read by a pulmonologist and any significant finding is exclusionary. Any findings suggestive of active TB are exclusionary.

[q] Sacroiliac joint and spine MRIs will be performed for subjects participating in the MRI substudy. Baseline sacroiliac joint and spine MRIs should be performed after confirmation of eligibility based on screening assessments for the study and before the first dose of IMP. If preferred, the sacroiliac joint and spine MRIs can be performed prior to the actual Baseline Visit. Further sacroiliac joint and spine MRIs will be performed at Weeks 16 and 52, within a window of ±5 days for sacroiliac joint MRI-positive subjects at Baseline participating in the substudy.

Has been changed to:

[n] If a subject has had a recent x-ray of the chest within 3 months prior to the Screening Visit, it may be used as the Screening chest x-ray. ~~The chest x-ray has to be read by a pulmonologist and any significant finding is exclusionary.~~ Any findings suggestive of active TB are exclusionary.

[q] Sacroiliac joint and spine MRIs will be performed for subjects participating in the MRI substudy. Baseline sacroiliac joint and spine MRIs should be performed after confirmation of eligibility based on screening assessments for the study and before the first dose of IMP. ~~If preferred~~, The sacroiliac joint and spine MRIs can be performed **at Baseline or** prior to the actual Baseline Visit. Further sacroiliac joint and spine MRIs will be performed at Weeks 16 and 52, within a window of ±5 days for **all subjects participating in the substudy.**

Change #18

Section 6.1, Inclusion criteria 1 and 2

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.

Have been changed to:

1a. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject ~~or legal representative.~~

2a. 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.

Change #19

Section 6.2, Exclusion criteria #3 and #17

3. Subject previously participated in another study of a medication (systemic) under investigation within the 12 weeks or at least 5 half-lifes prior to the Screening Visit, whichever is greater, or is currently participating in another study of a medication (systemic) under investigation, with the exception of subjects who were screen failures in AS0010.

17. Subject has a diagnosis of inflammatory conditions other than AS, including but not limited to rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and reactive arthritis. Subjects with a diagnosis of Crohn's disease, ulcerative colitis, or other IBD are allowed as long as they have no active symptomatic disease at Screening or Baseline.

Has been changed to:

3a. Subject previously participated in another study of a medication (systemic) under investigation within the 12 weeks or at least 5 half-lifes prior to the ~~Screening~~ **Baseline** Visit, whichever is greater, or is currently participating in another study of a medication (systemic) under investigation, with the exception of subjects who were screen failures in AS0010.

17a. Subject has a diagnosis of inflammatory conditions other than AS, including but not limited to **psoriatic arthritis**, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus, and reactive arthritis. Subjects with a diagnosis of Crohn's disease, ulcerative colitis, or other IBD are allowed as long as they have no active symptomatic disease at Screening or Baseline.

Change #20

Section 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 for subjects with either of the following:

- ALT or AST ≥8x ULN
- ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

The PDILI criterion below requires immediate discontinuation of IMP for:

- 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%).

…

Evaluation of PDILI must be initiated as described in Section 12.6.1 with repeat tests performed in 2 weeks. Upon re-test, if ALT or AST values have reduced to <5xULN, the subject can continue with the study. However, if ALT or AST remains ≥5xULN and <8xULN after re-test, IMP should be temporarily withheld and subject should undergo a repeat test in 2 weeks. If ALT or AST values remain ≥5xULN even after the second re-test, then the subject should be permanently withdrawn from IMP and should be followed for possible PDILI.

Has been changed to:

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 for subjects with either of the following:

- ALT or AST ≥8x ULN
- ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

~~The PDILI criterion below requires immediate discontinuation of IMP for:~~

- 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%).

…

Evaluation of PDILI must be initiated as described in Section 12.6.1 with repeat tests performed in 2 weeks. Upon re-test, if ALT or AST values have reduced to <5xULN, the subject can continue with the study. However, if ALT or AST remains ≥5xULN and <8xULN after re-test, IMP should be temporarily withheld and subject should undergo a repeat test in 2 weeks. If ALT or AST values remain ≥5xULN even after the second re-test, then the subject should be ~~permanently withdrawn~~ **immediately discontinued** from IMP and should be followed for possible PDILI.

Change #21

Section 7.1, Description of investigational medicinal products, first bullet

- [redacted]

Has been changed to:

- [redacted]

Change #22

Section 7.8, Concomitant medications/treatments, paragraph 2

The following sentence has been added.

Medications listed in Table 7–2 are prohibited, restricted, or used as nonbiologic rescue therapy.

Change #23

Section 7.8, Concomitant medications/treatments, paragraph 2

Table 7–2 has been amended to include exclusionary and nonbiologic rescue therapy.

Table 7-2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
Analgesics • Acetaminophen/ paracetamol	Any change in dose/dose regimen within 14 days prior to BL	Stable dose/regimen permitted Ad hoc/PRN/"as needed use" permitted, but: **No** ad hoc/PRN/"as needed use" in the 24h prior to any study visit	Ad hoc/PRN/"as needed use" permitted, but: **No** ad hoc/PRN/"as needed use" in the 24h prior to any study visit
NSAID/COX-2 inhibitors	Any change in dose/dose regimen within 14 days prior to BL	Stable dose/ regimen permitted No change until Week 20 Visit	Nonbiologic rescue therapy will be at the Investigator's discretion with the following options for symptoms: • For subjects taking an NSAID/COX-2 inhibitor dosing can be optimized; a change can be made to a different NSAID/COX-2 inhibitor; changes from an NSAID to a COX-2 inhibitor or from a COX-2 inhibitor to an NSAID are also permitted up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 inhibitor may be taken at a given time. • For subjects not taking NSAID/COX-2 inhibitors either 1 NSAID, or 1 COX-2 inhibitor can be initiated, up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 inhibitor may be taken at a given time. • For subjects who cannot take NSAIDs/COX-2 inhibitors, topical NSAIDs are also a potential nonbiologic rescue therapy in regions where they are approved, up to the maximum approved or tolerated dose, whichever is lower.
Mild potency opioids permitted only: • Tramadol/any dose up to maximum approved dose • Codeine/only <90mg of codeine per dosage unit	Any change in dose/dose regimen within 14 days prior to BL	Dosing/schedule should remain stable for the first 20 weeks of the study	**Prohibited** for rescue therapy

Table 7-2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
Oral corticosteroids/average daily dose of ≤10mg/day prednisone or equivalent	Any change in dose/dose regimen within 14 days prior to BL	Permitted, but: • **No** steroid bursts/tapers • **No** increase in steroid dosing • **No** initiation of steroids until the Week 20 Visit	**Prohibited** for rescue therapy
Topical corticosteroids	None	Permitted	Not applicable
Corticosteroids: • Intramuscular • Intravenous • Intra-articular • Bursal	Use within 28 days prior to BL	**Prohibited** unless used as rescue therapy from Week 20 or later	Nonbiologic rescue therapy will be at the Investigator's discretion with the following options for symptoms: • Sacroiliac joint steroid injection(s), either unilateral or bilateral. For non-axial symptoms: • One peripheral joint (or bursa) may be injected with a steroid at or after any visit where nonbiologic rescue therapy eligibility is assessed; however, the same joint may not be injected more than once during the study and should not be injected within 4 weeks of a sacroiliac joint injection(s).
Intra-articular hyaluronic acid	Use within 8 weeks prior to the BL Visit or during the study	**Prohibited**	Not applicable
Any established antidepressant regimen	Any change in dose/dose regimen within 8 weeks prior to BL	Permitted	Not applicable

Table 7-2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
csARDs/formerly known as DMARDs			
• Azathioprine • Cyclosporine • Cyclophosphamide • Mycophenolic acid • Mycophenylate mofetil • Any other small molecule DMARDs	Use within 8 weeks prior to BL	**Prohibited**	**Prohibited** for rescue
• Methotrexate (MTX)	Use within 12 weeks prior to BL unless Inclusion Criterion #9 is met	Permitted MTX (≤25mg/week)	For non-axial symptoms: • MTX may be added or increased to a maximum dose of 25mg/week, or the maximum tolerated dose, whichever is lower, in accordance with local standard of care. The route of administration may be changed from oral to sc or from sc to oral, at any visit at Week 20 or later. It is strongly recommended that subjects taking MTX are also taking folic acid supplementation.
• Leflunomide (LEF)	Use in the 6 months prior to the BL Visit (unless a cholestyramine washout has been performed; in which case, use up to 28 days prior to the BL Visit is acceptable) unless Inclusion Criterion Criterion #9 is met	Permitted LEF (≤20mg/day or an average of 20mg/day if not dosed daily)	For non-axial symptoms: • 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.

Table 7-2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
• Hydroxychloroquine (HCQ) (and other anti-malarials) • Sulfasalazine (SSZ) • Apremilast	Use within 8 weeks prior to BL unless Inclusion Criterion #10 is met	Permitted	For non-axial symptoms: • HCQ may be added or increased to a maximum dose of 400mg/day or the maximum tolerated dose, whichever is lower. Other anti-malarials may be used in accordance with local standard of care. • SSZ may be added or increased up to a maximum dose of 3g/day (up to 4g/day if in accordance with local standard of care), or the maximum tolerated dose, whichever is lower. • Apremilast may be given at a maximum dose of 60mg/day and dosed as per Investigator's discretion or local label. Combination DMARDs are allowed except that LEF and MTX may not be given together.
JAK inhibitors			
• Eg, tofacitinib • Upadacitinib	Use within 8 weeks prior to BL	**Prohibited**	Not applicable

Table 7-2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
Biologic DMARDs			
TNFα inhibitors: • Infliximab (IFX) • Golimumab (GOL) • Certolizumab pegol (CZP) • Adalimumab (ADA) • Etanercept (ETN) • Biosimilar versions of any TNFα inhibitor	For IFX, ADA, GOL, and CZP, any use within the 12 weeks prior to the BL Visit For ETN, use within the 28 days prior to the BL Visit Any use of >1 TNFα in the history Subjects not meeting Inclusion Criterion #11.	**Prohibited**	Not applicable
Other biologics: • Abatacept • Alefacept • Efalizumab • Guselkumab • Sarilumab • Sirukumab • Tocilizumab • Others in development targeting IL-6 or IL-6R	Any use within 12 weeks prior to BL	**Prohibited**	Not applicable
• Ustekinumab	Any use within 24 weeks prior to BL	**Prohibited**	Not applicable
• Tildrakizumab	Any use within 4 months prior to BL	**Prohibited**	Not applicable
• Risankizumab	Any use within 5 months prior to BL	**Prohibited**	Not applicable
• Briakinumab	Any use within 6 months prior to BL	**Prohibited**	Not applicable

Table 7-2: Exclusionary, concomitant, and rescue medication

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
• Rituximab (incl. biosimilars), ocrelizumab	Any use within 12 months prior to BL	**Prohibited**	Not applicable
Anti-IL-17 therapy: • Bimekizumab • Secukinumab • Ixekizumab • Brodalumab • Others in development	Any exposure history	**Prohibited**	Not applicable

BL=Baseline; ADA=adalimumab; COX-2=cyclooxygenase 2; csARD=conventional synthetic antirheumatic drug; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; h=hour; HCQ=hydroxychloroquine; IFX=infliximab; JAK=Janus kinase; LEF=leflunomide; IL=interleukin; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; PRN=as needed; sc=subcutaneous; SSZ=sulfasalazine; TNFα=tumor necrosis factor alpha

[a] Note: any medication not listed here for rescue therapy must be approved by the Medical Monitor prior to starting that medication.

Change #24

Section 7.8.1, Permitted concomitant treatments (medications and therapies)

The following paragraphs have been moved to Table 7–2.

Subjects are allowed to use acetaminophen/paracetamol as needed except that PRN/as needed doses are not permitted within 24 hours before a study visit where efficacy assessments are performed.

Mild potency opioids are permitted during the study and the dosing/schedule should remain stable for the first 16 weeks of the study, but are not permitted as nonbiologic rescue therapy (see Section 5.1.3).

No steroid bursts/tapers, increase in steroid dosing or initiation of steroids are permitted during the study.

Subjects are permitted to decrease NSAID/COX-2 medications, analgesics (including opioids), DMARD(s) and/or oral corticosteroids and/or alter their regimen only at/after the Week 20 Visit except for reasons of intolerance/AEs/side effects.

Subjects who are receiving an established antidepressant regimen should be on a stable dose of the antidepressant for 8 weeks prior to Baseline.

The following paragraph has been changed to:

Whenever possible, physical therapy/physiotherapy/non-medication/complementary and alternative treatment(s) (including traditional Chinese medications) of AS should remain stable through the Week ~~16~~ **20** Visit.

The following paragraph has been deleted:

Subjects may be withdrawn from IMP at any time and continue treatment using other treatment options per the Investigator's discretion, as described in the Withdrawal criteria Section 6.3.

Change #25

Section 7.8.2, Prohibited concomitant treatments (medications and therapies)

Medications listed in Table 7–2 are prohibited or restricted as follows:

Has been changed to:

Prohibited concomitant treatments are described in Table 7–2.

Change #26

Section 7.8, Concomitant medications/treatments

The following changes have been made and are included in Table 7–2.

- The dosing/schedule of mild potency opioids should remain stable for the first ~~16~~ **20** weeks of the study

- Any change in dose/dose regimen of oral corticosteroids within 14 days prior to BL is exclusionary.
- Intramuscular, intravenous, intra-articular, and bursal corticosteroids use is prohibited unless used as rescue therapy.
- Any use of >1 TNFα in the history is exclusionary.
- Subjects not meeting Inclusion Criterion #11 are excluded.
- Apremilast may be given at a maximum dose of 60mg/day and dosed as per Investigator's discretion or local label.

Change #27

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

The outdated Table 7–2 has been deleted.

Change #28

Section 7.8.3, Nonbiologic rescue therapy

The section has been moved from Section 5.1.3 to Section 7.8. The following text has been added:

Nonbiologic rescue therapy will be at the Investigator's discretion as add-on therapy to bimekizumab at any time from Week 20 or later as described in Table 7–2.

Change #29

Section 8, Study procedures by visit, paragraph 2

Visit windows are ±3 days from Baseline (Day 1, first dose of IMP) at all visits through the Week 16 Visit and ±4 days from all visits thereafter. For the SFU Visit (20 weeks after the final dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days). The minimum amount of time between bimekizumab doses should be no less than 25 days and no more than 31 days from Baseline to Week 16 and 24 to 32 days thereafter.

Has been changed to:

Visit windows are ±3 days from Baseline (Day 1, first dose of IMP) at all visits through the Week 16 Visit and ±4 days from all visits thereafter. For the SFU Visit (20 weeks after the final dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days). The minimum amount of time between bimekizumab doses should be no less than 25 days and no more than 31 days from Baseline to Week 16 and 24 to 32 days thereafter. **When applying the allowed visit windows, it must be ensured that the time between these 2 visits does not exceed the allowed time between doses.**

Change #30

Section 8.1, Screening Visit (Visit 1), paragraph 1

The Screening Period will last for a minimum of 14 days and up to a maximum of 35 days.

Has been changed to:

The Screening Period will last for a minimum of **approximately** 14 days (**unless a screenfailed subject from AS0010 will be screened in AS0011**) and up to a maximum of 35 days.

The following text has been added.

An overview on rescreening/retesting requirements is provided in Section 5.1.1.1 and Section 5.1.1.2.

Change #31

Section 8.1, Screening Visit (Visit 1), bullet 18

Obtain a chest x-ray, unless one has been obtained within 3 months prior to the Screening Visit. The chest x-ray must be read by a qualified radiologist and/or pulmonary physician and any significant finding is exclusionary. Any findings suggestive of active TB are exclusionary.

Has been changed to:

Obtain a chest x-ray, unless one has been obtained within 3 months prior to the Screening Visit. ~~The chest x-ray must be read by a qualified radiologist and/or pulmonary physician and any significant finding is exclusionary.~~ Any findings suggestive of active TB are exclusionary.

Change #32

Section 9.7, MOS-12, paragraph 1, second sentence

The frequency with which each problem has been experienced during the previous 4 weeks is rated on a 6-point scale ranging from “none of the time” to “all of the time,” except sleep quantity, which is reported in hours.

Has been changed to:

The frequency with which each problem has been experienced during the previous 4 weeks is rated on a **5**-point scale ranging from “none of the time” to “all of the time,” except sleep quantity, which is reported in hours.

Change #33

Section 9.19, PHQ-9

Has been moved from Section 9.19 to Section 12.7.7 without any content change.

Change #34

Section 9.19, Occurrence of extra-articular manifestations

Information regarding dactylitis, PSO, uveitis, and IBD occurrences during the study will be captured as AEs. Enthesitis will be assessed regularly via the MASES performed at site visits as specified in Table 5-2.

Has been changed to:

Information regarding dactylitis, PSO, uveitis, and IBD ~~occurrences~~ **events** during the study will be captured as AEs. Enthesitis will be assessed regularly via the MASES performed at site visits as specified in Table 5-2.

Change #35

Section 9.20.1, Sacroiliac joint x-ray (AP Pelvis Joint Film for modified New York Criteria, paragraph 2, bullet 1

- Anterior posterior pelvis x-ray centrally read for one of the Phase 3 studies AS0010 or AS0011 and determined to be modified New York Criteria positive (+mNY); neither the reading nor the x-ray will be repeated.

Has been changed to:

- Anterior posterior pelvis x-ray centrally read for one of the Phase 3 studies AS0010 or AS0011 and determined to be modified New York Criteria positive (+mNY); neither the ~~reading~~ x-ray nor the ~~x-ray~~ reading will be repeated.

Change #36

Section 9.20.3, Sacroiliac joint and spine MRI assessment substudy, paragraphs 1, 2, and 3

While radiography can detect chronic bony changes (eg, sclerosis, erosions, bridging, and ankyloses), structural changes generally occur slowly and x-rays are insensitive; therefore, changes are difficult to detect in the relatively short duration of a randomized clinical study. Unlike radiography, MRI can be used to visualize inflammation in the sacroiliac joints and spine in addition to structural lesions. Inflammation of the sacroiliac joints and spine is a key feature of axSpA that is potentially amenable to treatment with bimekizumab. If bimekizumab is effective, it is expected that reduction in inflammation in the sacroiliac joints and spine can be detected using MRI within the 52-week Treatment Period of this study. Recently, a Danish study demonstrated significant changes in in ASspiMRI-a (Berlin modification) and SPARCC MRI assessed inflammation scores and in SPARCC MRI-assessed erosion scores within 12 weeks after initiation of adalimumab (see below for further description of these MRI scoring methods). The researchers concluded that MRI-assessed structural lesions change rapidly and may have value for assessing the effects of disease-modifying treatment in clinical trials (Pedersen et al, 2016).

...

Magnetic resonance imaging of the spine and sacroiliac joints will be performed in a substudy with approximately 15% of subjects at Baseline after confirmation of eligibility based on screening assessments and before the first dose of IMP. If needed, the sacroiliac joint and spine MRIs can be performed prior to the actual Baseline Visit after confirmation of eligibility based on Screening assessments.

...

A central reader will assess the Baseline MRIs to identify MRI-positive subjects as per the OMERACT criteria. Further MRIs of the spine and sacroiliac joint will be performed at Week 16 and Week 52 within a window of ±5 days only for those subjects who were MRI positive in the sacroiliac joint MRI at Baseline, and will be centrally read.

Has been changed to:

While radiography can detect chronic bony changes (eg, sclerosis, erosions, bridging, and ankyloses), structural changes generally occur slowly and x-rays are insensitive; therefore, changes are difficult to detect in the relatively short duration of a randomized clinical study. Unlike radiography, MRI can be used to visualize **active** inflammation in the sacroiliac joints and spine in addition to structural lesions. Inflammation of the sacroiliac joints and spine is a key feature of axSpA that is potentially amenable to treatment with bimekizumab. If bimekizumab is effective, it is expected that reduction in inflammation in the sacroiliac joints and spine can be detected using MRI within the 52-week Treatment Period of this study. Recently, a Danish study demonstrated significant changes in in ASspiMRI-a (Berlin modification) and SPARCC MRI assessed inflammation scores and in ~~SPARCC~~ MRI-assessed erosion scores within 12 weeks after initiation of adalimumab (see below for further description of these MRI scoring methods). The researchers concluded that MRI-assessed structural lesions change rapidly and may have value for assessing the effects of disease-modifying treatment in clinical trials (Pedersen et al, 2016). **In this study, MRI changes will be evaluated in the sacroiliac joint and spine to evaluate the effect of bimekizumab on objective signs of inflammation through the SPARCC and ASspiMRI scores as outlined below. In addition, exploratory evaluation of other chronic MRI features, such as erosions and fatty lesions, will be performed as indicators of disease modification associated with structural disease progression (Baraliakos et al, 2014).**

...

Magnetic resonance imaging of the spine and sacroiliac joints will be performed for consenting subjects in the MRI substudy after confirmation of eligibility based on screening assessments and before the first dose of IMP. If needed, the sacroiliac joint and spine MRIs can be performed at Baseline or prior to the actual Baseline Visit after confirmation of eligibility based on Screening assessments.

A central reader will assess the Baseline MRIs to identify MRI-positive subjects as per the OMERACT criteria. Further MRIs of the spine and sacroiliac joint for MRI-positive and MRI-negative subjects will be performed at Week 16 and Week 52 within a window of ±5 days for subjects participating in the MRI substudy. All MRIs will be centrally read.

Refusal to participate in the substudy will not affect a subject's opportunity to participate in the main study.

Change #37

Section 10.2, Pharmacogenomic variables, paragraph 3, sentence 2

...Candidate biomarker evaluations may include, but are not limited to, IL-17A/IL17-F pathway signaling and AS biology (eg, IL-17A, IL-17F, IL-23, IL-6, tumor necrosis factor, dendritic cell-specific transmembrane protein, and circulating osteoclast precursors). ...

Has been changed to:

...Candidate biomarker evaluations may include, but are not limited to, IL-17A/IL-17F pathway signaling and ~~AS~~ **axSpA** biology (eg, IL-17A, IL-17F, IL-23, IL-6, tumor necrosis factor, dendritic cell-specific transmembrane protein, and circulating osteoclast precursors). ...

Change #38

Section 12.2, Pregnancy

Should a subject become pregnant while participating in the study, the subject may be offered the option to enroll in a separate observational pregnancy follow-up study sponsored by UCB and conducted independently from AS0011. If the study is available locally, the AS0011 Investigator will be provided with locally approved information about the observational pregnancy follow-up study to inform the subject at the time the pregnancy is reported. Participation in this separate study will be voluntary and will not impact the therapeutic management of the subject nor interfere with termination and follow-up procedures as described in protocol AS0011.

This paragraph has been deleted.

Change #39

Section 12.6, Laboratory measurements, paragraph 1 and bullets

Clinical laboratory assessments consist of biochemistry, hematology, 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 (except the urine pregnancy test). Any unscheduled laboratory testing should also be collected using the central laboratory (with the exception of urgent safety laboratory measurements which should be performed locally and centrally simultaneously). Testing to exclude hepatitis B, hepatitis C, and HIV (see Exclusion Criterion #12, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12–2. A urine dipstick will be used for pregnancy testing. Rescreening requirements pertaining to laboratory assessments are summarized below:

- For CRP: If a subject will be rescreened for AS0011, the Screening CRP testing does not have to be repeated during Screening for AS0011 if the result is not older than 35 days at time of randomization at Baseline, otherwise, the CRP must be repeated.

- For all safety laboratory assessments: If a subject from AS0010 will be rescreened for AS0011, the Screening safety laboratory testing (hematology, biochemistry, urinalysis, urine drug screen, pregnancy testing as applicable, and IGRA TB testing) does not have to be repeated during Screening for AS0011 if the results are not older than 35 days at time of randomization at Baseline. Otherwise, if the results are older than 35 days, these tests must be repeated.

Has been changed to:

Clinical laboratory assessments consist of biochemistry, hematology, 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 (except the urine pregnancy test). Any unscheduled laboratory testing should also be collected using the central laboratory (with the exception of urgent safety laboratory measurements which should be performed locally and centrally simultaneously). Testing to exclude hepatitis B, hepatitis C, and HIV (see Exclusion Criterion #12, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12–2. A urine dipstick will be used for pregnancy testing. ~~Rescreening requirements pertaining to laboratory assessments are summarized below:~~

Rescreening and retesting rules are provided in Section 5.1.1.1 and Section 5.1.1.2.

- ~~For CRP: If a subject will be rescreened for AS0011, the Screening CRP testing does not have to be repeated during Screening for AS0011 if the result is not older than 35 days at time of randomization at Baseline, otherwise, the CRP must be repeated.~~
- ~~For all safety laboratory assessments: If a subject from AS0010 will be rescreened for AS0011, the Screening safety laboratory testing (hematology, biochemistry, urinalysis, urine drug screen, pregnancy testing as applicable, and IGRA TB testing) does not have to be repeated during Screening for AS0011 if the results are not older than 35 days at time of randomization at Baseline. Otherwise, if the results are older than 35 days, these tests must be repeated.~~

Change #40

Section 12.6.1, Evaluation of PDILI, last paragraph

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 12.6.1.2.1 are met, rechallenge with IMP may be appropriate.

Has been changed to:

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be ~~permanently~~ discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 12.6.1.2.1 are met, rechallenge with IMP may be appropriate.

Change #41

Section 12.6.1, Evaluation of PDILI, Table 12-3

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hyper-sensitivity**	**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 12.6.1.3); 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				
≥8xULN	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		
≥5xULN (and ≥2x Baseline) and <8xULN	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 12.6.1.2). IMP discontinuation required if any of the following occur:	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.6.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values:

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hyper-sensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
				• Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 4 weeks of monitoring without evidence of resolution		• ALT or AST remains ≥5xULN <8xULN, IMP should be temporarily withheld and subject should undergo repeat test in 2 weeks. Continue IMP if ALT or AST values <5xULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values. If ALT or AST remains ≥5xULN after second re-test, immediate, permanent IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[d]

Has been changed to:

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or 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. ~~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.[d] ~~Immediate, permanent IMP discontinuation.~~	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.6.1.3); 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.[e]
≥3xULN	NA	Yes				
≥8xULN	NA	NA				
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 12.6.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.6.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[e] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • ALT or AST remains ≥5xULN <8xULN, IMP should be temporarily withheld and subject should undergo repeat

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
				• Liver chemistry values continue to increase. • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 4 weeks of monitoring without evidence of resolution.		test in 2 weeks. Continue IMP if ALT or AST values <5xULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values. If ALT or AST remains ≥5xULN after second re-test, immediate, ~~permanent~~ IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[e]

Change #42

Section 12.6.1, Evaluation of PDILI, Table 12-3, footnotes

The following footnote has been added:

[d] **Details are provided in Section** 12.6.1.2.

Subsequent footnotes have been adjusted accordingly.

Change #43

Section 12.6.1.2, Immediate action: determination of IMP discontinuation, paragraph 2

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).

Has been changed to:

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).

Change #44

Section 12.6.1.2.1, IMP restart/rechallenge, paragraph 1

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 12–3), but for whom an alternative diagnosis is confirmed, ie, drug-induced liver injury is excluded, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

Has been changed to:

Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 12–3), but for whom an alternative diagnosis is confirmed, ie, drug-induced liver injury is excluded, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met **at the time of the rechallenge:**

Change #45

Section 12.7.7, PHQ-9

The following text was moved to Section 12.7.7.

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. The PHQ-9 scores for depression range from 0 to 27 with higher

scores indicating worse state. A score of 5 to 9 is considered to be minimal symptoms of depression. A score of 10 to 14 is considered minor depression, dysthymia, or mild major depression. A score of 15 to 19 is considered to indicate moderately severe major depression, and a score ≥20 is considered to be severe major depression.

The PHQ-9 will be completed by the subject at the visits specified in Table 5-2.

Refer to Section 6.3 for PHQ-9-related withdrawal criteria.

Change #46

Section 13.2, Medical and ankylosing spondylitis history

The Investigator or designee will obtain a complete medical history and a medical history related to AS (including EAMs, the date of diagnosis, and past treatments for AS as part of the Screening assessment and include all clinically relevant past or coexisting medical conditions, responses to AS treatment as available, Baseline GI-related symptoms, and surgeries. Findings will be recorded in the eCRF.

Has been changed to:

The Investigator or designee will obtain a complete medical history and a medical history related to AS (including EAMs, the date of diagnosis, and past treatments for AS, **and ASAS classification criteria as referenced in Section 19.1)** as part of the Screening assessment and include all clinically relevant past or coexisting medical conditions, responses to AS treatment as available, Baseline GI-related symptoms, and surgeries. Findings will be recorded in the eCRF.

Change #47

Section 15.3.1, Figure 15-1, Sequential testing procedure of primary/secondary efficacy endpoints

The time point (Week 16) was added to hypothesis #9 in the sequential testing procedure.

Change #48

Section 15.3.3, Subgroup analyses, bullet #3

Subgroup analyses using descriptive statistics will be performed on the primary efficacy variable. The following variables for subgroup analyses will be defined:

- ...
- Disease duration (<2 years; ≥2 years)

Has been changed to:

Subgroup analyses using descriptive statistics will be performed on the primary efficacy variable. The following variables for subgroup analyses will be defined:

- ...
- Disease duration (<**5** years; ≥**5** years)

Change #49

Section 16.1, Informed consent, paragraph 3

Prior to participation in the study, the 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.

Has been changed to:

Prior to participation in the study, the 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.

Change #50

Section 16.2, Subject identification cards

Upon signing the Informed Consent Form, 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.

Has been changed to:

Upon signing the Informed Consent Form, 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.

Change #51

Section 18, References

The following reference has been added:

Baraliakos X, Heldmann F, Callhoff J, Listing J, Appelboom T, Brandt J, et al. Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis. 2014;73:1819-25.

The following reference has been deleted:

~~Sieper J, Poddubnyy D. Axial spondyloarthritis.Lancet. 2017;1;390(10089):73-84.~~

Change #52

Section 19.1, ASAS Classification Criteria for axial SpA

The following table has been added:

Table 19-1: ASAS classification criteria for axial SpA (for subjects with chronic back pain of at least 3 months and age at onset <45 years)

Imaging criteria	**ASAS clinical criteria for axial SpA**
Sacroiliitis (MRI or radiographs[a]) plus ≥1 SpA feature	HLA-B27 plus ≥2 other SpA features
SpA features[b]	
Inflammatory back pain[c]	Psoriasis
Arthritis	Crohn's disease/ulcerative colitis
Enthesitis (heel)	HLA-B27
Uveitis	Elevated CRP
Dactylitis	

ASAS=Assessment of SpondyloArthritis International Society; axSpA=axial spondyloarthritis; CRP=C-reactive protein; HLA-B27=human leukocyte antigen B27; MRI=magnetic resonance imaging; NSAID=nonsteroidal anti-inflammatory drug; SpA=spondyloarthritis

[a] Active inflammatory lesions of sacroiliac joints with definite bone marrow oedema/osteitis suggestive of sacroiliitis associated with spondyloarthritis in MRI or radiographic sacroiliitis Grade 2 to 4 bilaterally or Grade 3 to 4 unilaterally according to modified NY criteria. For this study, only MRI will be permitted for study entry for the imaging criterion.

[b] "Family history for SpA" and "Good response to NSAIDs" are excluded as SpA feature criteria.

[c] Inflammatory back pain according to ASAS criteria for axSpA defined as the presence of 4 out of 5 of the following parameters:

1. age at onset <45 years
2. insidious onset
3. improvement with exercise
4. no improvement with rest
5. pain at night (with improvement upon getting up)

19.4 Protocol Amendment 2

Rationale for the amendment

The purpose of this protocol amendment is an update of Inclusion criterion #6 to reflect the treatment guidelines for axSpA, as presented in the recent EULAR/ASAS and ACR/SPARTAN guidelines. The List of Abbreviations has been updated accordingly. In addition, a minor update for consistency has been made.

Modifications and changes

Global changes

No global changes have been made.

Specific changes

Change #1

Section 6.1, Inclusion criterion #6

6. Subjects must have at least 1 of the following:
   - Inadequate response to NSAID therapy, or
   - Intolerance to administration of at least 1 NSAID, or
   - Contraindication(s) to NSAID therapy

   Inadequate response to an NSAID is defined as lack of response for at least 4 weeks of continuous NSAID therapy at the highest tolerated dose of the administered NSAID or the lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for at least 4 weeks total duration.

Has been changed to:

6a. Subjects had to have either failed to respond to 2 different NSAIDs given at the maximum tolerated dose for a total of 4 weeks or have a history of intolerance to or a contraindication to NSAID therapy.

Change #2

Section 9.15, ASDAS

The variables related to ASDAS improvement are defined as follows:

- ASDAS-CII: ASDAS reduction (improvement) of ≥1.1 relative to Baseline
- ASDAS-MI: ASDAS reduction (improvement) of ≥2.0 relative to Baseline

The ASDAS variables will be derived from assessments at the visits specified in Table 5–2.

Has been changed to:

The variable related to ASDAS improvement is defined as follows:

- ASDAS-MI: ASDAS reduction (improvement) of ≥2.0 relative to Baseline

The ASDAS variables will be derived from assessments at the visits specified in Table 5–2.

19.5 Protocol Amendment 3

Rationale for the amendment

The purpose of this amendment is to change the sponsor company name from "UCB Biopharma SPRL" to "UCB Biopharma SRL" since the name of the legal form of the entity UCB Biopharma has changed into "société à responsabilité limitée" abbreviated "SRL".

In addition, a minor correction has been made.

Modifications and changes

Global changes

No global changes have been made.

Specific changes

Change #1

Sponsor name on the title page in the study contact information

Sponsor

UCB Biopharma SPRL

Allée de la Recherche 60

1070 Brussels

BELGIUM

Has been changed to:

Sponsor

UCB Biopharma **SRL**

Allée de la Recherche 60

1070 Brussels

BELGIUM

19.6 Protocol Amendment 4

Rationale for the amendment

The major purpose of this protocol amendment is to update the handling of missing data for the statistical analysis of the primary endpoint in response to a recent agency request. The COVID-19-free set was added in response to industry recommendations for evaluating the impact of the pandemic. In addition, other previously planned supportive analyses defined in the SAP were added for completeness.

Further key changes are summarized below.

- The introduction in Section 2 presenting a high level summary of bimekizumab indications in development and an overview of clinical studies has been updated to reflect the latest status.
- For some secondary and other endpoints in Section 4.2.1 and Section 4.3.1 (BASDAI, nocturnal spinal pain, ASQoL, SF-36, MOS12-item scale, and FACIT-Fatigue), wording changes have been implemented for consistency with the user manuals and to reflect precise description of the PRO tool and scoring (change in terminology but no change in the method). Similarly, corresponding small changes in Section 8 and Section 15.9.2 have been made for clarity and consistency with the revised description of the assessments.
- The definition of the secondary safety variables related to SAEs and AEs leading to withdrawal was changed to clarify these variables are related to treatment-emergent events. This definition is consistent with the SAP and common practice.
- Interim analyses as described in Section 5.1 and Section 15.8.1 have been updated to clarify that interim analyses will include data from the planned number of randomized study participants who completed the corresponding treatment period. In Section 15.8.1, the amendment clarifies that additional interim analyses or data cuts for regulatory purposes are permitted.
- A typographical error in Table 5–1 showing cross-study screening requirements for the PHQ-9, eC-SSRS, and the TB questionnaire (Q1) related criterion has been corrected.
- In line with the Exclusion Criterion 11 regarding infections, a specific infection related withdrawal criterion was added to clarify that subjects with serious or recurrent infections not responding to standard therapies are not exposed to immunomodulatory therapies until their infection is resolved. This is in line with most biologic therapies, including other anti-IL17s.
- In Table 7–2, the section providing details for mild potency opioids has been updated to clarify that the listed opioids reflect examples.
- Section 7.8.1 listing permitted concomitant treatments has been amended to enhance clarity on allowed medications including biologics for permanently discontinued subjects after at least 28 days of the final IMP dose.
- Throughout the protocol, vital sign assessments reported as pulse and blood pressure measurements were replaced with “vital sign” measurements for internal consistency. This update does not reflect a procedural change.
- The description of the ASQoL assessment in Section 9.2 has been amended with details regarding scoring.

- Language describing the BASFI component of the ASAS response has been updated for clarity to specifically mention "physical function" as opposed to "function". The header for Section 9.5 was updated accordingly.
- The presentation of the SF-36 assessment in Section 9.6 has been corrected to ensure consistency with the user manual and the author's recommendation (Maruish, 2011). Subsequently, wording changes for consistency throughout the protocol, mainly in Section 4.2.1 and Section 8 have been made.
- The presentation of the FACIT-Fatigue subscale in Section 9.10 has been corrected to ensure consistency with the user manual (FACIT.org). Subsequently, wording changes for consistency throughout the protocol, mainly in Section 4.3.1 and Section 8 have been made.
- The proposed SPARCC and ASspiMRI scoring systems to assess the level of MRI inflammation in the SIJ and spine, respectively, are currently well accepted. Methodology for scoring of MRI inflammation in the SIJ or spine is evolving, and the additional methods to evaluate the MRI inflammation data (for instance spine SPARCC) may be considered. Based on this approach, Section 9.20.3 has been amended accordingly.
- With progressive development of bimekizumab and based on the ongoing review of emerging safety data, depression has been removed as a safety topic of interest. Nevertheless, depression will continue to be monitored as a safety parameter by the PHQ9 and will be captured via routine AE reporting during the study. This update is considered a procedural change.
- Action to be taken in the event that a subject reports a pregnancy as described in Section 12.2 has been updated for consistency with protocols in other indications.
- Action to be taken if a subject presents with a PDILI event as described in Section 12.6.1 has been updated for consistency with protocols in other indications.
- Section 15.8.2 was amended to allow other adjudication committees as necessary.
- Study contact details have been updated to reflect recent changes.

At the same time, a few updates including consistency changes within the bimekizumab program, minor corrections, the list of abbreviations, a reference has been added for the FACIT-Fatigue, and minor formatting changes for the purpose of clarity have been made.

Modifications and changes

Global changes

The following change was made throughout the protocol:

- All instances that referred to "Administer the SF-36 PCS and MCS" have been corrected to "Administer the SF-36 questionnaire".
- All instances that referred to "FACIT-F" have been corrected to "FACIT-Fatigue", all instances that referred to "Administer the FACIT-F" have been corrected to "Administer the FACIT-Fatigue subscale" and the definition of the abbreviation was updated accordingly.

Specific changes

Change #1

Protocol/Amendment number details on the cover page

Protocol Amendment 4.2 (Germany)

Has been changed to:

Protocol Amendment **3**.2 (Germany)

Change #2

STUDY CONTACT INFORMATION

Sponsor Study Physician

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Straße 10 40789 Monheim am Rhein GERMANY
Phone:	[redacted]

Has been changed to:

Name:	[redacted]
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Straße 10 40789 Monheim am Rhein GERMANY
Phone:	[redacted]

Change #3

Section 2.2, Bimekizumab, paragraph 1, sentence 5

Bimekizumab is being developed for the treatment of patients with inflammatory diseases such as PsA, psoriasis (PSO), and axSpA.

Has been changed to:

Bimekizumab is being developed for the treatment of patients with inflammatory diseases such as PsA, psoriasis (PSO), ~~and~~ axSpA **and hidradenitis suppurativa**.

Change #4

Section 2.2.2.1, Completed studies, paragraph 1

Thirteen clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, UP0031 in 12 healthy volunteers, UP0042 in 48 Japanese and Caucasian healthy volunteers, RA0123 in 159 subjects with moderate-to-severe RA, PS0010 in 250 subjects with moderate-to-severe chronic plaque PSO and the corresponding extension study (PS0011), PS0016 in 49 subjects with moderate-to-severe chronic plaque PSO and the corresponding extension study (PS0018), UC0011 in 23 subjects with moderate-to severe active ulcerative colitis, AS0008 in 303 subjects with AS, and PA0008 in 206 subjects with PsA.

Has been changed to:

~~Thirteen~~ **Twenty** clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, UP0031 in 12 healthy volunteers, **UP0033 in 189 healthy volunteers, UP0034 in 56 healthy volunteers,** UP0042 in 48 Japanese and Caucasian healthy volunteers, **UP0074 in 37 healthy volunteers,** RA0123 in 159 subjects with moderate-to-severe RA, PS0010 in 250 subjects with moderate-to-severe chronic plaque PSO and the corresponding extension study (PS0011), PS0016 in 49 subjects with moderate-to-severe chronic plaque PSO and the corresponding extension study (PS0018), UC0011 in 23 subjects with moderate-to severe active ulcerative colitis, **HS0001 in 90 subjects with moderate to severe hidradenitis suppurativa,** AS0008 in 303 subjects with AS, ~~and~~ PA0008 in 206 subjects with PsA**, PS0008 in 478 subjects with moderate to severe chronic plaque PSO, PS0009 in 567 subjects with moderate to severe chronic plaque PSO and PS0013 in 435 subjects with moderate to severe chronic plaque PSO**.

Change #5

Section 2.2.2.2, Ongoing studies, paragraph 1

Several additional studies of bimekizumab in subjects with AS are ongoing:

Has been changed to:

Several additional studies of bimekizumab in subjects with ~~AS~~ **axSpA** are ongoing:

In addition, the following bullet has been added:

- AS0014 is a Phase 3, open-label extension study for AS0010 and AS0011.

Change #6

Section 4.2, Secondary variables

Section 4.2.1, Secondary efficacy variables

- …

- Change from Baseline in BASDAI at Week 16
- …
- Change from Baseline in nocturnal spinal pain (NRS) at Week 16
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) at Week 16
- Change from Baseline in the Short Form 36-Item Health Survey (SF-36) physical component summary (PCS) at Week 16
- …

Section 4.2.2, Secondary safety variables

…

- Incidence of serious adverse events (SAEs)
- Adverse events (AEs) leading to withdrawal from IMP

Has been changed to:

Section 4.2.1, Secondary efficacy variables

- …
- Change from Baseline in BASDAI **total score** at Week 16
- …
- Change from Baseline in nocturnal spinal pain **score** (NRS) at Week 16
- Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) **total score** at Week 16
- Change from Baseline in the Short Form 36-Item Health Survey (SF-36) physical component summary (PCS) **score** at Week 16
- …

Section 4.2.2, Secondary safety variables

…

- Incidence of **treatment-emergent** serious adverse events (SAEs)
- ~~Adverse events (AEs)~~ **TEAEs** leading to withdrawal from IMP

Change #7

Section 4.3.1, Other efficacy variables

- …
- Change from Baseline in BASDAI
- …

- Change from Baseline in total and nocturnal spinal pain (NRS)
- Change from Baseline in the average of Questions 5 and 6 of the BASDAI concerning morning stiffness
- …
- Change from Baseline in the SF-36 PCS
- Change from Baseline in the SF-36 mental component summary (MCS)
- Change from Baseline in sleep quality (Medical Outcomes Study [MOS 12-item] scale)
- Change from Baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)
- Change from Baseline in ASQoL
- …

Has been changed to:

- …
- Change from Baseline in BASDAI **total score**
- …
- Change from Baseline in total and nocturnal spinal pain **score** (NRS)
- Change from Baseline in the average **score** of Questions 5 and 6 of the BASDAI concerning morning stiffness
- …
- Change from Baseline in the SF-36 PCS **score**
- Change from Baseline in the SF-36 mental component summary (MCS) **score**
- Change from Baseline in sleep quality **score** (Medical Outcomes Study [MOS 12-item] scale)
- Change from Baseline in Functional Assessment of Chronic Illness Therapy~~-Fatigue~~ (FACIT~~-F~~)**-Fatigue subscale score**
- Change from Baseline in ASQoL **total score**
- …

Change #8

Section 5.1, Study description, paragraph 6, sentence 1

Interim analyses of all available data (including efficacy, safety, and PK) will be conducted after all randomized subjects have completed 24 weeks and 52 weeks of treatment or have withdrawn from IMP or the study.

Has been changed to:

Interim analyses of all available data (including efficacy, safety, and PK) will be conducted after ~~all~~ **the planned number of** randomized subjects have completed 24 weeks and 52 weeks of treatment or have withdrawn from IMP or the study.

Change #9

Section 5.1.1.2 Cross-study screening requirements

Table 5-1: Cross-study screening requirements, fourth row, second column

Table 5-1: Cross-study screening requirements

Assessment	Screening requirements
…	
PHQ-9, eC-SSRS, TB questionnaire (Q1)	Screening of a subject not eligible for AS0010 who will be screened for AS0011, and who did not meet the related Exclusion Criteria in AS0010.
…	

Has been changed to:

Table 5-1: Cross-study screening requirements

Assessment	Screening requirements
…	
PHQ-9, eC-SSRS, TB questionnaire (Q1)	Screening of a subject not eligible for AS0010 who will be screened for AS0011, and who did ~~not~~ meet the related Exclusion Criteria in AS0010.
…	

Change #10

Section 5.2, Schedule of study assessments

Table 5–2: Schedule of study assessments, 22nd row, first column

Protocol activity
…
• FACIT-F
…

Has been changed to:

Protocol activity
…
• FACIT ~~-F~~ **-Fatigue subscale**
…

Change #11

Section 6.3, Withdrawal criteria

The following bullet has been added:

12. Any subject who develops a clinically important infection or recurrent infections not responsive to standard therapy during the study must discontinue IMP until resolution of the infection. The Investigator should use clinical judgement in deciding whether the subject should restart IMP and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.

Change #12

Section 7.8, Concomitant medications/treatments

Table 7–2: Exclusionary, concomitant, and rescue medication, fourth row, first column

Drug class/dose
…
Mild potency opioids permitted only: • Tramadol/any dose up to maximum approved dose • Codeine/only <90mg of codeine per dosage unit
…

Has been changed to:

Drug class/dose
…
Mild potency opioids permitted only **eg,**: • Tramadol/any dose up to maximum approved dose • Codeine/only <90mg of codeine per dosage unit
…

Change #13

Section 7.8.1, Permitted concomitant treatments (medications and therapies)

The following text has been added:

Subjects are allowed to use any other medications, including biologics, after at least 28 days of their final dose of the IMP. This is applicable for subjects who discontinue from the study early, including those permanently withdrawn from IMP, or subjects who have completed the study treatment without entering the extension study and are in the SFU Period.

Change #14

Section 8.2, Baseline (Visit 2, Day 1, first dose of IMP), last bullet

and

Section 8.3.6, Week 16 (±3 days) (Visit 8), last bullet

- Measure BP and pulse approximately 30 minutes and 1 hour after dosing.

Has been changed to:

- Measure ~~BP and pulse~~ **vital signs** approximately 30 minutes and 1 hour after dosing.

Change #15

Section 9.1, ASAS20, 40, ASAS 5/6 response, and ASAS-PR, third bullet point

- Function section (represented by BASFI, Section 9.5)

Has been changed to:

- **Physical** Function ~~section~~ (~~represented~~ **measured** by BASFI, Section 9.5)

Change #16

Section 9.2, ASQoL, first paragraph

The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring health-related quality of life (HRQoL) in subjects with AS (Doward et al, 2003). The ASQoL has been used and has shown to be responsive in axSpA (Barkham et al, 2009; Haibel et al, 2008). The ASQoL score ranges from 0 to 18 with a higher score indicating worse HRQoL.

Has been changed to:

The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring health-related quality of life (HRQoL) in subjects with AS (Doward et al, 2003). The ASQoL has been used and has shown to be responsive in axSpA (Barkham et al, 2009; Haibel et al, 2008). ~~The~~ **Each statement on the** ASQoL **is given a** score ~~ranges~~ **of 1 = Yes or 0 = No. A score of "1" is given where the item is affirmed, indicating adverse quality of life. All item scores are summed to total score ranging** from 0 to 18 with a higher score indicating worse HRQoL.

Change #17

Section 9.4, BASDAI, second paragraph

The BASDAI is calculated as follows:

Has been changed to:

The BASDAI **total score** is calculated as follows:

Change #18

Section 9.5, Function – BASFI, heading

Has been changed to:

Section 9.5, Physical ~~F~~function – BASFI

Change #19

Section 9.6, SF-36, paragraphs 1 and 2

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 perceived stability or change in health (Health Transition) during the last year. 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.

Has been changed to:

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~~ **One additional** item ~~for perceived stability or change in~~ **asks respondents about** health **change** (Health Transition) ~~during~~ **over** the ~~last~~ **past** year. 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 **norm-based T-scores for the** 2 **SF-36** component summary **(PCS and MCS) and the 8 domain** scores are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general US **population (Maruish, 2011).**

An individual respondent's score that falls outside the T-score range of 45 to 55 should be considered outside the average range for the US general population. When considering group-level data, a score below 47 should be considered indicative of impaired functioning within that health domain or dimension. Similar to individual respondent data, group mean scores of 47 or greater should be considered average or above average as compared to the general US population. Higher scores indicate a better health status.

Change #20

Section 9.10, FACIT-F, heading and all paragraphs

The FACIT-F is a self-administered quality of life questionnaire targeted to the management of chronic illness within the past 7 days. The FACIT-F contains 13 questions with responses scored on a 5-point Likert scale from 0 (not at all) to 4 (very much). Scores range from 0 to 52 (Mease et al, 2011).

The FACIT-F will be assessed by the subject at the visits specified in Table 5-2.

Has been changed to:

Section 9.10, FACIT ~~-F~~-Fatigue subscale

The FACIT-F is a ~~self-administered quality of life questionnaire targeted to~~ **40-item measure that assesses self-reported fatigue and its impact upon daily activities and function over** ~~the management of chronic illness within~~ the past 7 days **(FACIT.org). The scale consists of 5 subscales (physical well-being, social/family well-being, emotional well-being, functional well-being, and fatigue). The fatigue subscale is the only one used in this study.** ~~The FACIT-F contains~~ **It is composed of** 13 ~~questions with responses~~ **items, all** scored ~~on a 5-point Likert scale~~ from 0 (~~n~~**N**ot at all) to 4 (~~v~~**V**ery much). ~~Scores range~~ **The FACIT-Fatigue subscale score ranges** from 0 to 52 ~~(Mease et al, 2011)~~ **with 0 being the worst possible score and 52 being the best possible score. To obtain a score from 0 to 52, all negatively worded questions have to be recoded, so that responses range from worst (0) to the best (4) outcome.**

The FACIT ~~-F-~~**Fatigue subscale** will be ~~assessed~~ **completed** by the subject at the visits specified in Table 5-2.

Change #21

Section 12.1.1.4 Other safety topics of interest, paragraph 1

Pre-specified safety topics of interest for the study are: infections (serious, opportunistic, fungal, and TB), neutropenia, hypersensitivity, suicidal ideation and behavior, depression, major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel diseases (with gastroenterology referral, as appropriate).

Has been changed to:

Pre-specified safety topics of interest for the study are: infections (serious, opportunistic, fungal, and TB), neutropenia, hypersensitivity, suicidal ideation and behavior, ~~depression,~~ major

cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel diseases (with gastroenterology referral, as appropriate).

Change #22

Section 9.20.3, Sacroiliac joint and spine MRI assessment substudy

The following sentence has been added at the end of the last paragraph:

Additional scoring systems of inflammation may be used as appropriate methodology becomes accepted.

Change #23

Section 12.2 Pregnancy, paragraph 1 and bullet points

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 entering all pregnancy information into the eCRF. An automatic notification will be sent to UCB's PS department. 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.
- A Safety Follow-Up Visit should be scheduled 20 weeks after the subject has discontinued her IMP.

Has been changed to:

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately **(within 24 hours)** notify UCB's PS department by entering all pregnancy information into the eCRF. An automatic notification will be sent to UCB's PS department. The subject should be **permanently** withdrawn from ~~the study~~ **IMP** 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.
- **The subject should return for an early ad-hoc study visit**.
- A Safety Follow-Up Visit should be scheduled 20 weeks after the ~~subject has discontinued her~~ **final dose of** IMP.

The Investigator should discuss with the subject the possibility to continue the study by attending the scheduled visits for assessments without IMP administration. The tests or assessments, which are considered contraindicated during the pregnancy should not be performed. The early ad-hoc study visit will be considered as the ET Visit if the subject does not wish to pursue the study investigations.

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

Change #24

Section 12.6.1 Evaluation of PDILI, paragraph 1

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 12.1.1.3), and, if applicable, also reported as an SAE (see Section 12.1.1.2).

Has been changed to:

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 **PDILI events meeting SAE criteria should be** 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 **within 24 hours of learning of their occurrence** as an AE of special interest (see Section 12.1.1.3), and, if applicable, also reported as an SAE (see Section 12.1.1.2).

Change #25

Section 12.7.1 Vital signs

The Investigator or designee should measure all vital signs (systolic and diastolic BP, temperature [oral, axillary, or otic], pulse rate) prior to dosing after the subject has been sitting for at least 5 minutes, and the subject should remain seated during the measurements. At Baseline/Day 1 and Week 16 collect pulse and BP prior to drug administration and then at approximately 30 minutes and 1 hour after dosing.

Has been changed to:

The Investigator or designee should measure all vital signs (systolic and diastolic BP, temperature [oral, axillary, or otic], pulse rate) prior to dosing after the subject has been sitting for at least 5 minutes, and the subject should remain seated during the measurements. At Baseline/Day 1 and Week 16**,** collect ~~pulse and BP~~ **vital signs** prior to drug administration and then at approximately 30 minutes and 1 hour after dosing.

Change #26

Section 15.1, Definition of analysis sets, fifth bullet

- The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviation affecting the primary efficacy variable. Important protocol deviations will

be predefined and subjects with important protocol deviations will be evaluated during a data evaluation meeting prior to unblinding of the data.

Has been changed to:

- The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviation affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will be evaluated during a data evaluation meeting prior to unblinding of the data. **Exclusions from the FAS will be considered important protocol deviations that also result in exclusion from the PPS.**

In addition, the following bullet has been added:

The coronavirus disease 2019 (COVID-19) free set will consist of all subjects in the RS who had no COVID-19 impact up to the primary efficacy endpoint. Further details will be defined as part of the SAP.

Change #27

Section 15.3.1.1 Analysis of the primary efficacy variable, paragraph 2, bullet #1, bullet #3 and paragraph 4

…

The primary endpoint is the ASAS40 response at Week 16. The primary efficacy analysis will evaluate the composite estimand in the RS. The composite estimand combines the clinically meaningful improvement from Baseline based on the ASAS40 response and not discontinuing treatment early due to an AE or lack of efficacy.

…

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria.

…

3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving ASAS40 at Week 16 and not discontinuing study treatment due to an AE or lack of efficacy through Week 16.

…

Any missing data at Week 16 that are not preceded by an intercurrent event (ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined multiple imputation (MI) model. 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 logistic regression for monotone missing data.

…

Has been changed to:

…

The primary endpoint is the ASAS40 response at Week 16. The primary efficacy analysis will evaluate the composite estimand in the RS. The composite estimand combines the clinically meaningful improvement from Baseline based on the ASAS40 response and not discontinuing treatment early ~~due to an AE or lack of efficacy~~. **In practice, this composite estimand is similar to non-responder imputation (NRI), referred to here as modified NRI.**

…

1. Population = Subjects ~~meeting~~ **enrolled according to** the protocol-specified inclusion/exclusion criteria **and randomized to IMP**.

…

3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment ~~due to an AE or lack of efficacy~~ prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving ASAS40 at Week 16 and not discontinuing study treatment ~~due to an AE or lack of efficacy~~ through Week 16.

…

~~Any m~~**M**issing data at Week 16 that are not preceded by an intercurrent event**, and any data after an intercurrent event will be imputed as non-responders** ~~(ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined multiple imputation (MI) model. 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 logistic regression for monotone missing data~~.

…

Change #28

Section 15.3.1.1.1 Supportive analyses

Supportive analyses for the primary efficacy variable will be conducted:

1. The analysis will be repeated based on the PPS to evaluate the effect of important protocol deviations on the analysis.
2. The analyses will be repeated for all subjects in the FAS to evaluate the consistency between the RS and the more restrictive FAS. This analysis will only be performed if the number of subjects in RS and FAS are different.
3. The analyses will also be repeated for all individual components of the ASAS40 response to explore the effect of the signs and symptoms of the individual components on the composite endpoint. Since all ASAS components are continuous variables (eg, change from Baseline in total spinal pain), an analysis of covariance (ANCOVA) with treatment, region, and prior

TNFα inhibitor exposure as fixed effects and the Baseline values as covariate will be used for the analysis.

Additional supportive analyses to evaluate varying assumptions related to the handling of missing data will also be performed and are described in Section 15.7.

Has been changed to:

Supportive analyses for the primary efficacy variable will be conducted**. The analyses will be repeated**:

1. ~~The analysis will be repeated b~~**B**ased on the PPS to evaluate the effect of important protocol deviations on the analysis.
2. ~~The analyses will be repeated f~~**F**or all subjects in the FAS to evaluate the consistency between the RS and the more restrictive FAS. This analysis will only be performed if the number of subjects in RS and FAS are different.
3. ~~The analyses will also be repeated f~~**F**or all individual components of the ASAS40 response to explore the effect of the signs and symptoms of the individual components on the composite endpoint. Since all ASAS components are continuous variables (eg, change from Baseline in total spinal pain), an analysis of covariance (ANCOVA) with treatment, region, and prior TNFα inhibitor exposure as fixed effects and the Baseline values as covariate will be used for the analysis.
4. **Using a modified composite estimand where intercurrent events are defined only as discontinuation due to adverse event or lack of efficacy.**
5. **Using a treatment policy imputation.**
6. **Using a tipping point analysis.**
7. **Using observed cases only (OC).**
8. **Using the COVID-19-free set.**

Further specification of ~~A~~**a**dditional supportive analyses to evaluate varying assumptions related to the handling of missing data will also be performed and are described in Section 15.7.

Change #29

Section 15.3.1.2 Analyses of the secondary efficacy variables, paragraph 2, first bullet point and paragraphs 4 and 5

…

Binary variables will be analyzed to evaluate the composite estimand in the RS as done for the primary efficacy variable. The composite estimand combines (1) achieving the given binary response and (2) not discontinuing prior to Week 16 due to an AE or lack of efficacy. The statistical hypothesis for the binary variables at Week 16 is that the conditional odds ratio for binary variables in the bimekizumab treatment group compared with the placebo treatment group is equal to 1.

…

- Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A hypothetical strategy for addressing intercurrent events will be implemented. This estimand targets the treatment difference in a scenario where withdrawal from study treatment due to an AE or lack of efficacy does not occur, such that outcomes for subjects without an intercurrent event are as observed, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16. A multiple imputation strategy will be used to impute data following an intercurrent event.

…

Any missing data at Week 16 that is not preceded by an intercurrent event (ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined MI model. The missing value will be replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by monotone regression for monotone missing data. The statistical model for the comparison of bimekizumab and placebo will be an ANCOVA with treatment, region, and prior TNFα inhibitor exposure as fixed effects and the Baseline value as covariate. The statistical hypothesis for the continuous variables at Week 16 is that the treatment difference between the bimekizumab treatment group and placebo is equal to 0.

All secondary efficacy variables will also be summarized based on observed case data.

Has been changed to:

…

Binary variables will be analyzed to evaluate the composite estimand in the RS**,** as done for the primary efficacy variable. The composite estimand combines (1) achieving the given binary response and (2) not discontinuing **treatment** prior to Week 16 ~~due to an AE or lack of efficacy~~. The statistical hypothesis for the binary variables at Week 16 is that the conditional odds ratio for binary variables in the bimekizumab treatment group compared with the placebo treatment group is equal to 1.

…

- Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment ~~due to an AE or lack of efficacy~~ prior to Week 16. A hypothetical strategy for addressing intercurrent events will be implemented. This estimand targets the treatment difference in a scenario where withdrawal from study treatment ~~due to an AE or lack of efficacy~~ does not occur, such that outcomes for subjects without an intercurrent event are as observed, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16. A multiple imputation strategy will be used to impute data following an intercurrent event.

…

Any missing data at Week 16 that is not preceded by an intercurrent event (ie, discontinuation of study medication ~~due to an AE or lack of efficacy~~) will be imputed based on a

predefined **multiple imputation (**MI**)** model. The missing value will be 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. The statistical model for the comparison of bimekizumab and placebo will be an ANCOVA with treatment, region, and prior TNFα inhibitor exposure as fixed effects and the Baseline value as covariate. The statistical hypothesis for the continuous variables at Week 16 is that the treatment difference between the bimekizumab treatment group and placebo is equal to 0.

All secondary efficacy variables will also be summarized based on observed case data. **Binary outcomes will also be summarized using the modified composite estimand.**

Change #30

Section 15.3.2 Analyses of other efficacy variables, bullet #3, paragraph 3 and the second bullet #3

…

3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to adverse event or lack of efficacy prior to the time point being summarized. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving the given variable at the specified time point and not discontinuing study treatment due to adverse event or lack of efficacy through that time point.

…

Any missing data that are not preceded by an intercurrent event as described above will be imputed based on a predefined multiple imputation model as described for the primary efficacy variable.

…

3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to the time point being summarized. A hypothetical strategy will be implemented in which outcomes for subjects without an intercurrent event are as observed at the given time point, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through the time point being summarized. A multiple imputation strategy will be used to impute data following an intercurrent event.

…

Has been changed to:

…

3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment ~~due to adverse event or lack of efficacy~~ prior to the time point being summarized. A composite strategy will be implemented in which a positive clinical outcome is defined as

achieving the given variable at the specified time point and not discontinuing study treatment ~~due to adverse event or lack of efficacy~~ through that time point.

…

Any missing data that are not preceded by an intercurrent event as described above will be imputed based on ~~a predefined multiple imputation model~~ **NRI** as described for the primary **and secondar**y efficacy variable**s**.

…

3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment ~~due to an AE or lack of efficacy~~ prior to the time point being summarized. A hypothetical strategy will be implemented in which outcomes for subjects without an intercurrent event are as observed at the given time point, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through the time point being summarized. A multiple imputation strategy will be used to impute data following an intercurrent event.

…

Change #31

Section 15.7, Handling of dropouts or missing data, paragraphs 1 and 2, bullet #1 and paragraph 4

The analysis for the primary and secondary efficacy variables will include the use of MI. In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by regression for monotone missing data. The multiple imputation procedures planned for the primary and secondary efficacy analyses are based on an assumption of data missing at random (MAR).

The sensitivity of results to the approach for handling missing data will be evaluated via supportive analyses using different missing data mechanisms. The following supportive analyses for the primary efficacy variable and for those secondary efficacy variables that are part of the hierarchical testing will be conducted:

1. Deviations from the MAR pattern will be evaluated using a reference-based MI approach. Intermittent missing data will be imputed using the MCMC method. The remaining monotone missing data will be assumed to follow a missing not at random (MNAR) pattern. These data will be imputed using a reference-based approach in which the MI model is based on data from the placebo group, thereby assuming that monotone missing data follow a trajectory similar to the placebo group (Mallinckrodt, 2013). The estimand in this procedure is the difference in outcome improvement in all randomized subjects at the planned endpoint of the study attributable to the initially randomized medication (Mallinckrodt et al, 2012).

…

The same procedure described as in the primary efficacy analyses will be used.

…

Has been changed to:

The **primary** analysis for the primary ~~and secondary efficacy~~ variables ~~will~~ will **use a conservative approach to handling missing data that is similar to non-responder imputation. The sensitivity of results to the approach for handling missing data will be evaluated via supportive analyses using different missing data mechanisms.**

In instances where ~~include the use of MI. In~~ MI **is used**, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by regression for monotone missing data. The **planned** multiple imputation procedures ~~planned for the primary and secondary efficacy analyses~~ are based on an assumption of data missing at random (MAR).

~~The sensitivity of results to the approach for handling missing data will be evaluated via supportive analyses using different missing data mechanisms.~~ The following supportive analyses for the primary efficacy variable ~~and for those secondary efficacy variables that are part of the hierarchical testing~~ will be conducted:

1. ~~Deviations from the MAR pattern will be evaluated using a reference-based MI approach. Intermittent missing data will be imputed using the MCMC method. The remaining monotone missing data will be assumed to follow a missing not at random (MNAR) pattern. These data will be imputed using a reference-based approach in which the MI model is based on data from the placebo group, thereby assuming that monotone missing data follow a trajectory similar to the placebo group (Mallinckrodt, 2013). The estimand in this procedure is the difference in outcome improvement in all randomized subjects at the planned endpoint of the study attributable to the initially randomized medication (Mallinckrodt et al, 2012).~~ **Multiple imputation as described above will be performed using the modified composite estimand as specified for the use with the secondary variables. The definition of an intercurrent event is changed from all treatment discontinuation, to discontinuation of treatment due to AE or lack of efficacy.**

…

~~The same procedure described as in the primary efficacy analyses will be used.~~ **For the secondary and other efficacy variables, the binary endpoints will be analyzed using modified NRI, MI and OC, and the continuous endpoints will be analyzed using MI and OC.**

…

Change #32

Section 15.8.1, Interim analyses, paragraph 1

Two interim analyses will be performed: one after all randomized subjects have completed the Double-Blind Treatment Period and the Week 24 assessments, and one after all subjects have completed Week 52.

Has been changed to:

Two interim analyses will be performed: one after ~~all~~ **the planned number of** randomized subjects have completed the Double-Blind Treatment Period and the Week 24 assessments, and one after ~~all~~ **the planned number of** subjects have completed Week 52.

In addition, the following text has been added:

Additional interim analyses and data cuts may be performed for regulatory purposes.

Change #33

Section 15.8.2 Data monitoring and Adjudication Committees

The following text has been added:

Other adjudication committees may be added as necessary.

Change #34

Section 15.9.2, Power calculations for secondary endpoints in the hierarchical testing

…

For change from Baseline in BASDAI at Week 16, an adjusted between-treatment difference of - 1.38 with an SD=1.8 for bimekizumab and SD=1.4 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

…

For change from Baseline in nocturnal spinal pain at Week 16, the AS data from the certolizumab pegol study AS001 were used. An adjusted between-treatment difference of -1.88 with an SD=2.9 for bimekizumab and SD=2.4 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in ASQoL at Week 16, an adjusted between-treatment difference of - 2.39 with an SD=4.5 for bimekizumab and placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in SF-36 at Week 16, an adjusted between-treatment difference of 4.56 with an SD=8.1 for bimekizumab and SD=5.8 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

…

Has been changed to:

…

For change from Baseline in BASDAI **total score** at Week 16, an adjusted between-treatment difference of - 1.38 with an SD=1.8 for bimekizumab and SD=1.4 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

…

For change from Baseline in nocturnal spinal pain **score** at Week 16, the AS data from the certolizumab pegol study AS001 were used. An adjusted between-treatment difference of -1.88 with an SD=2.9 for bimekizumab and SD=2.4 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in ASQoL **total score** at Week 16, an adjusted between-treatment difference of - 2.39 with an SD=4.5 for bimekizumab and placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

For change from Baseline in SF-36 **PCS score** at Week 16, an adjusted between-treatment difference of 4.56 with an SD=8.1 for bimekizumab and SD=5.8 for placebo was used. With those assumptions, the endpoint is powered with >99% at the planned sample size.

…

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.

Approval Signatures

Name: as0011-protocol-amend-4

Version: 1.0

Document Number: CLIN-000166877

Title: AS0011 Protocol Amendment 4 - Phase 3 - Placebo-controlled - Double-blind

Approved Date: 17 Feb 2021

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 16-Feb-2021 11:37:45 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Qualified Person Date of Signature: 16-Feb-2021 14:12:45 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 17-Feb-2021 12:16:53 GMT+0000