PROTOCOL AS0009 AMENDMENT 3

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

PHASE 2B

EudraCT Number: 2017-001002-15

IND Number: 128708

Sponsor:
UCB Biopharma SRL
Allée de la Recherche 60
1070 Brussels
BELGIUM

Protocol/Amendment number	Date	Type of amendment
Final protocol	15 May 2017	Not applicable
Protocol amendment 1	17 July 2017	Not applicable
Protocol amendment 2	21 March 2018	Substantial
Protocol amendment 2.1 Czech Republic	08 Jun 2018	Substantial
Protocol amendment 3	06 Feb 2020	Non-substantial

STUDY CONTACT INFORMATION

Sponsor

UCB BIOPHARMA SRL

Allée de la Recherche 60

1070 Brussels

BELGIUM

Sponsor Study Physician

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

Clinical Project Manager

Name:	[redacted]
Address:	UCB Pharma Ltd. 208 Bath Road Slough SL1 3WE UNITED KINGDOM
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted], MSc
Address:	UCB Pharma Ltd. 208 Bath Road Slough SL1 3WE UNITED KINGDOM
Phone:	[redacted]

Clinical Monitoring Contract Research Organization (CRO)

Name:	PRA Health Sciences
Address:	4130 Park Lake Avenue, Suite 400 Raleigh, NC 27612 UNITED STATES
Phone:	+1 919 786 8200
Fax:	+1 919 786 8201

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175
Email	**Global:** DS_ICT@ucb.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40, 5/6	Assessment in Axial SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score-C-reactive protein
ASDAS-ID	Ankylosing Spondylitis Disease Activity Score Inactive Disease
ASQoL	Ankylosing Spondylitis Quality of Life
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
CDMS	clinical data management system
CI	confidence interval
COX-2	cyclooxygenase 2
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report form
CRO	contract research organization
CRP	C-reactive protein
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
DVU	disco-vertebral units
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram

eCRF	electronic Case Report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EDC	electronic data capture
ES	Enrolled Set
ET	Early Termination
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depression
HCQ	hydroxychloroquine
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IGRA	Interferon-Gamma Release Assay
IL17	Interleukin-17
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
iv	intravenous (ly)
IXRS	interactive voice or web response system
LEF	leflunomide

LTB	latent tuberculosis
MASES	Maastricht Ankylosing Spondylitis Enthesitis Score
MCID	minimal clinically important difference
MCMC	Markov Chain Monte Carlo
MedDRA®	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MTX	methotrexate
nr-axSpA	nonradiographic-axial spondyloarthritis
NRI	nonresponder imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria
OLE	open-label extension
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PD	pharmacodynamics
PDILI	potential drug-induced liver injury
PFS	prefilled syringe
PGADA	Patient's Global Assessment of Disease Activity
PK	pharmacokinetics
PS	Patient Safety
PsA	psoriatic arthritis
PSO	psoriasis
Q4W	every 4 weeks (monthly)
RA	rheumatoid arthritis
RCTC	Rheumatology Common Toxicity Criteria
SAE	serious adverse event
sc	subcutaneous(ly)
SD	standard deviation
SF-36	Short-Form 36-item Health Survey
SFU	Safety Follow-up
SI	sacroiliac
SOP	standard operating procedure

SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SS	Safety Set
SSZ	sulfasalazine
STIR	short-tau-inversion recovery
TEAE	treatment-emergent adverse event
TB	tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale

1 SUMMARY

AS0009 is a multicenter, 208-week, open-label extension (OLE) study to evaluate the long-term safety, tolerability, and efficacy of bimekizumab for eligible subjects with ankylosing spondylitis (AS) who complete AS0008 (Phase 2b).

AS0008 is a multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy and safety of bimekizumab in subjects with active AS. At Week 48 of AS0008, all subjects continuing into AS0009 will undergo the final lead-in study assessments and any nonoverlapping AS0009 study entry assessments, and will then receive their first open-label dose of bimekizumab.

In the AS0009 OLE study, bimekizumab will be administered at a dose of 160mg every 4 weeks (Q4W) subcutaneously (sc) for all subjects regardless of treatment received in AS0008.

Up to 285 subjects from the ongoing AS0008 Phase 2b study could be enrolled into this study.

The primary objective is to assess the long-term safety and tolerability of bimekizumab administered over a period of up to 204 weeks (~4 years). The primary safety variables are the incidences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs).

The secondary objective is to assess the long-term efficacy. The secondary efficacy variables include the Assessment of SpondyloArthritis International Society 40% response criteria (ASAS40) at Week 48, ASAS20 response at Week 48, and the change from Baseline of AS0008 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 48. The secondary safety variable is the withdrawal due to TEAEs.

Other objectives are to assess impact on enthesitis and on patient-reported quality of life and to assess the plasma concentrations and immunogenicity of bimekizumab.

The study duration for each subject is estimated to be up to a maximum of 224 weeks: an Open-Label Treatment Period of up to 204 weeks (~4 years), followed by a Safety Follow-up (SFU) Visit 20 weeks after the last dose of bimekizumab.

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, arthritis of inflammatory bowel disease [IBD], and undifferentiated spondyloarthritis) that have features in common with each other and distinct from other inflammatory arthritides, particularly rheumatoid arthritis (RA).

Axial SpA is a chronic inflammatory disease that impacts a substantial proportion of the population. Limited evidence exists regarding the exact prevalence of axSpA; 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).

The Assessment of SpondyloArthritis International Society (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 (SI joints and spine), including AS diagnosed with radiographic involvement and nonradiographic axial spondyloarthritis (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. 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, the spine may become fused over time. Objective signs of inflammation (such as enthesitis, dactylitis, peripheral arthritis, or uveitis), genetic features (such as the presence of human leukocyte antigen 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.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often rapidly effective for the symptoms (pain and stiffness) of axSpA (Poddubnyy, 2013; Poddubnyy et al, 2012), but many patients lose or never have symptomatic response and structural damage often progresses despite their use. Conventional disease-modifying antirheumatic drugs (DMARDs; eg, methotrexate [MTX] and sulfasalazine [SSZ]) have unproven 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 effective and approved treatment options such as tumor necrosis factor (TNF)-alpha inhibitors.

Recently, the interleukin-17 (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.

Bimekizumab (UCB4940) is an engineered, humanized full-length monoclonal antibody of immunoglobulin (Ig) G1 subclass of approximately 150,000 Dalton, which is expressed in a genetically engineered Chinese Hamster Ovarian cell line. Bimekizumab has a high affinity for human IL-17A and IL-17F and selectively and potently inhibits the activity of both isoforms in vitro.

Interleukin-17A and IL-17F are key pro-inflammatory 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, PSO, and axSpA.

2.1.1 Clinical studies

2.1.1.1 Completed studies

Seventeen clinical studies of bimekizumab have been completed: RA0124 in 30 healthy volunteers, UP0031 in 12 healthy volunteers, UP0033 in 189 healthy volunteers, UP0034 in 56 healthy volunteers, UP0042 in 48 healthy Japanese or Caucasian volunteers, UP0074 in 37 healthy volunteers, RA0123 in 159 subjects with moderate to severe RA, UP0008 in 39 subjects with mild-to-moderate plaque PSO, 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), PA0007 in 53 subjects with PsA, PA0008 in 206 subjects with PsA, UC0011 in 23 subjects with moderate to severe active ulcerative colitis, HS0001 in 90 subjects with moderate to severe hidradenitis suppurativa (HS), and AS0008 in 303 subjects with AS.

Information on the clinical data for bimekizumab from completed studies is available in the current version of the Investigator's Brochure (IB).

2.1.1.2 Ongoing studies

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

- Feeder studies AS0010 and AS0011:
  - 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.
  - AS0011 is a Phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active AS.
- 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.

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

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

2.1.2 Nonclinical studies

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

cecum and colon as compared to the control animals and low dose animals. Therefore, the gut-associated lymph node lesions observed in the first study are considered to be accidental and/or linked to exaggerated pharmacology and proliferation of *Balantidium coli* and are considered to be the result of a change in local mucosal immunity.

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

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this open-label study is to assess the long-term safety and tolerability of bimekizumab administered over a period of up to 204 weeks (~4 years).

3.2 Secondary objectives

The secondary objectives are:

- To assess the long-term efficacy of bimekizumab

3.3 Other objectives

The other objectives are:

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

4 STUDY VARIABLES

Changes from Baseline will be calculated relative to the Baseline of AS0008. Variables measured at the start of AS0009 will be referred to as AS0009 entry values.

4.1 Primary variables

4.1.1 Primary safety variables

The primary safety variables are the incidences of TEAEs and SAEs.

4.2 Secondary variables

4.2.1 Secondary safety variable

The secondary safety variable is the withdrawal due to TEAEs.

4.2.2 Secondary efficacy variables

The secondary efficacy variables are:

- ASAS40 response at Week 48
- ASAS20 response at Week 48
- Change from Baseline of AS0008 in BASDAI at Week 48

4.3 Other variables

4.3.1 Safety variables

Other safety variables are listed below.

- Change from Baseline and AS0009 entry value in clinical laboratory variables (hematology and biochemistry)
- Change from Baseline and AS0009 entry value in vital signs (pulse, temperature, and blood pressure) and body weight

4.3.2 Efficacy variables

Other efficacy variables are listed below and will be evaluated at scheduled visits in accordance with the schedules of assessments in Table 5–1 and Table 5–2.

- ASAS40 response
- ASAS20 response
- ASAS5/6 response
- ASAS partial remission
- Change from Baseline of AS0008 in Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP)
- Ankylosing Spondylitis Disease Activity Score Inactive Disease (ASDAS-ID)
- Change from Baseline of AS0008 in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Change from Baseline of AS0008 in Bath Ankylosing Spondylitis Functional Index (BASFI)
- Change from Baseline of AS0008 in Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Change from Baseline of AS0008 in the MASES Index
- Change from Baseline of AS0008 in Patient's Global Assessment of Disease Activity (PGADA)
- Change from Baseline of AS0008 in total and nocturnal spinal pain
- Change from Baseline of AS0008 in Short Form 36-item Health Survey (SF-36)
- Change from Baseline of AS0008 in Ankylosing Spondylitis Quality of Life (ASQoL)

- Change from Baseline of AS0008 in the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and Hospital Anxiety and Depression Scale-Depression (HADS-D) scores
- Depression and anxiety status "normal" as defined by HADS-D and HADS-A <8

4.3.3 PK variable

The PK variable is the plasma concentration of bimekizumab evaluated at scheduled visits in accordance with the schedule of assessments in Table 5–1 and Table 5–2.

4.3.4 Immunological variable

The immunological variable is the anti-bimekizumab antibody detection evaluated at scheduled visits in accordance with the schedule of assessments in Table 5–1 and Table 5–2.

5 STUDY DESIGN

5.1 Study description

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

The OLE study will assess the safety, tolerability, and efficacy of bimekizumab for a period of up to 204 weeks (~4 years). Bimekizumab will be administered at a dose of 160mg Q4W upon entry into AS0009, regardless of the dose received in AS0008.

Additionally, as described in (Section 5.1.1), other treatments may be used in addition to bimekizumab per Investigator discretion. Subjects not responding to treatment may be withdrawn from the treatment and study at the discretion of the Investigator.

Following study completion or early termination, subjects will return for a SFU Visit 20 weeks after their last dose of bimekizumab.

Schedules of study assessments are presented in Table 5–1 and Table 5–2.

A study schematic diagram of AS0009 is presented in Figure 5–1.

5.1.1 Rescue therapy

In this OLE study, some subjects may require additional treatment in addition to medications received during AS0008 to control their AS symptoms. The decision to implement such therapy will be at the discretion of the Investigator. Therapies that are permitted for their disease within the context of the study are provided in Section 7.8.1 (Permitted concomitant treatments). Concomitant medication that is currently not considered safe or best medical practice should be avoided. See Section 7.8.2 for medications that are specifically prohibited.

5.1.2 Study duration per subject

The study duration for each subject is estimated to be up to a maximum of 224 weeks:

- Open-Label Treatment Period: up to 204 weeks (~4 years)
- SFU Visit: 20 weeks after the final dose of bimekizumab

The subject may remain in the study until the study ends after 224 weeks, until the Sponsor decides to close the study, or until bimekizumab development is stopped by the Sponsor, whichever comes first. The Sponsor may consider transitioning the subject into another bimekizumab study or program.

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

5.1.3 Planned number of subjects and sites

Up to 285 subjects (from the ongoing AS0008 Phase 2b study) could be enrolled into this study at sites specified in AS0008.

5.1.4 Anticipated regions and countries

The regions planned for study conduct are the same as in AS0008 (Europe and North America).

5.2 Schedule of study assessments

Schedules of study assessments for Week 1 to Week 104 and for Week 108 to Week 208 are provided in Table 5–1 and Table 5–2.

Table 5–1: Schedule of study assessments (Week 1 through Week 104)

Protocol activity	Treatment Period																	
Weeks[a]	**EV[b]**	**4**	**12**	**16**	**24**	**28**	**36**	**40**	**48**	**52**	**60**	**64**	**72**	**76**	**84**	**88**	**96**	**100**
		8		**20**		**32**		**44**		**56**		**68**		**80**		**92**		**104**
Visit[a]	**1**	**2/3**	**4**	**H[c]**	**5**	**H[c]**	**6**	**H[c]**	**7**	**H[c]**	**8**	**H[c]**	**9**	**H[c]**	**10**	**H[c]**	**11**	**H[c]**
Informed consent	X[d]																	
Inclusion/exclusion	X[e]																	
Concomitant medications	X[f]	X	X		X		X		X		X		X		X		X	
Adverse events	X[f]	X	X		X		X		X		X		X		X		X	
eC-SSRS	X[e,f]	X	X		X		X		X		X		X		X		X	
HADS	X[f]		X		X		X		X		X		X		X		X	
ASQoL	X[f]		X		X		X		X		X		X		X		X	
BASDAI	X[f]		X		X		X		X		X		X		X		X	
BASFI	X[f]		X		X		X		X		X		X		X		X	
SF-36	X[f]		X		X		X		X		X		X		X		X	
PGADA	X[f]		X		X		X		X		X		X		X		X	
Total and nocturnal spinal pain	X[f]		X		X		X		X		X		X		X		X	
TB questionnaire	X[f]		X		X		X		X		X		X		X		X	
Vital signs (pulse, temperature, BP)[g]	X[e,f]	X	X		X		X		X		X		X		X		X	
Body weight	X[f]		X		X		X		X		X		X		X		X	
Physical examination[h]	X[f]								X								X	
MASES	X[f]		X		X		X		X				X				X	
BASMI	X[f]								X								X	
ECG	X[f]								X								X	

Table 5–1: Schedule of study assessments (Week 1 through Week 104)

Protocol activity	Treatment Period																	
Weeks[a]	**EV[b]**	**4**	**12**	**16**	**24**	**28**	**36**	**40**	**48**	**52**	**60**	**64**	**72**	**76**	**84**	**88**	**96**	**100**
		8		**20**		**32**		**44**		**56**		**68**		**80**		**92**		**104**
Visit[a]	**1**	**2/3**	**4**	**H[c]**	**5**	**H[c]**	**6**	**H[c]**	**7**	**H[c]**	**8**	**H[c]**	**9**	**H[c]**	**10**	**H[c]**	**11**	**H[c]**
Hematology/biochemistry/urine pregnancy[i, j]	X[f]		X		X		X		X		X		X		X		X	
Blood Sample for CRP[j]	X[f]		X		X		X		X		X		X		X		X	
Blood sample for bimekizumab plasma concentrations[j]	X[f]		X		X		X		X				X				X	
Blood sample for anti-bimekizumab antibodies[j]	X[f]		X		X		X		X				X				X	
IGRA TB test[k]	X								X								X	
IXRS	X	X	X		X		X		X		X		X		X		X	X
Bimekizumab administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

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

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

[b] **AS0009 entry will occur at the end of the lead-studies. At Week 48 of AS0008, all subjects continuing into AS0009 will undergo the final AS0008 study assessments and any nonoverlapping AS0009 entry assessments, and will then receive their first open label dose of bimekizumab.**

[c] From the Entry Visit onwards, self-administration training will be provided to the subject/caregivers/appropriate designee by the study nurse. At Week 8 and Week 12, the subject/caregiver/appropriate designee will perform administrations under the supervision of the site staff to ensure that study medication is being properly and safely injected.

[d] Ensure that a separate Informed Consent form was completed by the subject for AS0009 prior to study entry.

[e] To be performed prior to the first dose of open-label bimekizumab.

Table 5–1: Schedule of study assessments (Week 1 through Week 104)

Protocol activity	Treatment Period																	
Weeks[a]	EV[b]	4	12	16	24	28	36	40	48	52	60	64	72	76	84	88	96	100
		8		20		32		44		56		68		80		92		104
Visit[a]	1	2/3	4	H[c]	5	H[c]	6	H[c]	7	H[c]	8	H[c]	9	H[c]	10	H[c]	11	H[c]

[f] Assessment will be performed at Week 48 of the lead-in study AS0008 and will be used as the AS0009 entry value.
[g] At AS0009 study entry, collect pulse and BP prior to drug administration and then at 30 minutes and 1 hour after dosing. At all other visits collect pulse and BP prior to drug administration and once after dosing (any time). All other procedures will only be done prior to dosing.
[h] Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.
[i] If there has been a delay in menses, perform a urine pregnancy test.
[j] All blood samples are to be taken prior to dosing.
[k] It is recommended that the QuantiFERON TB Test be performed. This assessment will be performed at study entry, unless an IGRA negative result is available less than 6 weeks prior to the first dose of open-label bimekizumab.

Table 5–2: Schedule of study assessments (Week 108 through Week 208)

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

Table 5–2: Schedule of study assessments (Week 108 through Week 208)

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

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

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

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

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

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

Table 5–2: Schedule of study assessments (Week 108 through Week 208)

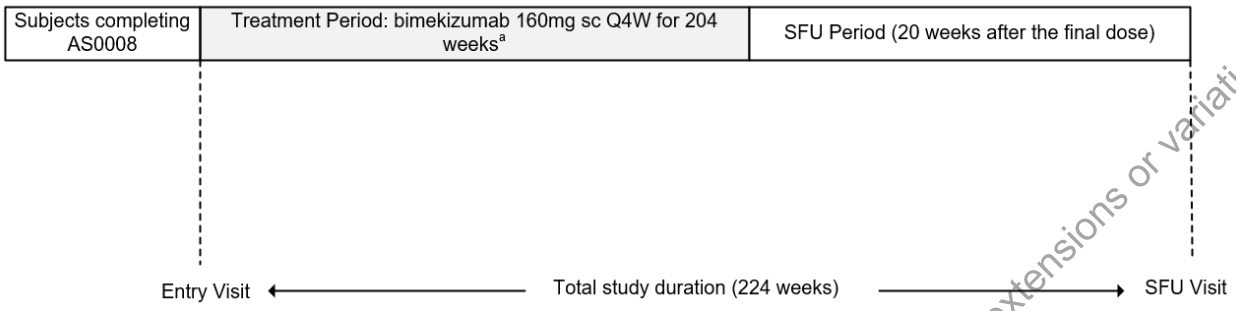
Protocol activity	Treatment Period																		
Weeks[a]	108	112	120	124	132	136	144	148	156	160	168	172	180	184	192	196	204	208/ET	SFU
		116		128		140		152		164		176		188		200			
Visit[a]	12	H[b]	13	H[b]	14	H[b]	15	H[b]	16	H[b]	17	H[b]	18	H[b]	19	H[b]	20	21	

[e] If there has been a delay in menses, perform a urine pregnancy test.
[f] All blood samples are to be taken prior to dosing.
[g] It is recommended that the QuantiFERON TB Test be performed. This assessment will be performed at study entry, unless an IGRA negative result is available less than 6 weeks prior to the first dose of open-label bimekizumab.

5.3 Schematic diagram

A study schematic diagram of AS0009 is provided in Figure 5–1.

Figure 5–1: Schematic diagram



IMP=investigational medicinal product; Q4W=every 4 weeks; sc=subcutaneous; SFU=Safety Follow-up
Note: Self-administration will be allowed after 3 months of treatment (from Week 16 onwards) as described in Table 5–1.
Note: Additionally, as described in Section 5.1.1 and Section 7.8.1; other treatments may be used in addition to bimekizumab per Investigator discretion. Subjects not responding to treatment may be withdrawn from the study at the discretion of the Investigator.
[a] Subjects will receive their final dose of IMP on Week 204 and the SFU Visit will be conducted 20 weeks after the last dose of IMP.

5.4 Rationale for study design and selection of dose

A dose of 160 mg Q4W was selected based on the current understanding of PK/PD of bimekizumab in PsA (data from PA0007) and a literature meta-analysis of biologics in AS. Based on this analysis, a dose of 160mg Q4W is expected to provide maximum response in most of the subjects. Based on the modeling outcome, UCB expects that the ASAS40 response would maximize at a dose of 160mg Q4W, and hence, this dose was selected for AS0009 (Diderichsen, 2016).

A bimekizumab dose of 160mg Q4W is currently being used in ongoing Phase 2b clinical studies.

Doses greater than 160mg have been previously studied in the development of bimekizumab. In the single ascending dose study UP0008, a single dose of bimekizumab 640mg was tested. In the multiple dose study PA0007, a bimekizumab 560mg loading dose followed by 2 subsequent 320mg doses every 3 weeks was tested. At exposure levels achieved at these doses, the compound had no significant safety concerns. In the previous clinical studies, bimekizumab was administered iv and in the current study bimekizumab will be administered sc (bioavailability of bimekizumab is 64%). Due to lower bioavailability, bimekizumab exposure is expected to be

lower with sc administration compared with after iv administration, therefore, the dose regimens are expected to be [redacted]

As more data for bimekizumab become available in this indication, doses and dosing regimen may be modified accordingly.

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 (ICF) 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 questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.

3. In the opinion of the Investigator, the subject is expected to benefit from participation in an OLE study.

4. Subject completed AS0008 without meeting any withdrawal criteria.

5. **Female** subjects must be postmenopausal, 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 until 20 weeks after last administration of IMP, and have a negative pregnancy test at the last visit of AS0008. The following methods are considered highly effective when used consistently and correctly:

   – combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)

   – progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)

   – intrauterine device (IUD)

   – intrauterine hormone-releasing system (IUS)

   – bilateral tubal occlusion

   – vasectomized partner

   – sexual abstinence if it is in accordance with a subject's preferred and common lifestyle. Subjects who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse until 20 weeks after the last dose of IMP. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.

   Male subjects with a partner of childbearing potential must be willing to use a condom when sexually active, up until 20 weeks after the last administration of IMP (anticipated 5 half-lives).

6.2 Exclusion criteria

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

1. Female subjects who plan to become pregnant during the study or within 20 weeks following the last dose of IMP. Male subjects who are planning a partner pregnancy during the study or within 20 weeks following the last dose.
2. Subjects with any current sign or symptom that may indicate a medically significant active infection (except for the common cold) or has had an infection requiring systemic antibiotics within 2 weeks of study entry. The medical monitor must be consulted prior to subject's entry into AS0009 in such cases.
3. Subjects who meet any withdrawal criteria in AS0008. For any subject with an ongoing SAE, or a history of serious infections (including hospitalizations) in the lead-in study, the Medical Monitor must be consulted prior to the subject's entry into AS0009.

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 and will be asked to complete the Early Termination Visit and SFU Visit (20 weeks after the last received dose) if any of the following events occur:

1. Subject withdraws his/her consent.
2. There is confirmation of a pregnancy in a female subject during the study, as evidenced by a positive pregnancy test.
3. The Sponsor or a regulatory agency requests withdrawal of the subject.
4. Subject develops an illness that in the opinion of the Investigator would interfere with his/her continued participation, if the risk of continuing participation outweighs the potential benefit.
5. Subject develops erythrodermic, guttate, or generalized pustular form of PSO.
6. Subject considered to have either a suspected new latent tuberculosis (LTB) infection or who develops active tuberculosis (TB) or nontuberculosis mycobacteria (NTMB) infection during the study (including but not limited to, conversion demonstrated by Interferon Gamma Release Assay (IGRA) or other diagnostic means) must be immediately discontinued from IMP and an unscheduled visit must be conducted as soon as possible, but not later than the next regular visit.

   The subject must be permanently withdrawn if further examinations result in a diagnosis of active TB, or if the subject is diagnosed with LTB infection 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 on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.

7. Subject is noncompliant with the study procedures or medications which may present a risk to the safety of the subject in the opinion of the Investigator.
8. Subject uses prohibited concomitant medications as defined in Section 7.8 that may present a risk to the safety of the subject in the opinion of the Investigator and/or the Medical Monitor.
9. Subject develops laboratory abnormalities (with or without clinical symptoms) of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) as defined in Section 6.3.1; neutrophils $<0.5x10^9$/L (neutropenia); lymphocytes $<0.5x10^9$/L (lymphopenia). Any laboratory value or change judged to be clinically significant by the Investigator should prompt consideration of whether the subject should continue on IMP. For clarification, laboratory values that are markedly abnormal as per Table 17-1 and Table 17–2 will be flagged to the Investigator and to the medical monitor but do not trigger mandatory withdrawal unless listed above. (Refer to Section 6.3.1 for withdrawal criteria in relation to potential drug-induced liver injury [PDILI].)
10. Subject has active suicidal ideation as indicated by a positive response ("Yes") to questions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated electronic Columbia-Suicide Severity Rating Scale (eC-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
11. Subjects with a HADS-D score ≥15 must be withdrawn. Any subject who has a HADS-D score of >10 should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.
12. Subjects with newly diagnosed IBD or with IBD flares during the study must:
    - Be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist
    - Discontinue IMP and be followed-up until resolution of active IBD symptoms

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

All subjects who withdraw from the study due to an AE must be followed until resolution of the event or until the event is considered stable. All subjects who withdraw from the study due to development of a laboratory abnormality must be closely monitored.

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

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

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with 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:

Subjects with either of the following:

- ALT or AST ≥5x upper limit of normal (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%).

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

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

  Evaluation of PDILI must be initiated as described in Section 9.4.1.

If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

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

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product

Bimekizumab will be supplied by UCB Clinical Trial Supply Operations or designee.

The IMP will consist of the following:

Bimekizumab will be supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative−free solution in a 1mL prefilled syringe (PFS). [redacted]

Further details of the IMP and specifications are provided in the Investigational Medicinal Product Handling Manual.

7.2 Treatment(s) to be administered

All subjects will receive bimekizumab 160mg Q4W sc (Section 5.1).

The IMP is to be administered in the clinic by study site staff as 1 sc injection for the 160mg dose. Suitable areas for sc injections are the lateral abdominal wall and upper outer thigh and upper arm if the IMP is injected by a healthcare provider or a caregiver. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard.

The IMP (bimekizumab) will be administered at the visits indicated in the schedules of assessments in Table 5–1 and Table 5–2. The minimum time between doses should be no less than 21 days and no more than 35 days for Q4W dosing.

Administration will occur at the study site for the first 3 months of AS0009.

Thereafter and in between the quarterly study visits at the site, the subjects will have the option to perform self-administration at home. From the Entry Visit onwards, self-administration training will be provided to the subject/and or caregivers/appropriate designee by the study nurse. At Week 8 and Week 12, the subject/caregiver/appropriate designee will perform administration under the supervision of the site staff to ensure that study medication is being properly and safely injected.

Once subjects/caregivers/appropriate designees as determined by the Investigator (or designee) have been trained, the study medication may be administered at home. The subject will receive the required number of injections at each visit needed to perform the monthly administrations at home. Subjects who are unable to or decide not to self‑administer or those without a family member/friend/caregiver (or appropriate designee) who can help will not be discontinued, but may continue to visit the site for study treatment administration only. If administered at home, the subject/caregiver (or appropriate designee) will document the date, body location, and time point of administration of study medication.

All used PFS will be disposed of by subjects/caregivers/appropriate designee as determined by the Investigator in an acceptable disposal (sharps) container directly after the administration. The subjects/caregivers return the documentation together with any used/unused containers at the next scheduled clinic visit.

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

7.3 Packaging

Bimekizumab will be packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. It will be suitably packaged in such a way as to protect the product from deterioration during transport and storage. Further information regarding storage and transport conditions are provided in the IMP Handling Manual.

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 GMP and will include any locally required statements. If necessary, labels will be translated into the local language.

7.5 Handling and storage requirements

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

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

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

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

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

In addition, the Investigator (or designee) will instruct the subject how to handle the IMP during the transport and how to store the IMP following the instruction guide. Cooler bags with freezer packs will be provided to the subjects. Specific attention will be put on the transport from site to home using cold bags, the subject will be instructed to put the IMP as quickly as possible into his/her refrigerator. In case of broken refrigerator, broken or lost syringes, the subject will inform the site immediately and new IMP will be prepared. All efforts should be made to follow the treatment scheme as per protocol.

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 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 Standard Operating Procedures (SOPs) or returned to UCB (or designee). Onsite destruction of used kits only may be allowed with prior approval from the Sponsor or designee after reconciliation. The subjects/caregivers (or appropriate designee) return the documentation together with any used/unused containers at the next scheduled clinic visit. 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 Treatment Period of this study, IMP will be administered in the clinic during the first 3 months of treatment (Visit 1 [Entry Visit] through Visit 4 [W12]) and compliance will be determined at the visit by study personnel. Thereafter, self-administration at home will be possible at the following weeks: Weeks 16, 20, 28, 32, 40, 44, 52, 56, 64, 68, 76, 80, 88, 92, 100, 104, 112, 116, 124, 128, 136, 140, 148, 152, 160, 164, 172, 176, 184, 188, 196, and 200. Dates and time of self-administration will be captured using a subject diary. All used PFS will be disposed of by subjects/caregivers/appropriate designee as determined by the Investigator in an acceptable disposal (sharps) container directly after the administration.

Drug accountability must be recorded on the Drug Accountability Form. If a subject is noncompliant with the study procedures or medications that may present a risk to the safety of the subject in the opinion of the Investigator, then the subject should be withdrawn as described in Section 6.3.

7.8 Concomitant medications/treatments

All concomitant medications, including over the counter products, herbal, traditional remedies, vitamin/mineral supplements, other dietary supplements, "nutraceuticals," and hormones must be recorded in the subject's source documentation (eg, clinical chart) and 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.

The Investigator should examine the acceptability of all concomitant procedures, medications, topical preparations, and dietary supplements not explicitly prohibited in this study, and if necessary, discuss with the Medical Monitor.

In order to ensure that appropriate concomitant therapy is administered, subjects will be instructed to consult with the Investigator prior to taking any medication (either self-administered nonprescription drugs or prescription therapy prescribed by another physician).

7.8.1 Permitted concomitant treatments (medications and therapies)

Medication changes are permitted at any time after enrollment into this OLE study. Medication changes and additions are permitted with the following guidelines:

- Nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs (MTX, SSZ, leflunomide [LEF], and/or joint injections may be given if deemed appropriate by the Investigator as outlined below. Subjects may receive these add-on therapies while continuing to receive bimekizumab. Under no circumstances should subjects have a concomitant biologic agent while receiving bimekizumab.
  - For subjects taking NSAIDs/cyclooxygenase 2 (COX-2) inhibitors, a change can be made to a different NSAID/COX-2. Changes from an NSAID to a COX-2 inhibitor or from a COX-2 inhibitor to an NSAID are permitted up to the maximum approved or tolerated dose, whichever is less. Only 1 NSAID/COX-2 inhibitor may be taken at a given time.
  - For subjects not taking NSAID/COX-2 inhibitors, either 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.
  - Methotrexate in oral or sc administration may be added or increased to a maximum dose of 25mg/week, or to the maximum tolerated dose, whichever is lower, for peripheral arthritis symptoms. The route of administration may be changed from oral to sc or from sc to oral. It is strongly recommended that subjects taking MTX should also take folic acid supplementation.
  - Sulfasalazine may be added or increased up to a maximum dose of 3g/day, or the maximum tolerated dose, whichever is lower, for peripheral arthritis symptoms.
  - Leflunomide may be started or increased to a maximum dose of 20mg/day (or an average of 20mg/day if not dosed daily), or the maximum tolerated dose, whichever is lower, for peripheral arthritis symptoms. Leflunomide (LEF) should not be used concomitantly with MTX.
  - Hydroxychloroquine may be started or increased to a maximum of 400mg/day.
  - Combination DMARDs (optimally 2) are allowed except that LEF and MTX may not be given together.
  - No other oral DMARDs are permitted during this OLE study.
- Steroid tapers for disease activity or disease-related reasons are allowed with an average daily dose of 20mg prednisone or prednisone equivalent per day for a maximum of 14 days.
- Up to 1 injection per joint for up to 3 discrete joints is permitted per 12-month period with the exception of the sacroiliac joints, which may each be injected up to twice per year. Injected joints are censored for the joint examination.
- Intra-articular hyaluronic acid injections are permitted into joints for which they are approved as per local labels.
- Intra-bursal corticosteroid injections are also permitted at the discretion of the Investigator.

- A decrease in dose or dosing frequency of any agent (except bimekizumab) is permitted at any time.
- Subjects with persistent active disease in spite of added concomitant therapy/therapies mentioned above may be withdrawn from the study at the discretion of the Investigator.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Medications listed in Table 7–1 are prohibited or restricted as follows:

Table 7–1: Prohibited or restricted medications

Drug class	Dose	Comments
Analgesics, including opioid analgesics (acetaminophen/paracetamol, etc)	Any dose	Any ad hoc use in the 24 hours prior to any study visit is prohibited. Stable doses of analgesics (including opioids) permitted.
TNF inhibitors -infliximab -adalimumab -etanercept -golimumab -certolizumab pegol	Any dose	This applies to biosimilar versions of any TNF inhibitor.
Any non-TNF biologic medications	Any dose	Any exposure history is prohibited.
All other DMARDs	Any dose	Only permitted medications as per Section 7.8.1.

DMARD=disease-modifying antirheumatic drug; TNF=tumor necrosis factor

Subjects who take prohibited medications may be withdrawn from study treatment but followed until the SFU Visit. The decision to withdraw a subject for taking prohibited medications should be made in consultation with the Medical Monitor.

Vaccines

Administration of live, attenuated vaccines is not allowed during the conduct of the study or for 20 weeks after the last dose of IMP. Administration of non-live, inactivated vaccines is allowed during the study at the discretion of the Investigator.

Live vaccinations include, but are not limited to, the following: anthrax vaccine, intranasal influenza vaccine, measles-mumps-rubella vaccine, polio live oral vaccine, smallpox vaccine, TB Bacillus Calmette-Guérin vaccine, typhoid live oral vaccine, varicella vaccine, and yellow fever vaccine.

7.9 Blinding

This is an open-label study. All subjects' treatment assignments during the lead-in study AS0008 will remain blinded until final database lock of AS0008.

7.10 Randomization and numbering of subjects

This is an OLE study and no randomization will be performed. All subjects will receive bimekizumab 160mg Q4W sc (see Section 5.1 for further details).

Subjects will continue with the 5-digit subject numbers assigned by the interactive web or voice response system (IXRS) in the preceding study.

8 STUDY PROCEDURES BY VISIT

The schedules of study assessments (Table 5–1 and Table 5–2) provide a general overview of study assessments. A list of procedures to be completed at each visit is provided in the sections that follow.

- Visit windows of ±7 days on either side of the scheduled dosing are permitted for all visits other than the SFU Visit (see below); however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±7 days is relative to the first dose (AS0009 entry) and applicable for all subsequent visits. Changes to the dosing schedule outside of the 14-day window must be discussed with the Medical Monitor.
- The minimum time between doses should be no less than 21 days and no more than 35 days for Q4W dosing.
- For the SFU Visit (20 weeks after the last dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

The Investigator should make efforts to maintain the original visit schedule. Changes to the dosing schedule outside of the allowed windows must be discussed with the Medical Monitor and may result in subject withdrawal.

8.1 AS0009 study entry (Visit 1)

The AS0009 entry assessments noted with an asterisk **"*"** will be obtained at the Week 48 Visit of AS0008 and do not need to be recorded on the eCRF for this study.

The following procedures or assessments will be performed prior to administration of IMP, unless otherwise noted:

- Ensure that a separate ICF was completed by the subject for AS0009 (must be done prior to any AS0009 study procedures)
- Assessment of inclusion/exclusion criteria
- Concomitant medications*
- Record AEs*
- eC-SSRS*
- HADS*
- ASQoL*
- BASDAI*

- BASFI*
- SF-36*
- PGADA*
- Total and nocturnal spinal pain*
- TB questionnaire*
- Measure vital signs (temperature and blood pressure [BP])*
- Body weight*
- Physical examination (includes evaluation of signs and symptoms of active TB and risk for exposure to TB).*
- MASES*
- Bath Ankylosing Spondylitis Metrology Index (BASMI)*
- Electrocardiogram (ECG)*
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)*
  - CRP*
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations*
- Perform a urine pregnancy test if there has been a delay in menses
- IGRA TB test (unless an IGRA negative result is available less than 6 weeks prior to the first dose of open-label bimekizumab)
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.2 Week 4 (Visit 2) and Week 8 (Visit 3)

All procedures or assessments will be performed prior to administration of IMP.

- Concomitant medications
- Record AEs
- eC-SSRS
- Measure vital signs (temperature, pulse, and BP) Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.3 Week 12 (Visit 4), Week 24 (Visit 5), Week 36 (Visit 6), Week 72 (Visit 9)

The following procedures or assessments will be performed prior to administration of IMP, unless otherwise noted:

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- MASES
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.4 Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, Week 92, Week 100, and Week 104

- Subjects will be given the opportunity for self-administration of bimekizumab. Adverse events will be captured spontaneously if the subject decides to visit the site to receive the bimekizumab administration.

8.5 Week 48 (Visit 7) and Week 96 (Visit 11)

The following procedures or assessments will be performed prior to administration of IMP, unless otherwise noted:

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Physical examination (includes evaluation of signs and symptoms of active TB and risk for exposure to TB)
- MASES
- BASMI
- ECG
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- IGRA TB test
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.6 Week 60 (Visit 8) and Week 84 (Visit 10)

The following procedures or assessments will be performed prior to administration of IMP, unless otherwise noted:

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
- Perform a urine pregnancy test if there has been a delay in menses
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.7 Week 108 (Visit 12), Week 132 (Visit 14), and Week 180 (Visit 18)

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- BASDAI
- BASFI
- PGADA
- Total and nocturnal spinal pain

- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
- Perform a urine pregnancy test if there has been a delay in menses
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.8 Week 112, Week 116, Week 124, Week 128, Week 136, Week 140, Week 148, Week 152, Week 160, Week 164, Week 172, Week 176, Week 184, Week 188, Week 196, and Week 200

- Subjects will be given the opportunity for self-administration of bimekizumab. Adverse events will be captured spontaneously if the subject decides to visit the site to receive the bimekizumab administration.

8.9 Week 120 (Visit 13) and Week 168 (Visit 17)

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- MASES

- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.10 Week 144 (Visit 15) and Week 192 (Visit 19)

- Concomitant medications
- Record AEs
- eC SSRS
- HADS
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- MASES
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- IGRA TB test
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.11 Week 156 (Visit 16)

The following procedures or assessments will be performed prior to administration of IMP, unless otherwise noted:

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- BASDAI
- BASFI
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Physical examination (includes evaluation of signs and symptoms of active TB and risk for exposure to TB)
- BASMI
- ECG
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
- Perform a urine pregnancy test if there has been a delay in menses
- Contact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.12 Week 204 (Visit 20)

The following procedures or assessments will be performed prior to administration of IMP, unless otherwise noted:

- Concomitant medications
- Record AEs
- eC-SSRS

- HADS
- BASDAI
- BASFI
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
- Perform a urine pregnancy test if there has been a delay in menses
- BASMIContact the IXRS
- Administer bimekizumab (after all other visit assessments are completed)

8.13 Week 208 (Visit 21)/Early Termination Visit

The following procedures or assessments will be performed:

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Physical examination (includes evaluation of signs and symptoms of active TB and risk for exposure to TB)

- MASES
- ECG
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- Contact the IXRS

8.14 SFU Visit

The following procedures or assessments will be performed:

- Concomitant medications
- Record AEs
- eC-SSRS
- ASQoL
- BASDAI
- BASFI
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Physical examination
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- IGRA TB test
- Contact the IXRS

8.15 Unscheduled Visit

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

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

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

- Record concomitant medication
- Record AEs
- eC-SSRS
- Measure vital signs (temperature, pulse, and BP)
- Physical examination
- Record 12-lead ECG
- If medically indicated, obtain blood sample(s) for standard safety laboratory tests (hematology, serum chemistry)
- Obtain urine sample for standard safety laboratory tests (including urine pregnancy test in women of childbearing potential).

9 ASSESSMENT OF SAFETY

9.1 Adverse events

9.1.1 Definition of AE

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 posttreatment periods required by the protocol, must be reported in the Case Report form (CRF) 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 study entry.

Adverse events that occurred during the AS0008 lead-in study and are still deemed ongoing at the time of enrolment (signed ICF) will be captured in the database and followed up, as described in Section 9.1.6.

9.1.2 AEs of special interest

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

Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (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.

9.1.3 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, depression, 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.

9.1.4 Procedures for reporting and recording AEs

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.

9.1.5 Description of AEs

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

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

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

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

9.1.6 Follow-up of AEs

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and other safety topics of interest; further details regarding follow-up of PDILI events are provided in Section 9.4.1.5. Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

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

9.1.7 Rule for repetition of an AE

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

9.1.8 Pregnancy

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

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

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

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

UCB's Drug Safety department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow-up.

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

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

9.1.9 Suspected transmission of an infectious agent via a medicinal product

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as an SAE; such cases must be reported immediately, recorded in the AE module of the 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.

9.1.10 Overdose of investigational medicinal product

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

9.1.11 Safety signal detection

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

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

As appropriate for the stage of development and accumulated experience with the IMP, medically qualified personnel at UCB may identify additional safety measures (eg, AEs, vital

signs, laboratory or ECG results) for which data will be periodically reviewed during the course of the study.

In addition, Cardiovascular and Neuropsychiatric Adjudication Committees will also periodically review and monitor the safety data from this study and advise UCB. Details are provided in the Adjudication Committee Charters. Serious AEs

9.1.12 Definition of SAEs

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 9.1.2], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

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

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

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

9.1.13 Procedures for reporting serious adverse events

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

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

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

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

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

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

9.1.14 Follow-up of SAEs

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and other safety topics of interest; further details regarding follow-up of PDILI events are provided in Section 9.4.1.5. Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

9.2 Immediate reporting of AEs

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the above definitions regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AEs of special interest as defined in Section 9.1.2

9.3 Anticipated SAEs

The following list of Anticipated SAEs (Table 9–1) has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol. Note that listed events will not be regarded as anticipated SAEs if they are life threatening or if they result in the death of the study subject.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.1.13.

Table 9–1: Anticipated SAEs 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.

9.4 Laboratory measurements

Clinical laboratory assessments consist of serum chemistry, and hematology (Table 9-2). A centralized laboratory will be used to supply all laboratory test supplies and analyze all blood samples for hematology, and biochemistry measurements. Any unscheduled laboratory testing should also be collected using the central laboratory.

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

Table 9-2: Laboratory measurements

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

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

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

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

9.4.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1 , with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 9.1.2), and, if applicable, also reported as an SAE (see Section 9.1.12).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 9-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 9.4.1.1). 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 9.4.1.5).

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

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

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

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

Table 9-3 summarizes the approach to investigate PDILI.

Table 9-3: 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 9.4.1.4); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[e]
≥3xULN	NA	Yes				
≥5xULN	NA	NA	Need for hepatology consult to be discussed. (required if ALT or AST ≥8xULN) Medical Monitor must be notified within 24hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate IMP discontinuation[d].		

Table 9-3: 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 (and ≥2x baseline) and <5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow-up requirements) [c]	Further investigation – immediate IMP discontinuation not required (see Section 9.4.1.2). 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 ≥3xULN (and ≥2xbaseline) after 2 weeks of monitoring without evidence of resolution	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48hours at the site with HCP (see Section 9.4.1.4).	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: • Discontinue IMP if levels remain ≥3xULN (and ≥2x baseline) without evidence of resolution[e] Continue to monitor until values normalize, stabilize, or return to within baseline values[e].

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 9.4.1.1. 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 9.4.1.2.

[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.

9.4.1.1 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 9.4.1.4) and SAE report (if applicable).

9.4.1.2 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 9-3 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.

9.4.1.3 IMP restart/rechallenge

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

9.4.1.4 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are included, but not limited to those listed in Table 9–4 (laboratory measurements) and Table 9–5 (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 9–4):

Table 9–4: 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 heterophil antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)
	Type 1 anti-liver kidney microsomal antibodies (qualitative and quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen [a]
Chemistry	Amylase
	ALT, AST
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR [b]
	Serum pregnancy test
	PK sample

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

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

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

The following additional PDILI information is to be collected (Table 9–5):

Table 9–5: 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

9.4.1.5 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 9-3. 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.

9.5 Other safety measurements

9.5.1 Vital signs

The Investigator or designee should measure all vital signs (systolic and diastolic blood pressure [BP], temperature [oral, axillary, or otic], pulse rate) after the subject has been sitting for at least 5 minutes, and the subject should remain seated during the measurements. Body temperature should be obtained prior to dosing with IMP at study visits when IMP is administered. At AS0009 study entry, collect pulse and BP prior to drug administration and then at 30 minutes and 1 hour after dosing. At all other visits collect pulse and BP prior to drug administration and once after dosing (any time).

9.5.2 Body weight

The Investigator or designee will measure the weight of the subject in kilograms at the time points listed in Table 5–1 and Table 5–2. The same scale should be utilized throughout the study where possible.

9.5.3 Physical examination

The physical examination should be conducted by the Investigator or designee at the time points listed in Table 5–1 and Table 5–2 and will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; gastrointestinal; musculoskeletal; hepatic; neurological (including limb reflexes); and mental status. Findings considered clinically significant changes since the physical examination at the Baseline of the lead-in study will be recorded as AEs.

9.5.4 12-lead ECG

The Investigator or designee will perform the ECG at the time points listed in Table 5–1 and Table 5–2. The ECGs will be read locally.

9.5.5 Tuberculosis and TB risk factor assessment and management

All subjects will be assessed for TB at prior to administration of IMP in AS0009 and at the time points specified in the Schedules of Assessments (Table 5–1 and Table 5–2) through physical examination for signs and symptoms of TB, laboratory testing (Section 9.5.5.1), and subject questionnaire (Section 9.5.5.2).

Prior to administration of IMP, subjects will have an IGRA test (QuantiFERON TB Test is recommended) and examination for signs and symptoms of TB unless an IGRA negative result is available less than 6 weeks prior to the first dose of open-label bimekizumab. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB.

Test Conversion

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

Latent TB

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

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

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

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

Active TB or NTMB infection

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

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

9.5.5.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB Test is recommended) will be performed at study entry (unless an IGRA negative result is available less than 6 weeks prior to the first dose of open-label bimekizumab) and should be repeated at Week 48, Week 96, Week 144, Week 192, and the SFU Visit for all subjects. The test results will be reported as positive, negative, or indeterminate. UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, subject must undergo appropriate study-specified withdrawal procedures.

9.5.5.2 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed at AS0009 entry, every 12 weeks throughout the study, at Week 208, and at the SFU Visit . The questionnaire will assist with the identification of subjects who may require therapy for TB. A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection.

Subjects with a confirmed latent TB (where no prophylactic treatment is initiated) or active TB infection must be withdrawn from the study (as further detailed in Section 9.5.5).

9.5.5.3 Tuberculosis management

LTB infection and active TB identified during study

During the study, subjects who develop evidence of LTB infection or active TB must immediately stop further administration of 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 or LTB infection should be withdrawn from the study and receive appropriate TB or prophylaxis therapy.

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

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

The subject should be transferred to the care of his/her physician and managed according to the best available standard of care. Subjects identified as having converted to active TB during the study must be withdrawn and scheduled to return for the ET Visit as soon as possible, but no later than the next scheduled study visit and complete all ET Visit assessments.

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

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

9.5.6 Pregnancy testing

A urine pregnancy test will be performed at any scheduled or unscheduled visit if there is suspicion of pregnancy and will be confirmed with a serum pregnancy test if the urine test is positive.

Pregnancy test results must be negative prior to administering IMP.

9.5.7 Assessment of suicidal ideation and behavior

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

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

10 ASSESSMENT OF EFFICACY

The timing for all assessments described below is specified in Table 5–1 and Table 5–2.

10.1 ASAS20, ASAS40, ASAS 5/6 response and ASAS partial remission

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

- PGADA (see Section 10.7)
- Pain assessment (the total spinal pain NRS score; Section 10.8)
- Function (represented by BASFI, Section 10.4)
- Inflammation (the mean of the BASDAI Questions 5 and 6, concerning [redacted])
- 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 partial remission response is defined as a score of ≤2 units on a 0 to 10 unit scale in all 4 domains listed above for ASAS20.

10.2 ASDAS-CRP

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 [redacted] (BASDAI Question 2 result, Section 10.3)
- 0.058 x [redacted] (BASDAI Question 6 result, Section 10.3)
- 0.110 x PGADA (Section 10.7)
- 0.073 x [redacted] (BASDAI Question 3 result, Section 10.3)
- 0.579 x (natural logarithm of the CRP [mg/L] + 1)

[redacted], PGADA, [redacted] 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 following definition applies for ASDAS Disease Activity categories:

- ASDAS-ID: ASDAS <1.3
- ASDAS-Moderate Disease: ASDAS ≥1.3, <2.1
- ASDAS-High Disease activity: ASDAS ≥2.1, ≤3.5
- ASDAS-very High Disease activity: ASDAS >3.5

10.3 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 [redacted] (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. Question 2 of the BASDAI asks the subject [redacted] factor in the calculation of ASDAS-CRP. Question 3 of the BASDI asks the subject to [redacted] factor in the calculation of ASDAS-CRP. Question 6 of the BASDAI asks the [redacted], and the score is used as the [redacted] factor in the calculation of ASDAS-CRP.

The BASDAI is calculated as follows:

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

10.3.1 [redacted] item of the BASDAI

[redacted] 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 [redacted] item of the BASDAI as for the total BASDAI score, ie, a change of 1 unit on the NRS.

10.4 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 and 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.

10.5 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.

10.6 MASES

Enthesitis is assessed via 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.

10.7 PGADA

Subjects will score their 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).

10.8 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). When responding to each question, the subject is to consider the average amount of pain in the preceding week.

10.9 Short-Form 36-item Health Survey

The SF-36 (Version 2, standard recall) is a 36-item generic health-related quality of life (HRQoL) instrument that uses a recall period of 4 weeks. Items are grouped into 8 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.

10.10 ASQoL

The ASQoL, a validated disease-specific 18-item questionnaire, has been developed specifically for measuring 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 higher score indicating worse HRQoL.

10.11 HADS

The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with chronic plaque PSO (Langley et al, 2010; Dauden et al, 2009). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal whereas a score of 15 and above is considered severe (Snaith and Zigmond, 1994).

11 ASSESSMENT OF IMMUNOGENICITY

The Investigator or designee will obtain blood samples for measurement of bimekizumab plasma concentrations and antibodies to bimekizumab at the time points specified in Table 5–1 and 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.

12 STUDY MANAGEMENT AND ADMINISTRATION

12.1 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.

12.2 Monitoring

UCB (or designee) will monitor the study to meet the sponsor's monitoring 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 eCRFs 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.

12.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. They should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of CRFs are not considered acceptable source documents.

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or quality of life questionnaires, for example. Source documents should be kept in a secure, limited access area.

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

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

12.2.2 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 CRF should be supported by source documents, unless otherwise specified in Section 12.2.1.

12.3 Data handling

12.3.1 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 SAE Report Form (see Section 9.1.13) while also entering the event in the appropriate eCRF section. The safety database and the clinical database will be reconciled during the study and discrepancies will be corrected as needed.

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

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

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

12.3.2 Database entry and reconciliation

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

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

12.3.3 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.

12.4 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.

12.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, 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.

12.6 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).

12.7 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.

13 STATISTICS

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

13.1 Definition of analysis sets

The Enrolled Set (ES) will consist of all subjects who have given informed consent for AS0009.

The Safety Set (SS) will consist of all subjects who receive at least 1 dose of the IMP in AS0009.

The Full Analysis Set (FAS) will consist of all enrolled subjects who receive at least 1 dose of the IMP and have a valid measurement for at least 1 efficacy variable at AS0009 study entry.

13.2 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, standard deviation (SD), median, minimum, and maximum unless stated otherwise.

Two subpopulations will be defined for this study. Subpopulation 1 will consist of all subjects who do not receive rescue therapy according to the criteria outlined in Section 5.1.1. Subpopulation 2 will consist of all subjects who receive rescue therapy according to the criteria outlined in Section 5.1.1. Analyses of the primary and secondary variables will also be done on both subpopulations.

Changes from Baseline will be calculated relative to the Baseline of studies AS0008. Variables measured at the start of AS0009 will be referred to as AS0009 entry values.

13.3 Planned safety analyses

13.3.1 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.

Adverse events will be summarized descriptively by treatment group at completion of the lead-in study, primary system organ class, high level term, and preferred term. This summary will include raw incidence rates, exposure adjusted incidence rate (EAIR) with associated 95% confidence interval, and the exposure adjusted event rate (EAER), where the EAIR and EAER are expressed per 100 patient-years of exposure.

Patient exposure at risk in days will be defined as date of last administration of bimekizumab - date of first administration of bimekizumab +20 weeks. If a subject has an adverse event with fatal outcome, patient exposure at risk is censored at the date of death.

The extent of exposure to IMP in AS0009 will be summarized using descriptive statistics by treatment group at AS0009 entry.

Change from AS0009 entry values in laboratory and vital signs variables will be summarized descriptively by visit and by treatment group at completion of the lead-in study.

The results of the eC-SSRS will be summarized by visit and by treatment group at completion of the lead-in study using number of subjects and percentages with events in: each of the eC-SSRS questions, suicidal behavior, suicidal ideation, suicidal behavior and ideation, and self-injurious behavior without suicidal intent.

All safety analyses will be conducted for both subpopulations.

13.4 Planned efficacy analyses

Secondary and other efficacy variables will be summarized for all subjects in the FAS; efficacy analyses will be performed over the 208 weeks (4 years).

Responder variables (eg, ASAS20 response) will be derived relative to Baseline of AS0008, and summarized descriptively. Percentages will be summarized descriptively by visit, by randomized treatment group, and by treatment group at completion of the lead-in study.

Change from Baseline of AS0008 of all continuous variables will be summarized descriptively by visit, by randomized treatment group, and by treatment group at completion of the lead-in study.

13.4.1 Subgroup analysis

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

- Region
- Previous TNF inhibitor exposure
- Concomitant NSAID status at AS0009 entry

13.5 Planned immunogenicity analyses

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

Bimekizumab plasma concentration and anti-bimekizumab antibody appearance will be summarized by visit, by randomized treatment group, and by treatment group at completion of the lead-in study. The first occurrence of anti-bimekizumab antibody positivity as well as persistent and transient anti-bimekizumab antibody positivity will be summarized by visit, by randomized treatment group, and by treatment group at completion of the lead-in study. Figures on persistent and transient anti-bimekizumab antibody positivity over time and on the relationship between ASAS40 response and anti-bimekizumab antibody positivity over time will be produced.

13.6 Other analyses

Other variables will be summarized using descriptive statistics using the treatment group at completion of lead-in study.

13.7 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 safety or efficacy 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

13.8 Handling of dropouts or missing data

Missing binary efficacy variables will be imputed using nonresponder imputation (NRI). In NRI, each subject with missing data or who has prematurely finished the study will be counted as a nonresponder.

For missing continuous efficacy variables, a multiple imputation (MI) approach will be used. 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.
Non-monotone missing data (ie, intermittent missing data) will be imputed several times with the Markov Chain Monte Carlo (MCMC) method and monotone missing data will be imputed using

a monotone regression model. Each set of imputed data will then be summarized and the summaries will be combined into a single inference (Carpenter and Kenward, 2013).

Safety data will not be imputed.

As a sensitivity analysis, all efficacy variables will be analyzed based on observed data. Subjects with missing data or who have prematurely finished the study will be treated as missing.

13.9 Planned interim analysis and data monitoring

An interim analysis and data cuts may be performed for regulatory and publication purposes.

13.10 Determination of sample size

There is no formal sample size for this study. The sample size is determined by the number of subjects in AS0008 who are eligible for AS0009. Up to 285 subjects from AS0008 could be enrolled into this study.

14 ETHICS AND REGULATORY REQUIREMENTS

14.1 Informed consent

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

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

Prior to participation in the study, the written ICF 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 ICF. 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 ICF 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 ICF 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 ICF. An eCRF must not be started, nor may any study specific procedure be performed for a given subject, without having obtained his/her written consent to participate in the study.

14.2 Subject identification cards

Upon signing the Informed Consent, 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.

14.3 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, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

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

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

14.4 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).

14.5 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.

15 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.

16 REFERENCES

Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an Interleukin-17A Inhibitor, in Ankylosing Spondylitis. N Engl J Med. 2015;373:2534-48.

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

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, UK: 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 (EMEA) Jul 2002.

Creemers MC, Franssen MJ, van't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis. 2005;64:127-9.

Dauden E, Griffiths CE, Ortonne JP, Kragballe K, Molta CT, Robertson D, et al. Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. J Eur Acad Dermatol Venereol. 2009;23(12):1374-82.

Diderichsen PM, Cox E (Quantitative Solutions BV, Breda, NL). Comparative effectiveness modeling of treatment in ankylosing spondylitis. Final Report. UCB Celltech; 2016 Feb. Project report No.: UCB-MBMA-AS-164.

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.

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, 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.

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.

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 [Internet]. Cornwall, UK: Menopause Terminology; C2015 [cited 2016 Jan 25]. Available from: http://www.imsociety.org/menopause_terminology.php.

Ivanov II, Frutos Rde L, Manel N, Yoshinaga K, Rifkin DB, Sartor RB, et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe. 2008;4:337–49.

Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, Hsu MC, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. J Am Acad Dermatol. 2010;63(3):457-65.

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(4):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.

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

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, Poddubnyy 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(2):418-29.

Poddubnyy D. Axial spondyloarthritis: is there a treatment of choice? Ther Adv Musculoskelet Dis. 2013(1);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.

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, van der Heijde D, Landewé 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. 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, 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.

Snaith RP, Zigmond AS. The hospital anxiety and depression scale, with the irritability-depression-anxiety scale and the Leeds situational anxiety scale manual. 1994.

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 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 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.

17 APPENDICES

17.1 Markedly abnormal laboratory values

Table 17-1 Definitions of markedly abnormal hematology values

Parameter (SI units)	Markedly Abnormal Definition	
	Low	High
Hemoglobin (g/dL)	<LLN AND >2.0 decrease from baseline	N/A
Hemoglobin (g/dL)	<8.0	N/A
Leukocytes (total x 1000)	<2.0	N/A
Lymphocytes (x 1000)	<0.5	N/A
Neutrophils (x 1000)	<1.0	N/A
Platelets (x 1000)	<50	N/A

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

Table 17–2: Definitions of markedly abnormal biochemistry values

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

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

17.2 Protocol Amendment 1

Rationale for the amendment

The purpose of this protocol amendment is the following:

- Clarify procedures and assessments during visits
- Revise language around self-administration of bimekizumab
- Revise language around description of vital signs
- Remove MRI substudy
- Remove serology tests
- Remove inclusion of Data Monitoring Committee
- Clarified language around vaccinations

Modifications and changes

Global Changes

Change #1

Removal of the MRI substudy from the protocol. As a result, all mention of MRIs in the entire document was removed to include the list of abbreviations. The following sections had MRI information deleted:

- Summary, 2nd to last paragraph, last sentence
- Section 3.3 Other objectives, bullet 5
- Section 4.3.2 Efficacy variables, bullet 14
- Section 5.1.2 Imaging evaluation
- Table 5-1 Schedule of study assessments (Week 1 through Week 104): MRI for subjects in the MRI substudy in AS0008 protocol activity row and footnote l
- Table 5-2 Schedule of study assessments (Week 108 through Week 208): MRI for subjects in the MRI substudy in AS0008 protocol activity row and footnote h
- Sections 8.1, 8.5, 8.11, 8.12: Obtain MRI of spine and the SI joint if the subject is participating in the MRI substudy
- Section 10.12 MRI Assessment (SPARCC and ASspiMRI)

The following global change was made for all visits in Section 8 that included a vital signs measurement:

Change #2

Vital signs (prior to drug administration, and 30 minutes and 1 hour after dosing)*

Has been changed to:

Measure vital signs (temperature, dose, and blood pressure [BP])*

Change #3

Vital signs (prior to drug administration and once after dosing)

Has been changed to:

Measure vital signs (temperature, dose, and BP)

Specific changes

Change #1

List of Abbreviations

The following abbreviations have been deleted:

- ASspiMRI-a Ankylosing Spondylitis spine Magnetic Resonance Imagine-activity• DMC Data Monitoring Committee
- MRI Magnetic Resonance Imaging

Change #2

Table 5-1: Schedule of study assessments

eC-SSRS was added to Weeks 4 and 8 schedule of assessments table.

Change #3

Table 5-1: Schedule of study assessments

Vital signs was added to Weeks 4 and 8 schedule of assessments table.

Change #4

Table 5-2: Schedule of study assessments

Removal of the IXRS from the schedule of assessments table for Week 196.

Change #5

Section 7.8.2: Prohibited concomitant treatments (medications and therapies); Vaccines

Administration of live, attenuated vaccines is not allowed during the conduct of the study or for 20 weeks after the last dose of IMP. Administration of non-live, attenuated vaccines is allowed during the study at the discretion of the Investigator.

Has been changed to:

Administration of live, attenuated vaccines is not allowed during the conduct of the study or for 20 weeks after the last dose of IMP. Administration of non-live, **inactivated** vaccines is allowed during the study at the discretion of the Investigator.

Change #6

Section 8.2: Week 4 (Visit 2) and Week 8 (Visit 3)

eC-SSRS was added to Weeks 4 and 8 procedures or assessments bulleted list.

Change #7

Section 8.2: Week 4 (Visit 2) and Week (Visit 3)

"Measure vital signs (temperature, pulse, and BP)" was added to Weeks 4 and 8 procedures or assessments bulleted list.

Change #8

Section 8.4: Week 16, Week 20, Week 28, Week 32, Week 40, Week 44, Week 52, Week 56, Week 64, Week 68, Week 76, Week 80, Week 88, Week 92, Week 100, and Week 104

Administer bimekizumab (after all other visit assessments are completed)

Has been changed to:

Subjects will be given the opportunity for self-administration of bimekizumab. Adverse events will be captured spontaneously if the subject decides to visit the site to receive the bimekizumab administration.

Change #9

Section 8.8: Week 112, Week 116, Week 124, Week 128, Week 136, Week 140, Week 148, Week 152, Week 160, Week 164, Week 172, Week 176, Week 184, Week 188, Week 196, and Week 200

Administer bimekizumab (after all other visit assessments are completed)

Has been changed to:

Subjects will be given the opportunity for self-administration of bimekizumab. Adverse events will be captured spontaneously if the subject decides to visit the site to receive the bimekizumab administration.

Change #10

Section 9.1.11: Safety signal detection, 4th paragraph

In addition, an independent Data Monitoring Committee (DMC) will periodically review and monitor the 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 the safety data from this study. Details are provided in the Adjudication Committee Charters.

Has been changed to:

In addition, **Cardiovascular and Neuropsychiatric Adjudication Committees** will **also** periodically review and monitor the safety data from this study and advise UCB. Details are provided in the **Adjudication Committee Charters.**

Change #11

Section 9.5: Laboratory measurement, 1st paragraph, last sentence

The following sentence has been deleted:

Testing to rule out hepatitis B, hepatitis C, and HIV will be performed at AS0009 entry in addition to those measurements listed in Table 9 2.

17.3 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment is as follows:

- To update the study contact details for the sponsor study physician, clinical project manager and clinical trial biostatistician.
- Amend the open-label treatment period for clarification, as per request from the regulatory agency.
- Amend the study procedures and assessments to be performed at the Safety Follow-up visit. Efficacy assessments were removed since they are not required at the SFU visit.
- Amend the time frame for the availability of negative results from the QuantiFERON TB Test, to be aligned with the TB Standard Operating Procedure.
- Include additional wording to the inclusion criteria (criterion #5) listing acceptable methods of contraception for female subjects.
- Amend the exclusion criteria (criterion #2) to include further clarification on when to consult the medical monitor.
- To revise the withdrawal criteria section to provide instructions for the management of subjects with newly diagnosed IBD or with IBD flares during the study.
- To revise and clarify the SAE criteria for pregnancy for consistency.
- Amend the table for identification/exclusion of alternative etiology to include ALT and AST.
- Amend and remove wording from the criteria determined for handling of dropouts or missing data.

Modifications and changes

Global change

The following global change was made for the duration of the open-label treatment period and period for administration of bimekizumab:

208 weeks (4 years)

Has been changed to:

204~~208~~ weeks (~4 years)

Specific changes

Change #1

List of Abbreviations

The following abbreviations have been added:

IUD	intrauterine device

IUS	intrauterine hormone-releasing system
MCMC	Markov Chain Monte Carlo
RCTC	Rheumatology Common Toxicity Criteria

Change #2

Sponsor Study Physician

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

Clinical Project Manager

Name:	[redacted], PhD
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Str.10 40789 Monheim am Rhein GERMANY
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted], Senior Biostatistician
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]

Has been changed to:

Sponsor Study Physician

Name:	**[redacted], MD, MSc, PhD** [redacted]~~, MD~~
Address:	**UCB Pharma Ltd.** ~~UCB BIOSCIENCES Inc.~~

	208 Bath Road ~~8010 Arco Corporate Drive~~ **Slough, SL1 3WE** ~~Raleigh, NC 27617~~ **UNITED KINGDOM** ~~UNITED STATES~~
Phone:	[redacted]

Clinical Project Manager

Name:	[redacted], ~~PhD~~
Address:	UCB BIOSCIENCES GmbH Alfred-Nobel-Str.10 40789 Monheim am Rhein GERMANY
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted], **MS**~~Senior Biostatistician~~
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]

Change #3

Section 5.1 Study design, 3rd paragraph

Additionally, as described in (Section 5.1.1), other treatments may be used in addition to bimekizumab per Investigator discretion. Subjects not responding to treatment may be withdrawn from the study at the discretion of the Investigator.

Has been changed to:

Additionally, as described in (Section 5.1.1), other treatments may be used in addition to bimekizumab per Investigator discretion. Subjects not responding to treatment may be withdrawn from the **treatment and** study at the discretion of the Investigator.

Change #4

Section 5.1.2 Study duration per subject

The study duration for each subject is estimated to be up to a maximum of 224 weeks:

- Open Label Treatment Period: up to 208 weeks (4 years)
- SFU Visit: 20 weeks after the final dose of bimekizumab

The subject may remain in the study until the study ends after 4 years (224 weeks of treatment), until the Sponsor decides to close the study, or until bimekizumab development is stopped by the Sponsor, whichever comes first. The Sponsor may consider transitioning the subject into another bimekizumab study or program.

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

Has been changed to:

The study duration for each subject is estimated to be up to a maximum of 224 weeks:

- Open-Label Treatment Period: up to **204**~~8~~ weeks (~4 years)
- SFU Visit: 20 weeks after the final dose of bimekizumab

The subject may remain in the study until the study ends after **224 weeks**~~4 years (208 weeks of treatment)~~, until the Sponsor decides to close the study, or until bimekizumab development is stopped by the Sponsor, whichever comes first. The Sponsor may consider transitioning the subject into another bimekizumab study or program.

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

Change #5

Section 5.2 Schedule of study assessments, Table 5-1

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

Has been changed to:

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

Change #6

Section 5.2 Schedule of study assessments (Week 1 through Week 104), Table 5-1 (Schedule of study assessments [Week 1 through Week 104]), Footnote 'k'

k It is recommended that the QuantiFERON TB GOLD test be performed. This assessment will be performed at study entry, unless an IGRA negative result is available less than 4 weeks prior to the first dose of open-label bimekizumab.

Has been changed to:

k It is recommended that the QuantiFERON TB ~~GOLD test~~ **Test** be performed. This assessment will be performed at study entry, unless an IGRA negative result is available less than **6**4 weeks prior to the first dose of open-label bimekizumab.

Change #7

Section 5.2 Schedule of study assessments (Week 1 through Week 104), Table 5-2 (Schedule of study assessments [Week 108 through Week 208]), Footnote 'g'

g It is recommended that the QuantiFERON TB GOLD test be performed. This assessment will be performed at study entry, unless an IGRA negative result is available less than **6**4 weeks prior to the first dose of open-label bimekizumab.

Has been changed to:

g It is recommended that the QuantiFERON TB ~~GOLD test~~ **Test** be performed. This assessment will be performed at study entry, unless an IGRA negative result is available less than **6**4 weeks prior to the first dose of open-label bimekizumab.

Change #8

Section 6.1 Inclusion criteria (criterion #5)

5. **Female** subjects must be postmenopausal (at least 1 year), 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 until 20 weeks after last administration of study medication, and have a negative pregnancy test at the last visit of AS0008.

   Male subjects with a partner of childbearing potential must be willing to use a condom when sexually active, up until 20 weeks after the last administration of study medication (anticipated 5 half-lives).

Has been changed to:

5. **Female** subjects must be postmenopausal (at least 1 year), 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 until 20 weeks after last administration of study medication, and have a negative pregnancy test at the last visit of AS0008. **The following methods are considered highly effective when used consistently and correctly:**

- **combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)**
- **progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)**
- **intrauterine device (IUD)**
- **intrauterine hormone-releasing system (IUS)**
- **bilateral tubal occlusion**
- **vasectomized partner**
- **sexual abstinence if it is in accordance with a subject's preferred and common lifestyle. Subjects who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse until 20 weeks after the last dose of IMP. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.**

Male subjects with a partner of childbearing potential must be willing to use a condom when sexually active, up until 20 weeks after the last administration of study medication (anticipated 5 half-lives).

Change #9

Section 6.2 Exclusion criteria (criterion #2)

2. Subjects with any current sign or symptom that may indicate a medically significant active infection (except for the common cold) or has had an infection requiring systemic antibiotics within 2 weeks of study entry.

Has been changed to:

2. Subjects with any current sign or symptom that may indicate a medically significant active infection (except for the common cold) or has had an infection requiring systemic antibiotics within 2 weeks of study entry. **The medical monitor must be consulted prior to subject's entry into AS0009 in such cases.**

Change #10

Section 6.3 Withdrawal criteria

The following was added to the withdrawal criteria:

12. Subjects with newly diagnosed IBD or with IBD flares during the study must:

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

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

Change #11

Section 8.1 AS0009 study entry (Visit 1), bullet #22

- IGRA TB test (unless an IGRA negative result is available less than 4 weeks prior to the first dose of open-label bimekizumab)

Has been changed to:

- IGRA TB test (unless an IGRA negative result is available less than **64** weeks prior to the first dose of open-label bimekizumab)

Change #12

Section 8.14 SFU Visit (Visit 23)

The following procedures or assessments will be performed:

- Concomitant medications
- Record AEs
- eC-SSRS
- HADS
- ASQoL
- BASDAI
- BASFI
- SF-36
- PGADA
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Physical examination

- MASES
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- IGRA TB test
- Contact the IXRS

Has been changed to:

The following procedures or assessments will be performed:

- Concomitant medications
- Record AEs
- eC-SSRS
- ~~HADS~~
- ASQoL
- BASDAI
- BASFI
- ~~SF-36~~
- ~~PGADA~~
- Total and nocturnal spinal pain
- TB questionnaire
- Measure vital signs (temperature, pulse, and BP)
- Body weight
- Physical examination
- ~~MASES~~
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - CRP
  - Anti-bimekizumab antibodies and bimekizumab plasma concentrations
- Perform a urine pregnancy test if there has been a delay in menses
- IGRA TB test

- Contact the IXRS

Change #13

Section 9.1 Definition of AE

The following was added to the definition of AEs:

Adverse events that occurred during the AS0009 lead-in study and are still deemed ongoing at the time of enrolment (signed ICF) will be captured in the database and followed up, as described in Section 9.16 .

Change #14

Section 9.1.8 Pregnancy, 5th paragraph

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective for a medical condition or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report Form.

Has been changed to:

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

Change #15

Section 9.4.1.4 Testing: identification/exclusion of alternative etiology, Table 9-4 (PDILI laboratory measurements)

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

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

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

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

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

Has been changed to:

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA
	Cytomegalovirus IgM antibody
	Epstein-Barr viral capsid antigen IgM antibody (if unavailable, obtain heterophile antibody or monospot testing)
Immunology	Anti-nuclear antibody (qualitative and quantitative)
	Anti-smooth muscle antibody (qualitative and quantitative)

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

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

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

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

Change #16

Section 9.5.5 Tuberculosis and TB risk factor assessment and management, 2nd paragraph

Prior to administration of IMP, subjects will have an IGRA test (QuantiFERON TB GOLD is recommended) and examination for signs and symptoms of TB unless an IGRA negative result is available less than 4 weeks prior to the first dose of open label bimekizumab. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB.

Has been changed to:

Prior to administration of IMP, subjects will have an IGRA test (QuantiFERON TB **Test**~~GOLD~~ is recommended) and examination for signs and symptoms of TB unless an IGRA negative result is available less than **64** weeks prior to the first dose of open label bimekizumab. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB.

Change #17

Section 9.5.5.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD is recommended) will be performed at study entry (unless an IGRA negative result is available less than 4 weeks prior to the first dose of open-label bimekizumab) and should be repeated at Week 48, Week 96, Week 144, Week 192, and the SFU Visit for all subjects. The test results will be reported as positive, negative, or indeterminate. UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, subject must undergo appropriate study-specified withdrawal procedures.

Has been changed to:

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB **Test**~~GOLD~~ is recommended) will be performed at study entry (unless an IGRA negative result is available less than **64** weeks prior to the first dose of open-label bimekizumab) and should be repeated at Week 48, Week 96, Week 144, Week 192, and the SFU Visit for all subjects. The test results will be reported as positive, negative, or indeterminate. UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, subject must undergo appropriate study-specified withdrawal procedures.

Change #18

Section 13.8 Handling of dropouts or missing data

Missing binary efficacy variables will be imputed using nonresponder imputation (NRI). In NRI, each subject with missing data or who has prematurely finished the study will be counted as a nonresponder.

For missing continuous efficacy variables, a multiple imputation (MI) approach will be used. 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. Non-monotone missing data (ie, intermittent missing data) will be imputed several times with the Markov Chain Monte Carlo (MCMC) method and monotone missing data will be imputed using a monotone regression model. Each set of imputed data will then be summarized and the summaries will be combined into a single inference (Carpenter and Kenward, 2013).

Imputation of efficacy data will be performed for only those assessments that the patient had in PA0008. Safety data will not be imputed.

As a sensitivity analysis, all efficacy variables will be analyzed based on observed data. Subjects with missing data or who have prematurely finished the study will be treated as missing.

Has been changed to:

Missing binary efficacy variables will be imputed using nonresponder imputation (NRI). In NRI, each subject with missing data or who has prematurely finished the study will be counted as a nonresponder.

For missing continuous efficacy variables, a multiple imputation (MI) approach will be used. 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. Non monotone missing data (ie, intermittent missing data) will be imputed several times with the Markov Chain Monte Carlo (MCMC) method and monotone missing data will be imputed using a monotone regression model. Each set of imputed data will then be summarized and the summaries will be combined into a single inference (Carpenter and Kenward, 2013).

~~Imputation of efficacy data will be performed for only those assessments that the patient had in PA0008.~~ Safety data will not be imputed.

As a sensitivity analysis, all efficacy variables will be analyzed based on observed data. Subjects with missing data or who have prematurely finished the study will be treated as missing.

Change #19

Section 17.1 Markedly abnormal laboratory values, Tables 17-1 (Definitions of markedly abnormal hematology values) and 17-2 (Definitions of markedly abnormal biochemistry values)

Amended units in both table headers:

	Markedly Abnormal Definition	
Parameter (SI units)	Low	High

Has been changed to:

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

Change #20

Section 17.1 Markedly abnormal laboratory values, Table 17-1 (Definitions of markedly abnormal hematology values), abbreviations in table footer:

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

Has been changed to:

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

Change #21

Section 17.1 Markedly abnormal laboratory values, Table 17-2 (Definitions of markedly abnormal biochemistry values), abbreviations in table footer:

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

Has been changed to:

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

17.4 Protocol Amendment 3

Rationale for the amendment

Key changes are summarized below. The purposes of the amendment are:

- 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".
- To clarify that changes from Baseline will be calculated only in relation to the Baseline of AS0008 for efficacy variables.
- To add ASAS partial remission as an "other efficacy variable".
- To clarify that interim analyses may be performed as needed.
- To clarify that protected adults will not be enrolled in the study.
- To update the Sponsor contact information.
- To confirm that treatment-emergent adverse events only are to be considered in primary and secondary safety variables.
- To harmonize language related to other safety topics of interest with other studies.
- To harmonize the description of bimekizumab with other studies.
- To update the clinical part of the introduction.

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

Modifications and changes

Global changes

No global changes have been made.

Specific changes

Change #1

Sponsor name on the title page and in study contact information

Sponsor name:

UCB Biopharma SPRL

Allée de la Recherche 60

1070 Brussels

BELGIUM

Has been changed to:

Sponsor name:

UCB Biopharma **SRL**

Allée de la Recherche 60

1070 Brussels

BELGIUM

Change #2

Study contact information

Sponsor Study Physician

Name:	[redacted], MD, MSc, PhD
Address:	UCB Pharma Ltd. 208 Bath Road Slough, SL1 3WE UNITED KINGDOM
Phone:	[redacted]

Clinical Project Manager

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

Clinical Trial Biostatistician

Name:	[redacted], MS
Address:	UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES
Phone:	[redacted]

Has been changed to:

Sponsor Study Physician

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

Clinical Project Manager

Name:	[redacted]
Address:	UCB Pharma Ltd. 208 Bath Road Slough SL1 3WE UNITED KINGDOM
Phone:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted] MSc
Address:	UCB Pharma Ltd. 208 Bath Road Slough SL1 3WE UNITED KINGDOM
Phone:	[redacted]

Change #3

Section 1 Summary, paragraphs 5 and 6

The primary objective is to assess the long-term safety and tolerability of bimekizumab administered over a period of up to 204 weeks (~4 years). The primary safety variables are the incidences of adverse events (AEs) and serious adverse events (SAEs).

The secondary objective is to assess the long-term efficacy. The secondary efficacy variables include the Assessment of SpondyloArthritis International Society 40% response criteria (ASAS40) at Week 48, ASAS20 response at Week 48, and the change from Baseline and

AS0009 entry value in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 48. The secondary safety variable is the withdrawal due to AEs.

Has been changed to:

The primary objective is to assess the long-term safety and tolerability of bimekizumab administered over a period of up to 204 weeks (~4 years). The primary safety variables are the incidences of **treatment-emergent** adverse events (**TE**AEs) and serious adverse events (SAEs).

The secondary objective is to assess the long-term efficacy. The secondary efficacy variables include the Assessment of SpondyloArthritis International Society 40% response criteria (ASAS40) at Week 48, ASAS20 response at Week 48, and the change from Baseline **of AS0008** ~~and AS0009 entry value~~ in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 48. The secondary safety variable is the withdrawal due to **TE**AEs.

Change #4

Section 2.1.1 Clinical studies

Four clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, UP0031 in 12 healthy volunteers, and PA0007 in 53 subjects with PsA.

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

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

An additional Phase 1 study, UP0031, evaluated the relative bioavailability and safety and tolerability of 2 bimekizumab formulations (a [redacted]-based formulation 2x80mg and an [redacted]-based formulation 1x160mg) administered by sc injection to healthy volunteers. Results show similar geometric means for AUC between the 2 bimekizumab formulations (2 x 80mg=653.8day*µg/mL; 1x160mg=628.3day*µg/mL) and the relative bioavailability for the bimekizumab 1x160mg versus 2x80mg formulations was calculated as 96.1% with a 95%

confidence interval (CI): 72.7,127.0. The wide 95% CI was expected due to the small sample size in UP0031.

Bimekizumab has also been investigated in a Phase 1b, proof of concept, randomized, placebo-controlled, multiple-dose study (PA0007). A total of 53 subjects have been randomized. The primary objective of PA0007 was to assess the safety and PK of multiple dose administration of iv bimekizumab in subjects with PsA. Four active doses and a placebo were tested. Drug was administered as a loading dose of bimekizumab 80mg, 160mg, 240mg, or 560mg at Week 1, and 2 additional doses of bimekizumab 40mg, 80mg, 160mg, or 320mg at Week 4 and Week 7. In each treatment group, subjects received a total of 3 doses of bimekizumab, administered every 3 weeks. There were no unexpected clinically relevant safety findings and all doses were well tolerated. The PK was linear across the tested dose range and no change in PK was observed following multiple doses. Observed changes in inflammatory biomarkers were consistent with expectations based on the IL-17A and IL-17F mechanism of action. The exploratory analysis showed clinically relevant improvement in activity of PsA and in skin involvement in those subjects with concomitant active psoriatic lesions. Data from the top 3 bimekizumab dose groups pooled showed that by Week 9, 80% [95% CI: 62.7, 90.5] of subjects achieved an American College of Rheumatology 20% response criteria response (vs 16.7% [95% confidence interval (CI): 4.7, 44.8] in the placebo group) and 100% [95% CI: 79.6, 100.0] of 26 subjects with active psoriatic lesions had achieved a Psoriasis Area and Severity Index 75% response (vs 0% [95% CI: 0.0, 43.4] in the placebo group).

Infections (mostly nasopharyngitis) were the most commonly reported events in both the active (36.8% of subjects) treatment and the placebo group (35.7% of subjects). None of the infections were considered serious or required treatment with antibiotics. Two subjects in the active treatment group experienced 1 local candida infection each (oropharyngitis and vulvovaginitis, respectively) that were nonserious and resolved with topical therapy. There was a reduction in mean neutrophil count in the active treatment group, although this drop was not clinically relevant and a clear relationship with dose or time was not evident. Interleukin-17 plays a significant role in regulating neutrophil recruitment and granulopoiesis and thus, receipt of an anti-IL-17 antibody may be associated with effects on neutrophil count. Previous clinical experience with administration of anti-IL-17 antibodies in humans indicates that this potential risk is low and reversible. Some increases in liver function tests were reported, but none had a convincing relationship to exposure to investigational medicinal product (IMP).

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

Several additional studies of bimekizumab are ongoing. RA0123 is a Phase 2a, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the safety, PK,

pharmacodynamics (PD), and efficacy of multiple doses of bimekizumab administered as add-on therapy to stable certolizumab pegol (CZP; Cimzia®) therapy in subjects with moderate to severe RA. UC0011 is a Phase 2 study, which will evaluate the efficacy, safety, tolerability, and PK of an iv loading dose and 2 sc maintenance doses of bimekizumab in subjects with moderate to severe active ulcerative colitis. PS0016 will evaluate the pharmacodynamic response, safety and PK and PS0010 will evaluate the pharmacodynamics, PK, safety, and efficacy of bimekizumab administered sc to subjects with PSO. PA0008 is a Phase 2, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the efficacy and safety of bimekizumab in subjects with active PsA

AS0008 is a multicenter, Phase 2b, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy and safety of bimekizumab in subjects with active AS. The current Phase 2b OLE study (AS0009) will allow access to bimekizumab for subjects who completed the lead-in study AS0008, while allowing the collection of further data on the long-term safety and efficacy of bimekizumab in this subject population.

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

Has been changed to:

Section 2.1.1 Clinical studies

Section 2.1.1.1 Completed studies

Seventeen clinical studies of bimekizumab have been completed: RA0124 in 30 healthy volunteers, UP0031 in 12 healthy volunteers, UP0033 in 189 healthy volunteers, UP0034 in 56 healthy volunteers, UP0042 in 48 healthy Japanese or Caucasian volunteers, UP0074 in 37 healthy volunteers, RA0123 in 159 subjects with moderate to severe RA, UP0008 in 39 subjects with mild-to-moderate plaque PSO, 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), PA0007 in 53 subjects with PsA, PA0008 in 206 subjects with PsA, UC0011 in 23 subjects with moderate to severe active ulcerative colitis, HS0001 in 90 subjects with moderate to severe hidradenitis suppurativa (HS), and AS0008 in 303 subjects with AS.

Information on the clinical data for bimekizumab from completed studies is available in the current version of the Investigator's Brochure (IB).

Section 2.1.1.2 Ongoing studies

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

- Feeder studies AS0010 and AS0011:
  - 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.
  - AS0011 is a Phase 3, double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active AS.

- 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.

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

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

Change #5

Section 4.1.1 Primary safety variables

The primary safety variables are the incidences of AEs and SAEs.

Has been changed to:

The primary safety variables are the incidences of **TE**AEs and SAEs.

Change #6

Section 4.2.1 Secondary safety variables

The secondary safety variable is the withdrawal due to AEs.

Has been changed to:

The secondary safety variable is the withdrawal due to **TE**AEs.

Change #7

Section 4.2.2 Secondary efficacy variables

The secondary efficacy variables are:

- ASAS40 response at Week 48
- ASAS20 response at Week 48
- Change from Baseline and AS0009 entry value in BASDAI at Week 48

Have been changed to:

The secondary efficacy variables are:

- ASAS40 response at Week 48
- ASAS20 response at Week 48
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in BASDAI at Week 48

Change #8

Section 4.3.2 Efficacy variables

Other efficacy variables are listed below and will be evaluated at scheduled visits in accordance with the schedules of assessments in Table 5–1 and Table 5–2.

- ASAS40 response
- ASAS20 response
- ASAS5/6 response
- Change from Baseline and AS0009 entry value in Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP)
- Ankylosing Spondylitis Disease Activity Score Inactive Disease (ASDAS-ID)
- Change from Baseline and AS0009 entry value in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Change from Baseline and AS0009 entry value in Bath Ankylosing Spondylitis Functional Index (BASFI)
- Change from Baseline and AS0009 entry value in Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Change from Baseline and AS0009 entry value in the MASES Index
- Change from Baseline and AS0009 entry value in Patient's Global Assessment of Disease Activity (PGADA)
- Change from Baseline and AS0009 entry value in total and nocturnal spinal pain
- Change from Baseline and AS0009 entry value in Short Form 36-item Health Survey (SF-36)
- Change from Baseline and AS0009 entry value in Ankylosing Spondylitis Quality of Life (ASQoL)
- Change from Baseline and AS0009 entry value in the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and Hospital Anxiety and Depression Scale-Depression (HADS-D) scores
- Depression and anxiety status “normal” as defined by HADS-D and HADS-A <8

Have been changed to:

Other efficacy variables are listed below and will be evaluated at scheduled visits in accordance with the schedules of assessments in Table 5–1 and Table 5–2.

- ASAS40 response
- ASAS20 response
- ASAS5/6 response

- **ASAS partial remission**
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in Ankylosing Spondylitis Disease Activity Score-C-reactive protein (ASDAS-CRP)
- Ankylosing Spondylitis Disease Activity Score Inactive Disease (ASDAS-ID)
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in Bath Ankylosing Spondylitis Functional Index (BASFI)
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in Bath Ankylosing Spondylitis Metrology Index (BASMI)
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in the MASES Index
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in Patient's Global Assessment of Disease Activity (PGADA)
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in total and nocturnal spinal pain
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in Short Form 36-item Health Survey (SF-36)
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in Ankylosing Spondylitis Quality of Life (ASQoL)
- Change from Baseline **of AS0008** ~~and AS0009 entry value~~ in the Hospital Anxiety and Depression Scale-Anxiety (HADS-A) and Hospital Anxiety and Depression Scale-Depression (HADS-D) scores
- Depression and anxiety status "normal" as defined by HADS-D and HADS-A <8

Change #9

Section 4.3.3 PK variable

The PK variable is the plasma concentration of bimekizumab evaluated at scheduled visits up to 208 weeks (4 years) in accordance with the schedule of assessments in Table 5–1 and Table 5–2.

Has been changed to:

The PK variable is the plasma concentration of bimekizumab evaluated at scheduled visits ~~up to 208 weeks (4 years)~~ in accordance with the schedule of assessments in Table 5–1 and Table 5–2.

Change #10

Section 4.3.4 Immunological variable

The immunological variable is the anti-bimekizumab antibody detection evaluated at scheduled visits up to 208 weeks (4 years) in accordance with the schedule of assessments in Table 5–1 and Table 5–2.

Has been changed to:

The immunological variable is the anti-bimekizumab antibody detection evaluated at scheduled visits ~~up to 208 weeks (4 years)~~ in accordance with the schedule of assessments in Table 5–1 and Table 5–2.

Change #11

Table 5-1: Schedule of study assessments (Week 1 through Week 104) and Table 5-2: Schedule of study assessments (Week 108 through Week 208), footnote a

[a] Visit windows are ±7 days from the scheduled visit day (relative to the first dose) with a minimum of 21 days and a maximum of 35 days in between doses at all visits except the SFU Visit.

Has been changed to:

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

Change #12

Section 6.1 Inclusion criteria, Criteria #1 and #2

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent Form (ICF) is signed and dated by the subject or by legal representative.
2. Subject or legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete questionnaires), 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 (ICF) is signed and dated by the subject ~~or by legal representative.~~

2a. Subject ~~or legal representative~~ is considered reliable and capable of adhering to the protocol (eg, able to understand and complete questionnaires), visit schedule, or medication intake according to the judgment of the Investigator.

Change #13

Section 6.3.1, Potential drug-induced liver injury IMP discontinuation criteria, paragraph 2

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

Has been changed to:

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

Change #14

Section 7.1, Description of investigational medicinal product, paragraph 3

Bimekizumab will be supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative−free solution in a [redacted] for sc injection.

Has been changed to:

Bimekizumab will be supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative-free solution in a 1mL prefilled syringe (PFS). [redacted] for sc injection.

Change #15

Section 8.14, SFU Visit, section header

SFU Visit (Visit 23)

Has been changed to:

SFU Visit ~~(Visit 23)~~

Change #16

Section 9.1.3, Other safety topics of interest

Section 9.1.3 AEs for special monitoring

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

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB, see Section 9.5.5), cytopenias, hypersensitivities, suicide

ideation or behavior (assessed using the eC-SSRS), depression and anxiety (assessed using the HADS, see Section 10.11), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 9.4.1), malignancies, and inflammatory bowel diseases.

Has been changed to:

Section 9.1.3, ~~AEs for special monitoring~~ 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, depression, 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.

Change #17

Section 9.1.6, Follow-up of AEs, paragraph 1

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and AESMs; further details regarding follow-up of PDILI events are provided in Section 9.4.1.5. Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

Has been changed to:

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and ~~AESMs~~ **other safety topics of interest;** further details regarding follow-up of PDILI events are provided in Section 9.4.1.5. Information on SAEs obtained after clinical database lock will be captured through the Patient Safety (PS) database without limitation of time.

Change #18

Section 9.1.14, Follow-up of SAEs

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and AESMs; further details regarding follow-up of PDILI events are provided in Section 9.4.1.5. Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

Has been changed to:

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow-up. This follow-up requirement applies to AEs, SAEs, AESIs, and ~~AESMs~~ **other safety topics of interest**; further details regarding follow-up of PDILI events are provided in Section 9.4.1.5. Information on SAEs obtained after clinical database lock will be captured through the PS database without limitation of time.

Change #19

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, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 9.4.1.4); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[d]
≥3xULN	NA	Yes				
≥5xULN	NA	NA	Need for hepatology consult to be discussed. (required if ALT or AST ≥8xULN) Medical Monitor must be notified within 24hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation		

Laboratory value			Immediate		Follow-up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN (and ≥2x baseline) and <5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow-up requirements) [c]	Further investigation – immediate IMP discontinuation not required (see Section 9.4.1.2). 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 ≥3xULN (and ≥2xbaseline) after 2 weeks of monitoring without evidence of resolution	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48hours at the site with HCP (see Section 9.4.1.4).	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: • Discontinue IMP if levels remain ≥3xULN (and ≥2x baseline) without evidence of resolution[d] Continue to monitor until values normalize, stabilize, or return to within baseline values[d].

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

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

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

[c] Details provided in Section 9.4.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

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.	Immediate ~~permanent~~ IMP discontinuation[d].	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 9.4.1.4); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[e]
≥3xULN	NA	Yes				
≥5xULN	NA	NA	Need for hepatology consult to be discussed. (required if ALT or AST ≥8xULN) Medical Monitor must be notified within 24hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate ~~permanent~~ IMP discontinuation[d].		

Laboratory value			Immediate		Follow-up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN (and ≥2x baseline) and <5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow-up requirements) [c]	Further investigation – immediate IMP discontinuation not required (see Section 9.4.1.2). 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 ≥3xULN (and ≥2xbaseline) after 2 weeks of monitoring without evidence of resolution	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48hours at the site with HCP (see Section 9.4.1.4).	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: • Discontinue IMP if levels remain ≥3xULN (and ≥2x baseline) without evidence of resolution[e] Continue to monitor until values normalize, stabilize, or return to within baseline values[e].

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 9.4.1.1. 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 9.4.1.2.

[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.

Change #20

Section 9.4.1.2, Immediate action: determination of IMP discontinuation, paragraph 2

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 9-3 for details).

Has been changed to:

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 9-3 for details).

Change #21

Section 13.4, Planned efficacy analyses

Secondary and other efficacy variables will be summarized for all subjects in the FAS; efficacy analyses will be performed over the 208 weeks (4 years).

Responder variables (eg, ASAS20 response) will be derived relative to Baseline and AS0009 entry values, and summarized descriptively. Percentages will be summarized descriptively by visit, by randomized treatment group, and by treatment group at completion of the lead-in study.

Change from Baseline or AS0009 entry values of all continuous variables will be summarized descriptively by visit, by randomized treatment group, and by treatment group at completion of the lead-in study.

Has been changed to:

Secondary and other efficacy variables will be summarized for all subjects in the FAS; efficacy analyses will be performed over the 208 weeks (4 years).

Responder variables (eg, ASAS20 response) will be derived relative to Baseline **of AS0008** ~~and AS0009 entry values~~, and summarized descriptively. Percentages will be summarized descriptively by visit, by randomized treatment group, and by treatment group at completion of the lead-in study.

Change from Baseline **of AS0008** ~~or AS0009 entry values~~ of all continuous variables will be summarized descriptively by visit, by randomized treatment group, and by treatment group at completion of the lead-in study.

Change #22

Section 13.9, Planned interim analysis and data monitoring

No formal interim analysis is planned for this study.

Has been changed to:

An interim analysis and data cuts may be performed for regulatory and publication purposes.

Change #23

Section 14.1, Informed consent, paragraph 3

Prior to participation in the study, the written ICF 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 ICF. 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 written ICF 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 ICF. 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 #24

Section 14.2, Subject identification cards

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

Has been changed to:

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

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

18 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: as0009-protocol-amend-3

Version: 1.0

Document Number: CLIN-000146755

Title: AS0009 Clinical Study Protocol Amendment 3

Approved Date: 07 Feb 2020

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 06-Feb-2020 10:05:45 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Qualified Person Date of Signature: 06-Feb-2020 11:26:07 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 07-Feb-2020 08:22:56 GMT+0000