PROTOCOL AS0013 AMENDMENT 3

A MULTICENTER, PHASE 2A, RANDOMIZED, INVESTIGATOR-BLIND, SUBJECT-BLIND, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BIMEKIZUMAB AND CERTOLIZUMAB PEGOL IN SUBJECTS WITH ACTIVE ANKYLOSING SPONDYLITIS

PHASE 2A

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SERIOUS ADVERSE EVENT REPORTING

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AE	adverse event
AESI	adverse event of special interest
AESM	adverse event for special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40, 5/6	Assessment in SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-ID	Ankylosing Spondylitis Disease Activity Score inactive disease
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score major improvement
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
BA	bioavailability
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BCG	Bacille Calmette-Guérin
BMI	body mass index
BP	blood pressure
BSA	body surface area
CD	cluster of differentiation
CDC	Centers for Disease Control
CDMS	clinical data management system
CHO	Chinese Hamster Ovarian
CI	confidence interval
COX-2 inhibitor	cyclooxygenase 2 inhibitor
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report

C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CZP	certolizumab pegol
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
DVU	disco-vertebral unit
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EPM	Exploratory Project Manager
ES	Enrolled Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSH	follicle-stimulation hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
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
HbcAg	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
hs-CRP	high sensitivity C-reactive protein
hPDSC	human periosteum-derived stem cell
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
ICF	Informed Consent form
IEC	Independent Ethics Committee

IGRA	Interferon-Gamma Release Assay
IIV	interindividual variability
IL	interleukin
im	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
im	intramuscular
iv	intravenous
IRT	interactive response technology
LTB	latent tuberculosis
LTBI	latent tuberculosis infection
MAR	missing at random
MCID	minimal clinically important difference
MCP-Mod	multiple comparison procedure – modeling
MCS	mental component summary
MedDRA®	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMP	matrix metalloproteinase
mNY	Modified New York (criteria)
MOS	Medical Outcomes Study
MRI	magnetic resonance imaging
MTB	mycobacterium tuberculosis
MTX	methotrexate
nr-axSpA	nonradiographic-axial spondyloarthritis
NRI	nonresponder imputation
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria
NYHA	New York Heart Association
OPV	oral polio vaccine
PCS	physical component summary
PD	pharmacodynamics

PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamics Per-Protocol Set
PET	positron-emission tomography
PET-CT	positron-emission tomography – computed tomography
PET-MRI	positron-emission tomography – magnetic resonance imaging
PFS	pre-filled syringe
PGADA	Patient's Global Assessment of Disease Activity
PhGADA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetics
PK-PPS	Pharmacokinetics Per-Protocol Set
PPS	Per-Protocol Set
PS	Patient Safety
PsA	psoriatic arthritis
PSO	psoriasis
Q2W	every 2 weeks
Q4W	every 4 weeks (monthly)
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RCTC	Rheumatology Common Toxicity Criteria
RIF	mycobacterium tuberculosis rifampin
RNA	ribonucleic acid
RS	Randomized Set
RUV	residual unexplained variability
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SFU	Safety Follow-up
SI	sacroiliac
SpA	spondyloarthritis
SOP	standard operating procedure
SS	Safety Set
SSZ	sulfasalazine
STIR	short-tau-inversion recovery

SUV_{AUC}	standardized uptake value by area under the curve
$t_{½}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
VAS	visual analog scale

1 SUMMARY

This is a Phase 2a, multicenter, randomized, subject-blind, investigator-blind, parallel-group, study to investigate the efficacy and safety of bimekizumab (also known as UCB4940) and certolizumab pegol ([CZP]; Cimzia®) in adult subjects with active ankylosing spondylitis (AS).

Eligible subjects will have active AS, determined by documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS (van der Linden et al, 1984), including symptoms for ≥3 months and age of onset <45 years. Furthermore, subjects will have moderate to severe active disease at Screening (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4 and spinal pain ≥4 [BASDAI Question 2]).

The primary objective of the study is to evaluate the efficacy of bimekizumab administered subcutaneously (sc) every 2 weeks (Q2W) for 12 weeks compared to CZP in the treatment of subjects with active AS. The primary efficacy variable is the change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 12. The secondary objective of the study is to assess the safety and tolerability of bimekizumab. The secondary efficacy variables include the determination of ASDAS inactive disease (ASDAS-ID) and ASDAS major improvement (ASDAS-MI) at Week 12. Primary safety variables include the incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to withdrawal from investigational medicinal product (IMP).

Other exploratory objectives of the study are to evaluate the effect of bimekizumab or CZP on changes in bone formation, to assess the pharmacokinetics (PK) and immunogenicity of bimekizumab, to obtain additional biomarkers and clinical and imaging data as applicable, and to assess the efficacy and safety of bimekizumab or CZP during the Treatment Period and the Treatment Extension Period.

Multiple sites in North America, Europe, and the Asian-Pacific (APAC) region will randomize at least 60 subjects in a 2:1 ratio to receive either bimekizumab or CZP.

The study consists of a Screening Period (2 to 4 weeks), Treatment Period (12 weeks), Treatment Extension Period (36 weeks), and a Safety Follow-up (SFU) Period (20 weeks after the final dose of the IMP). Therefore, the maximum duration of the study is 68 weeks.

Screening Period

The Screening Period will last for a minimum of 2 weeks and up to 4 weeks. During the Screening Period, the Investigator will assess the eligibility of subjects according to the inclusion and exclusion criteria. The Screening Period will also enable washout of any medications not permitted for use during the study.

Treatment Period

At Baseline/Day 1, subjects will be randomized in a 2:1 ratio to receive the following blinded study treatments during the Treatment Period:

- Bimekizumab 160mg sc Q2W from Week 0 through Week 10. In addition, subjects will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 4) in order to maintain the blind vs the certolizumab pegol (CZP) loading dose at these visits.
- Certolizumab pegol 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10.

The IMP will be administered sc in the clinic by trained site personnel.

Treatment Extension Period

After completing the 12-week Treatment Period, subjects will enter a 36-week Treatment Extension Period and will receive the following treatments:

- Subjects randomized to bimekizumab during the Treatment Period will receive bimekizumab 320mg sc every 4 weeks (Q4W) from Week 12 to Week 44.
- Subjects randomized to CZP during the Treatment Period will receive CZP 400mg Q4W from Week 12 to Week 44.

Subjects not responding to treatment will be withdrawn from the study as per Investigator's discretion.

Safety Follow-Up Period

All subjects who complete the study or who discontinue early, including those withdrawn from study treatment, will have a SFU Visit at 20 weeks after their final dose of IMP.

2 INTRODUCTION

2.1 Axial spondyloarthritis

Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases (including axial spondyloarthritis [axSpA], psoriatic arthritis [PsA], reactive arthritis, the arthritis of inflammatory bowel disease [IBD], and undifferentiated 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 (sacroiliac [SI] joints and spine), including AS diagnosed with radiographic involvement and nonradiographic axSpA (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 an magnetic resonance imaging (MRI). However, the most characteristic feature is new bone formation leading to ankylosis of the SI joints and syndesmophytes attached to the vertebral bodies. As a result of extended syndesmophyte formation, over time the spine may become fused. Objective signs of inflammation (such as enthesitis, dactylitis, peripheral arthritis, or uveitis), genetic features (such as the presence of human leukocyte antigen [HLA] B27), and laboratory parameters (such as elevated C-reactive protein [CRP]) may also be present (Braun, 2012; Rudwaleit et al, 2009a; Braun and Sieper, 2007). Disability in axSpA is related to both the degree of inflammatory activity, causing pain, stiffness, fatigue, and poor quality of sleep, and to the degree of bony ankylosis, causing loss of spinal mobility. Patients with AS show radiographic progression of disease with X-ray identified sacroiliitis, while "Bamboo spine" may develop when the outer fibers of the fibrous ring of the intervertebral discs ossify, which results in the formation of marginal syndesmophytes between adjoining vertebrae.

Nonsteroidal anti-inflammatory drugs 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 clinically meaningful response and structural damage often progresses despite their use. Conventional disease-modifying antirheumatic drugs (DMARDs, eg, methotrexate [MTX] and sulfasalazine [SSZ]) have no proven efficacy in axial disease, but may benefit patients with peripheral joint disease (Haibel et al, 2007; Braun et al, 2006; Haibel et al, 2005). Therefore, DMARDs are recommended only in patients with predominantly peripheral manifestations (Braun et al, 2011). Patients who are intolerant of or have inadequately responded to nonsteroidal anti-inflammatory drugs (NSAIDs), or those in whom NSAIDs are contraindicated, have approved treatment options such as tumor necrosis factor (TNF) inhibitors.

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

Treatment with tumor necrosis factor alpha (TNFα)-antagonists has demonstrated marked improvement in almost all features of AS, a subset of the axSpA population. For AS, many of the processes which lead to inflammation and subsequent damage, as in RA, are driven by dysregulated TNFα production, including extracellular matrix degradation due to matrix metalloproteinase (MMP) production (Davis and Mease, 2008).

2.2 Bimekizumab

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 (CHO) cell line. Bimekizumab has high affinity for human IL-17A and human IL-17F and selectively and potently inhibits the activity of both isoforms in vitro. Interleukin-17A and IL-17F are key proinflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases. Therefore, bimekizumab permits an evaluation of the potential for additional efficacy, which may be conferred by dual inhibition of both cytokines, in patients suffering from diseases in which both cytokines are active. Bimekizumab is being developed for the treatment of patients with inflammatory diseases such as PsA, psoriasis (PSO), and axSpA.

2.2.1 Clinical experience with bimekizumab

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

- UP0008 was a Phase 1, First-in-Human (FIH) randomized, subject-blind, investigator-blind, placebo-controlled, single-dose, dose-escalating study in 39 subjects with mild-to-moderate plaque PSO. In this study bimekizumab was administered by intravenous (iv) infusion of single ascending doses and was well tolerated at doses of up to 640mg. The maximum tolerated dose was not reached, and no safety issues were identified. Dose-proportional PK was displayed between bimekizumab 8mg and 640mg. The median t½ ranged between 17.00 days and 25.55 days across the treatment groups. Dose-dependent improvements in the psoriatic lesion of interest were observed after bimekizumab administration for all features of plaque PSO in the study.
- RA0124 was an open-label, parallel-group, single-dose study to evaluate the absolute bioavailability (BA), dose proportionality, and safety and tolerability of 2 dose levels of bimekizumab given by sc injection versus bimekizumab given by iv infusion in 30 healthy subjects. Similar BA was observed for the 2 doses tested (0.656 and 0.631 for the bimekizumab 80mg and bimekizumab 160mg doses, respectively). No new safety issues were observed versus previous studies when bimekizumab was administered sc as a single dose of 80mg or 160mg, or iv at a dose of 160mg.
- PA0007 was a randomized, subject-blind, investigator-blind, placebo-controlled, multiple-dose administration study to evaluate the safety, PK, and pharmacodynamic (PD) profiles of bimekizumab administered iv to subjects with active PsA who had an inadequate response to at least 1 nonbiologic disease-modifying antirheumatic drug (DMARD) and/or 1 approved biologic DMARD. Bimekizumab was administered to 4 cohorts of subjects as a loading dose of 240mg, 80mg, 160mg, or 560mg followed by 2 maintenance doses at 3-weekly intervals of 160mg, 40mg, 80mg, or 320mg, respectively. There were no unexpected clinically relevant safety findings and all doses were well tolerated.
- UP0031, evaluated the relative bioavailability, safety and tolerability of 2 bimekizumab formulations (a histidine-based formulation 2x80mg and an acetate-based formulation 1x160mg) administered by sc injection to healthy volunteers. Results showed similar geometric means for AUC between the 2 bimekizumab formulations (2x80mg=653.8day*µg/mL; 1x160mg=628.3day*µg/mL) and the relative BA 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.

Additional studies of bimekizumab are ongoing. RA0123 is a Phase 2a, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the safety, PK, PD, and efficacy of multiple doses of bimekizumab administered as add-on therapy to stable CZP therapy in subjects with moderate to severe RA. UC0011 is a Phase 2a 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. PS0010, PS0011, PS0016, and PS0018 are Phase 2 studies, which will evaluate the PD, PK, safety, and/or efficacy

of bimekizumab administered sc to subjects with PSO. PA0008 and AS0008 are Phase 2b double-blind, randomized, placebo-controlled, multiple-dose studies to evaluate the efficacy and safety of bimekizumab in subjects with active PsA or AS, respectively.

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

2.2.2 Nonclinical studies with bimekizumab

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 has induced primary lesions to the mucosa associated lymphoid tissue via a pharmacologically-related mechanism. In a second repeat-dose study, none of the minor apoptosis/necrosis findings observed in gut associated lymph nodes were seen. In animals given the highest dose of bimekizumab in the study (20mg/kg/week), a slightly higher number of protozoa (*Balantidium coli*) was observed in the cecum and colon as compared to the control animals and low dose animals. Therefore, 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.

2.3 Certolizumab pegol

Treatment with TNFα-antagonists has demonstrated marked improvement in almost all features of AS, a subset of the axSpA population. For AS, many of the processes which lead to inflammation and subsequent damage, as in RA, are driven by dysregulated TNFα production, including extracellular matrix degradation due to matrix metalloproteinase (MMP) production (Davis and Mease, 2008).

The RAPID-axSpA study enrolled subjects with active axSpA with objective signs of inflammation, and the results indicated that baseline disease burden was similar between the AS and nr-axSpA subpopulations (Landewe et al, 2014; Sieper et al, 2013b). In the RAPID-axSpA study it was shown that CZP rapidly reduced the signs and symptoms of axSpA over 24 weeks of double-blind treatment in the broad axSpA population, including in the AS and the nr-axSpA subpopulations, and that the responses to the treatment were similar in both subpopulations (Landewe et al, 2014; Sieper et al, 2013b) and maintained up to Week 96 (Mease et al, 2014; Sieper et al, 2014).

Certolizumab pegol has a high affinity for human TNFα and binds with a dissociation constant (KD) of 90pM. Tumor necrosis factor alpha (TNFα) is a key pro-inflammatory cytokine with a central role in inflammatory processes.

Certolizumab pegol does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody, and therefore does not fix complement or cause

antibody-dependent cell-mediated cytotoxicity in vitro. It does not induce apoptosis in vitro in human peripheral blood-derived monocytes or lymphocytes, or neutrophil degranulation.

2.3.1 Clinical experience with CZP

Certolizumab pegol is indicated for the treatment of adult patients with active AS in multiple countries around the world.

After the loading dose, the recommended maintenance dose of CZP for adult subjects with AS is CZP 200mg Q2W or CZP 400mg Q4W.

Additional information on the clinical data for CZP is available in the current version of the IB and the product information available in each country.

2.4 Study rationale

The first TNF blockers used for the treatment of patients with active AS showed great promise. (Brandt et al, 2000). However, despite good effects on signs and symptoms, C-reactive protein and inflammation as detected by MRI, the TNFα inhibitors did not appear to prevent new bone formation in the spine (van der Heijde et al, 2008). A 12-year longitudinal study shows that the higher the disease activity, the more the structural damage in the spine, and thus concluding that inflammation and new bone formation are related (Ramiro et al, 2014). Understanding the role of different cytokines in driving new bone formation allows for improved treatments for AS patients. There is a growing association, and interest, for the involvement of IL-17 signaling in bone pathology during spondyloarthritis disease progression. The role of IL-17A in driving bone loss and destruction is well documented (Chabaud et al, 2001). More recently, in vitro studies demonstrated that mesenchymal cells incubated in the presence of IL 17A and bone differentiation medium leads to the formation of extracellular calcified bone matrix with an increase in alkaline phosphatase activation (Osta et al, 2014), suggesting that IL-17A may have a role not only in bone destruction, but under the right conditions in driving new bone formation. Wein et al, demonstrated in in vivo mouse models that in the absence of Schnurri3, a key gene in osteoblast differentiation, leads to increased bone mass; a response enhanced in the presence of IL-17A (Wein et al, 2012). The presence of Schnurri3 and osteoclasts activation at a site of bone inflammation leads to bone destruction, however in the absence of these, the same inflammation will induce new bone formation. In the AS patient at the syndesmophytes when mesenchymal cells from vertebral ligaments are inflamed in the physical absence of osteoclasts, this will induce new bone formation (Miossec, 2017). Recently, IL 17-producing γδ-T cells have been associated with periosteal bone formation for fracture repair (Ono et al, 2016); the periosteum is also implicated in pathologic bone formation in SpA (Lories et al, 2009). Using a biomimetic human periosteum-derived stem cell (hPDSC) model of osteogenic differentiation demonstrated that either/both IL-17A or/and IL-17F are able to drive pathologic bone formation (Shah et al, 2017). Inhibiting both IL-17A and IL-17F has the potential to impact the pathophysiology of new bone formation in AS patients.

AS0013, the current subject-blind and investigator-blind study has been designed to evaluate the efficacy and safety of bimekizumab in a clinical setting in subjects with AS. The features of bone lesions are both erosive and neo-appositive and it is not clear if the inflammatory and erosive process precedes the new formation of bone. 18F-fluoride positron-emission tomography – computed tomography (PET-CT) or 18F-fluoride positron-emission tomography – magnetic resonance imaging (PET-MRI) will be used to investigate the effects of bimekizumab on the

process of osteoproliferation as determined by the inhibition of osteoblast activity. Based on data showing that TNFα blockers have limited effect on osteoblast metabolism, the current study uses a TNFα inhibitor to show a potential differential inhibition of osteoblast activity between bimekizumab and CZP.

3 STUDY OBJECTIVE(S)

This is a Phase 2a, multicenter, randomized, subject-blind and investigator-blind, parallel-group study to evaluate the efficacy and safety of bimekizumab compared to CZP in subjects with active AS. The effect of study treatments on the process of osteoproliferation will be evaluated in a subgroup of subjects at selected sites.

3.1 Primary objective

The primary objective of the study is to evaluate the efficacy of bimekizumab administered sc Q2W for 12 weeks compared to CZP in the treatment of subjects with active AS.

3.2 Secondary objective

The secondary objective of the study is as follows:

- To assess the safety and tolerability of bimekizumab

3.3 Other exploratory objectives

The other exploratory objectives of the study are as follows:

- To evaluate the effect of bimekizumab or CZP on changes in bone formation
- To assess the PK and immunogenicity of bimekizumab
- To assess additional biomarker, clinical, and imaging data as available
- To assess the efficacy and safety of bimekizumab or CZP during the Treatment Extension Period

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable for this study is as follows:

- Change from Baseline in ASDAS at Week 12

4.1.2 Secondary efficacy variables

The secondary efficacy variables for this study are as follows:

- ASDAS-ID at Week 12
- ASDAS-MI at Week 12

4.1.3 Other efficacy variables

Assessment time points for the other efficacy variables are specified in Table 5–1. The following efficacy variables are exploratory and are assessed over the Treatment Period and Treatment Extension Period, as applicable:

- Change from Baseline in ASDAS
- ASAS20 response
- ASAS40 response
- Time to ASAS20 response
- Time to ASAS40 response
- ASAS partial remission
- Change from Baseline in BASDAI
- Changes in bone formation as measured by standardized uptake value by area under the curve (SUV_{AUC}) and derived from PET-MRI or PET-CT at Baseline, Week 12, and Week 48

4.2 Safety variables

4.2.1 Primary safety variables

The primary safety variables for this study are as follows:

- Incidence of AEs and SAEs
- Adverse events leading to withdrawal from IMP

4.2.2 Other safety variables

The other safety variables for this study are as follows:

- Change from Baseline in vital signs (blood pressure, temperature, pulse rate) and body weight
- Change from Baseline in physical examination
- Change from Baseline in standard 12-lead electrocardiogram (ECG) intervals (RR, PR, QRS, QT, and QT intervals corrected for heart rate using Fridericia's formula [QTcF])
- Change from Baseline in clinical laboratory values (hematology, biochemistry, and urinalysis)

4.3 Other PK and PD variables

4.3.1 Other PK variables

The PK variables are plasma concentrations of bimekizumab and CZP.

4.3.2 Other PD variables

The PD variables assessed at time points specified in Table 5–1 are the blood or blood derivative (eg, plasma) concentrations of cytokines and chemokines of relevance to IL-17A/F signaling

pathway, TNF signaling pathway, AS biology, and bone metabolism. Additional variables may include, but will not be limited to, serum complement concentrations and mononuclear cell subtypes.

4.4 Other immunological variable(s)

Immunological variables will allow evaluation of immunogenicity as well as immunological biomarkers. Anti-bimekizumab antibody and anti-CZP antibody detection prior to and following study treatment will be evaluated.

4.5 Other nonhereditary pharmacogenomic variables

Where local regulations permit, blood and urine will be collected at specific time points specified in Table 5–1 and stored for up to 20 years to allow for potential exploratory analyses of ribonucleic acid (RNA), proteins, and metabolite biomarkers relevant to AS, bone metabolism. and the inflammatory and immune response processes. The nature and format of these tentative analyses will be determined at a later stage.

4.6 Other pharmacogenetic variables

Additional blood samples will be collected from subjects who consent to participate in the pharmacogenetic substudy at specific time points specified in Table 5–1 and stored at -80°C for up to 20 years. Pharmacogenetic biomarkers may be measured to evaluate the relationship to response to treatment with bimekizumab, AS disease biology, bone metabolism, and inflammatory and immune response processes. The nature and format of these tentative sub-study analyses will be determined when the results of the main study are made available.

5 STUDY DESIGN

5.1 Study description

AS0013 is a multicenter, randomized, subject-blind and investigator-blind, parallel-group study to evaluate the efficacy and safety of bimekizumab compared to CZP in adult subjects with active adult-onset AS.

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

- Subjects will have active adult-onset AS, meeting Modified New York criteria for AS with:
  - BASDAI score ≥4
  - Spinal pain score ≥4 (from BASDAI Question 2).
- hs-CRP levels should be above the upper limit of normal (ULN) at the Screening Visit. One re-test of hs-CRP is permitted during the Screening Period upon discretion of the Investigator.
- Subject must have had an inadequate response to, have a contraindication to, or has been intolerant to at least 2 NSAIDs (inadequate response to an NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID.) If taking NSAIDs at study entry, subjects must be on a stable dose for 2 weeks prior to Baseline.

- In addition, the subject may not have been exposed to more than 1 TNF antagonist prior to the Baseline Visit and may not be a primary failure to any TNF antagonist therapy (defined as no response within the first 12 weeks of treatment with the TNF antagonist.

At least 60 subjects will be randomized to 1 of 2 treatment arms in a 2:1 ratio and will receive either bimekizumab or CZP up to Week 44 (final dose of IMP).

AS0013 will include a Screening Period of 2 to 4 weeks, a 12-week Treatment Period, a 36-week Treatment Extension Period, and a 20-week Safety Follow-up Period (after the final dose of IMP).

In approximately 25 subjects at selected sites, a PET-MRI or PET-CT scan will be performed at Screening and during the study at Week 12 and Week 48/Early Withdrawal Visit if PET-positive lesions were observed in the previous scan.

5.1.1 Screening Period (minimum of 2 and up to 4 weeks)

Assessments of eligibility as described in Section 6 will be initiated during the 2- to 4-week Screening Period. The informed consent will be obtained as described in Section 8.1. The Screening Period will also enable the washout of medications not permitted for use during the study.

The assessments at the Screening Visit are presented in Table 5–1.

5.1.2 Treatment Period (Week 0 to Week 12)

Eligible subjects will be randomized in a 2:1 ratio to receive the following blinded study treatments:

- Bimekizumab 160mg sc Q2W from Week 0 through Week 10. In addition, subjects will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 4) in order to maintain the blind vs the CZP loading dose at these visits.
- CZP 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10.

Study treatments will be prepared and administered by appropriately trained unblinded site personnel.

5.1.3 Treatment Extension Period (Week 12 to Week 48)

After completing the 12-week Treatment Period, subjects will enter a 36-week Treatment Extension Period and will receive the following treatments:

- Subjects randomized to bimekizumab during the Treatment Period will receive bimekizumab 320mg sc Q4W from Week 12 to Week 44.
- Subjects randomized to CZP during the Treatment Period will receive CZP 400mg Q4W from Week 12 to Week 44.

Subjects not responding to treatment during the Treatment Period will be withdrawn from the study as per Investigator's discretion and will not enter the Treatment Extension Period.

The assessments during the Treatment Extension Period are presented in Table 5–1.

5.1.4 Safety Follow-up Period (Week 48 to Week 64)

All subjects who complete the study or who discontinue from the study early, including those withdrawn from the IMP treatment, will have a SFU Visit at 20 weeks after their final dose of IMP. The assessments at the SFU Visit are presented in Table 5–1.

5.2 Safety monitoring strategy

An independent Data Monitoring Committee (DMC) will review study safety data on an ongoing basis. Details will be available in the DMC charter. Cardiovascular and Neuropsychiatric Adjudication Committees will review and monitor cardiovascular and neuropsychiatric events. Further details are provided in Section 12.5.

5.3 Imaging evaluation

In a subpopulation of AS0013, a PET-MRI or PET-CT scan of the entire spine will be performed at selected sites in approximately 25 subjects at Screening, and during the study at Week 12 and Week 48/Early Withdrawal Visit if PET-positive lesions were observed in the previous scan.

The PET-MRI or PET-CT scan should be performed after confirmation of eligibility for the study based on screening assessments. All subjects at selected sites are eligible provided that a separate Informed Consent form (ICF) for the imaging evaluation has been signed.

5.4 Study duration per subject

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

- Screening Period: minimum of 2 weeks and up to 4 weeks
- Treatment Period: 12 weeks
- Treatment Extension Period: 36 weeks
- Safety Follow-up Period: 20 weeks after the final dose of IMP for subjects completing the study or discontinuing from the study early, including those withdrawn from study treatment.

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

5.5 Planned number of subjects and site(s)

It is anticipated that approximately 120 subjects will be screened in order to enroll at least 60 subjects in the main study and at least 25 subjects in the PET-CT or PET-MRI substudy at multiple sites.

5.6 Anticipated regions and countries

The study sites will be located in North America, Europe, and APAC countries with possible extension to other regions.

5.7 Schedule of assessments

Table 5–1: Schedule of assessments

Study Period	SCr	Treatment Period							Treatment Extension Period									SFU[a]
Visit[b]/Week (Visit window ±3 days)	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**	**V18**
Procedures	**SV**	**BL W0**	**W2**	**W4**	**W6**	**W8**	**W10**	**W12**	**W16**	**W20**	**W24**	**W28**	**W32**	**W36**	**W40**	**W44**	**W48 /WD**	**W64**
Written informed consent[c]	X																	
Demographic data	X																	
AS history	X																	
Inclusion/exclusion criteria	X	X[d]																
Significant past medical history and concomitant diseases	X	X[e]																
Prior and concomitant medications[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HADS	X	X		X		X		X	X	X	X	X	X	X	X	X	X	
BASDAI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BASFI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PGADA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PhGADA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Total and nocturnal spinal pain (NRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Table 5–1: Schedule of assessments

Study Period	SCr	Treatment Period							Treatment Extension Period									SFU[a]
Visit[b]/Week (Visit window ±3 days)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Procedures	SV	BL W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 /WD	W64
Physical examination (incl. height and weight)[g]	X							X			X			X			X	
Vital signs (BP, pulse, temperature)[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG (local)	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Tuberculosis questionnaire	X							X			X			X			X	X
IGRA TB test[i]	X																X	
Pregnancy test[j]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Hematology/ biochemistry/urinalysis[k]	X	X	X	X	X	X	X	X			X			X			X	X
Serology (HIV, Hepatitis B and C, HLA-B27)[k, l]	X																	
Blood samples for cytokines, complement, and biomarker analysis[k]		X		X				X			X			X			X	X
Blood sampling for bimekizumab and CZP plasma concentrations[k]		X		X				X			X			X			X	X
Bimekizumab and CZP antibody detection[k]		X		X				X			X			X			X	X

Table 5–1: Schedule of assessments

Study Period	SCr	Treatment Period							Treatment Extension Period									SFU[a]
Visit[b]/Week (Visit window ±3 days)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Procedures	SV	BL W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 /WD	W64
Blood sample for hs-CRP[k]	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Blood samples for pharmacogenetic variables		X						X									X	
Blood samples for nonhereditary pharmacogenomic variables		X		X				X									X	X
Urine samples for biomarker research		X		X				X									X	
Chest X-ray or CT scan of chest [m]	X																X	
Sacroiliac joint X-ray[n]	X																	
PET-MRI or PET-CT scan as a substudy at selected sites[o]	X							X									X	
Contact the IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration[p]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

AS=ankylosing spondylitis; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BL=Baseline; BP=blood pressure; CT=computed tomography; C-SSRS=Columbia Suicide Severity Rating Scale; CZP=certolizumab pegol; ECG=electrocardiogram; HADS=Hospital Anxiety and Depression Scale; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLA-B27=human leukocyten antigen B27; hs-CRP=high sensitivity C-reactive protein; IGRA=Interferon-Gamma Release Assay; IMP=investigational medicinal product; IRT=interactive response technology; NRS=numeric rating scale; PET-CT=positron-emission tomography-computer tomography; PET-MRI=positron-emission tomography – magnetic resonance imaging; PGADA=Patient's Global Assessment of Disease Activity; PhGADA=Physician's Global Assessment of Disease Activity; Q2W=every 2 weeks; Q4W=every 4 weeks; SCr=Screening; SFU=Safety Follow-Up; SV=Screening Visit; TB=tuberculosis; V=Visit; W=Week;

Table 5–1: Schedule of assessments

Study Period	SCr	Treatment Period							Treatment Extension Period									SFU[a]
Visit[b]/Week (Visit window ±3 days)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Procedures	SV	BL W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 /WD	W64

WD=Early Withdrawal Visit; WHO=World Health Organization

[a] Safety Follow-Up Visit occurs 20 weeks after the final dose for all subjects who complete the study or who discontinue early, including those withdrawn from study treatment.

[b] Visit windows of ±3 days from the first dose at all visits through Week 48. The SFU Visit window is -3 and +7 days from the final dose.

[c] A separate Informed Consent Form is required for subjects participating in the 2 sub-studies: 1) with biomarker, pharmacogenetic and nonhereditary pharmacogenomic blood-samples and 2) PET-MRI or PET-CT scans.

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

[e] Ensure that there are no significant changes in the medical history.

[f] Prior and concomitant medication at Screening and Baseline; concomitant medication only at all other visits.

[g] The physical examination includes the evaluation of signs and symptoms of active TB, risk for exposure to TB, height (Screening only) and weight (Screening, Week 12 and Week 48/WD only).

[h] Vital signs (blood pressure, pulse rate, and temperature) are to be measured prior to drug administration at all visits and at 30 minutes and 1 hour after dosing at Baseline/Day 1.

[i] QuantiFERON TB test or another WHO-validated IGRA test such as Elispot test, if QuantiFERON TB test is not locally available.

[j] Pregnancy testing will performed on serum at Screening and on urine at all other visits. Pregnancy test results must be negative prior to administering IMP.

[k] At dosing visits, all blood samples are taken prior to dosing. Blood samples for IMP and anti-IMP antibody detection will be processed as per instructions in the laboratory manual. After Screening, until Week 12, hs-CRP data will not be sent to the Investigator to protect the blinded nature of the treatment assignments.

[l] Subjects who have evidence of or test positive for hepatitis B by any of the following criteria: 1) positive for hepatitis B surface antigen (HBsAg+); 2) positive for anti-hepatitis B core antibody (HBcAb+) are excluded; a positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab), and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction) are also excluded.

[m] If a subject has had a recent radiograph or CT scan of the chest within 3 months prior to the Screening Visit, it may be used as the Screening chest X-ray. The chest X-ray/CT scan of the chest at Week 48/WD is to be done if medically indicated only (eg, positive TB-test).

[n] If subjects have a previous X-ray documenting AS meeting eligibility criteria, they are eligible for study entry after reconfirming their eligibility by central reading. If no X-ray is available one must be performed at Screening. If the previous X-ray is more than 1 year old, and central read criteria for randomization are not met, another X-ray may be performed if permitted by local guidelines.

[o] A PET-MRI or PET-CT scan should be done up to 2 weeks before Baseline and within 2 weeks after the W12 and W48/WD Visit if PET-positive lesions are observed in the previous scan. If a subject withdraws from the study early, the PET-MRI or PET-CT scan must be repeated at the WD visit only, if the prior examination was done more than 12 weeks prior to the WD visit and the previous PET-scan showed positive lesions.

[p] CZP 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10 and 400mg Q4W from Week 12 to Week 44. Bimekizumab will be administered at a dose of 160mg sc Q2W from Week 0 through Week 10 and 320mg sc Q4W from Week 12 to Week 44. The IMP will be administered at the end of the visit after all assessments have been completed. Subjects randomized to bimekizumab will receive 1 placebo injection at Baseline

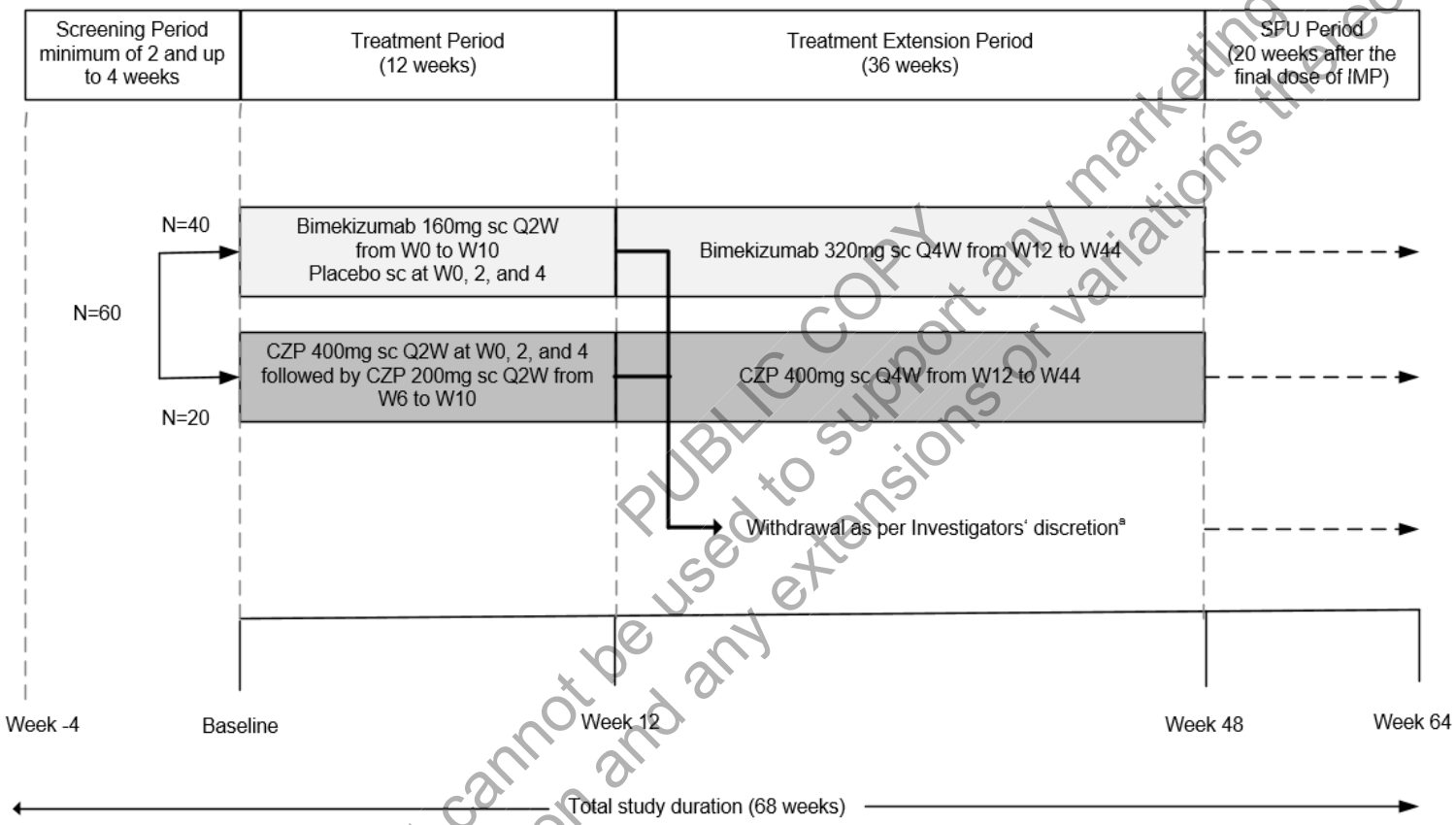
Table 5–1: Schedule of assessments

Study Period	SCr	Treatment Period							Treatment Extension Period									SFU[a]
Visit[b]/Week (Visit window ±3 days)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Procedures	SV	BL W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 /WD	W64

(Visit 2), Week 2 (Visit 3), and Week 4 (Visit 4).

5.8 Schematic diagram

Figure 5–1: Schematic diagram



CZP=certolizumab pegol; N=number of subjects; Q2W=every two weeks; Q4W=every 4 weeks; sc=subcutaneous(ly); SFU=Safety Follow-up, W=week

[a] Subjects not responding to treatment during the Treatment Period will be withdrawn from the study as per Investigator's discretion and will not enter the Treatment Extension Period.

5.9 Rationale for study design and selection of dose

AS0013 is a Phase 2a, multicenter, randomized, subject-blind and investigator-blind study to evaluate the efficacy and safety of bimekizumab and CZP in adult subjects with active AS. AS0013 includes a 12–week Treatment Period, a 36-week Treatment Extension Period, and a 20-week SFU Period. Rationales for the study design, selected population, and bimekizumab doses are provided below.

Study design

AS0013 was designed to evaluate the efficacy, safety and the process of osteoproliferation using PET imaging techniques at Screening and after 12 and 48 weeks of treatment. The scientific rationale suggesting a role for IL-17A treatment in bone formation as compared to TNFα treatment is provided in detail in Section 2.4.

While the primary evaluation will be conducted after 12 weeks, a 36-week Treatment Extension Period has been added in order to maintain the treatment blind after subjects have reached Week 12 (ie, the evaluation of the primary efficacy variable) and to allow continued access to IMP for subjects responding to treatment. This extension also allows further evaluation of the inhibition of the osteoproliferative effect of bimekizumab and CZP at Week 48 and to compare this to Baseline and Week 12.

Population

AS0013 was designed to evaluate the potential benefit of bimekizumab to prevent bone formation in subjects at risk of new bone formation (disease progression) and comparing the outcome to treatment with CZP. Inclusion criteria will ensure that all subjects have active AS. Some exclusion criteria are intended to eliminate subjects who may present an unacceptable safety risk were they to participate in this investigational study program. Active AS is defined by a BASDAI score ≥4 and a spinal pain score ≥4 (from BASDAI Question 2). The full list of inclusion and exclusion criteria is provided in Section 6.

Dose selection

The following dose regimens of bimekizumab and CZP will be evaluated during the Treatment Period:

- Bimekizumab 160mg sc Q2W from Week 0 through Week 10
- CZP 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10.

Exposure levels up to 8-fold greater than 160mg Q2W 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. Additionally, in the above clinical studies (UP0008 and PA0007), bimekizumab was administered iv and the current study proposes to administer the compound sc. The exposure of the drug is expected to be lower than after iv administration due to lower bioavailability following sc administration and, therefore, the dose regimens are expected to be safe. No safety concerns have been reported in ongoing clinical studies evaluating cumulative monthly doses of bimekizumab 320mg in other

populations including PA0008 in subjects with active PsA, AS0008 in subjects with active AS, and several ongoing studies in subjects with PSO.

Simulations were performed using a model to predict the dose response of ASAS20/40 at Week 12, ie, for a different endpoint than the primary efficacy endpoint being proposed in this study (Diderichsen and Cox, 2016). These simulations indicated that increasing doses above bimekizumab 320mg Q4W may not provide additional benefit in terms of efficacy.

The dose selected in the current study is bimekizumab 160mg Q2W instead of 320mg Q4W. Given that the PK of bimekizumab has been established to be linear in the exposure range (UP0008 and PA0007), the proposed dose of bimekizumab 160mg Q2W is expected to provide similar overall exposure and hence response compared to a dose of 320mg Q4W. Table 5–2 shows a comparable AUC_{tau} between bimekizumab 320Q4W and 160mg Q2W calculated over a period of similar time (14 days). In conclusion, the existing data suggest that at the proposed dose level, bimekizumab is well tolerated and the analysis suggests that maximum benefit is achieved at this exposure level.

Table 5–2: Exposure to bimekizumab by dose

Parameter	Bimekizumab dose		
	160mg Q2W sc	320mg Q4W sc	640mg SD iv from UP0008
AUC_{tau} or $AUC_{0\text{-inf}}$ (µg*day/mL)	442[a,b]	445[a,b]	3787[c,d]
C_{max} (µg/mL)	33[a]	38[a]	260[c]

iv=intravenous; Q2W=every 2 weeks; Q4W=every 4 weeks; sc=subcutaneous, SD=single dose
[a] Median model predicted
[b] Calculated over a period of 14 days
[c] Median observed in UP0008
[d] $AUC_{0\text{-inf}}$

The dose and regimen proposed for CZP is one of the currently approved dose regimens in axSpA (CZP 400mg loading dose + CZP 200mg maintenance dose Q2W) and has been widely tested in the clinic, and is in line with the dosing guidance from the labeling. The proposed dose of CZP has been tested in Phase 3 studies in subjects with axSpA. The results of these studies have shown a favorable risk-benefit profile for the treatment of subjects with axSpA.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.
2. Subject is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the Investigator.

3. Subject is male or female and at least 18 years of age.
4. Subject has a documented diagnosis of adult-onset AS as defined by documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS (1984) of at least 3 months' symptom duration and age of onset <45 years.
5. Subject has moderate to severe active disease at the Screening Visit as defined by each of the following:
   - BASDAI score ≥4
   - Spinal pain score ≥4 on a 0 to 10 numeric rating scale (NRS) (from BASDAI Item 2)
6. Subject must have had an inadequate response to, have a contraindication to, or has been intolerant to at least 2 NSAIDs (inadequate response to an NSAID is defined as lack of response to at least 14 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID).
7. Subject may not have been exposed to more than 1 TNF antagonist prior to the Baseline Visit and may not be a primary failure to any TNF antagonist therapy (defined as no response within the first 12 weeks of treatment with the TNF antagonist.
8. Subject has hs-CRP levels above the ULN at the Screening Visit. One re-test of hs-CRP is permitted during the Screening Period upon discretion of the Investigator.
9. **Female** subjects must be postmenopausal (at least 1 year; to be confirmed hormonally as part of the screening process, if less than 2 years since last menstrual period), permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) or, if of childbearing potential (and engaged in sexual activity that could result in procreation), must be willing to use a highly effective method of contraception up till 20 weeks after last administration of IMP, and have a negative pregnancy test at Visit 1 (Screening) and immediately prior to first dose. The following methods are considered highly effective when used consistently and correctly.
   - combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
   - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion
   - vasectomized partner (where postvasectomy testing had demonstrated sperm clearance)
   - 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 final dose of IMP (anticipated 5 half-lifes of bimekizumab). 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 is met:

1. Female subject who is breastfeeding, pregnant, or planning to become pregnant during the study or within 20 weeks following final dose of study drug. Male subject who is planning a partner pregnancy during the study or within 20 weeks following the final dose.
2. Subject who has previously received bimekizumab or CZP.
3. Subject has participated in another study of a medication under investigation within the last 3 months or at least 5 half-lives of the IMP, whichever is greater, or is currently participating in another study of a medication under investigation.
4. Subject has a known hypersensitivity to any excipients of bimekizumab or CZP.
5. Subject has received previous treatment with a polyethylene glycolylated (PEGylated) compound that resulted in a severe hypersensitivity reaction or an anaphylactic reaction
6. Subject has a total ankylosis of the spine or a diagnosis of any other inflammatory arthritis eg, RA, systemic lupus erythematosus, sardoidosis, psoriatic arthritis, or reactive arthritis. Subjects with a diagnosis of Crohn's disease or ulcerative colitis are allowed as long as they have no active symptomatic disease at Screening or Baseline.
7. Subject has a secondary, noninflammatory condition (eg, osteoarthritis, fibromyalgia) that in the Investigator's opinion is symptomatic enough to interfere with evaluation of the effect of study drug on the subject's primary diagnosis of active AS.
8. Subject has received previous or current biological treatment other than TNFα inhibitor treatment.
9. Subjects must not have used medications in the manner as detailed by the exclusion criteria in Table 7–2.
10. Subject has:
    - a history of chronic or recurrent infections (eg, more than 3 episodes requiring systemic antibiotics or antivirals during the preceding year). Minor illnesses like common cold or transient, localized infections that may have been treated with a short course of antibiotic therapy (up to 7 days) need not count in this assessment.
    - a serious or life-threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster) or hospitalization for any infection in the last 6 months.
    - any current sign or symptom that may indicate an active infection (except for common cold), or has had an infection requiring systemic antibiotics within 2 weeks prior to Baseline.
    - a high risk of infection in the Investigator's opinion (eg, subjects with leg ulcers, indwelling urinary catheter, prior prosthetic joint infection at any time, subjects who are permanently bedridden or wheelchair assisted).

11. Subject has a history of or current clinically active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus or current active Candidiasis (local or systemic)
12. Subject has acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Subjects who have evidence of, or test positive for, hepatitis B or hepatitis C are excluded as follows:
    - A positive test for the hepatitis B virus (HBV) is defined as: 1) positive for hepatitis B surface antigen (HBsAg+), or 2) positive for anti-hepatitis B core antibody (HBcAb+).
    - A positive test for the hepatitis C virus (HCV) is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab), and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).
13. Subjects with known TB infection, at high risk of acquiring TB infection, with latent TB infection (LTBI), or current or history of NTMB infection (refer to Section 12.7.5 for details on determining full TB exclusion criteria).
14. Subject has a primary immunosuppressive condition, including taking immunosuppressive therapy following an organ transplant or has had a splenectomy.
15. Subjects with concurrent malignancy or a history of malignancy (including surgically resected uterine/cervical carcinoma-in-situ) during the past 5 years will be excluded with the following exceptions that may be included:
    a. ≤3 excised or ablated basal cell carcinomas of the skin
    b. One squamous cell carcinoma of the skin (stage T1 maximum) successfully excised or ablated only (other treatments, ie, chemotherapy, do not apply) with no signs of recurrence or metastases for more than 2 years prior to Screening
    c. Actinic keratosis(-es)
    d. Squamous cell carcinoma-in-situ of the skin successfully excised or ablated more than 6 months prior to Screening
16. Subject has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
17. Subject has a history of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
18. Subject has a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic hematological, endocrine, pulmonary, cardiac (eg, congestive heart failure New York Heart Association [NYHA] Grade 3 and 4), gastrointestinal (GI) (note: subjects with active peptic ulcer disease are excluded; subjects with a history of peptic ulcer disease are allowed), or neurological disease.
19. Subjects has a history of uncompensated heart failure, fluid overload, or myocardial infarction, or evidence of new-onset ischemic heart disease or in the opinion of the Investigator other serious cardiac disease, within 12 weeks prior to Baseline.

20. Subjects with presence of significant uncontrolled neuropsychiatric disorder, active suicidal ideation, or positive suicide behavior using the "Baseline" version of the Columbia-Suicide Severity Rating Scale (C-SSRS) and the Hospital Anxiety and Depression Scale (HADS) with either of the following criteria:
    - Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either question 4 or question 5 of the "Screening/Baseline" version of the C-SSRS at screening.
    - HADS Depression score ≥10 or Anxiety score ≥15.
21. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), *alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

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

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

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

    If a subject has >ULN ALT, AST, or ALP that does not meet the exclusion limit at Screening, repeat the tests, if possible, prior to dosing to ensure there is no further ongoing clinically relevant increase. In case of a clinically relevant increase, inclusion of the subject must be discussed with the Medical Monitor.
22. Subjects with clinically significant laboratory abnormalities (eg, creatinine >1.5xULN, neutropenia <1.5x10^9/L, hemoglobin <8.5g/dL, lymphocytes <1.0 x10^9/L, white blood cell (WBC) count <3.0x10^9, platelets <100 x10^9/L). Individual screening tests for which the results are in error, borderline, or indeterminate for inclusion in the study, can be repeated once for confirmation during the Screening Period if they are within 25% of the exclusion limit. Upon retesting, subjects whose results remain outside this threshold should not be randomized.
23. Subject has an estimated glomerular filtration rate (GFR) as measured by Chronic Kidney Disease Epidemiology Collaboration <60mL/min/1.73m^2
24. Subject has a 12-lead ECG with changes considered to be clinically significant upon medical review (eg, QT corrected for heart rate [QTc] using Fridericia's correction [QTcF] >450ms, bundle branch block, evidence of myocardial ischemia).

25. Subjects has received any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (12 months prior to Baseline for the TB Bacille Calmette-Guérin [BCG] vaccine) (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted). Live vaccines are not allowed during the study or for 20 weeks after the final dose of IMP.

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

    – Anthrax vaccine
    – Intranasal influenza vaccine
    – Measles-mumps-rubella (MMR) vaccine
    – Polio live oral vaccine (OPV)
    – Smallpox vaccine
    – Tuberculosis BCG vaccine (within 12 months prior to Baseline)
    – Typhoid live oral vaccine
    – Varicella vaccine
    – Yellow fever vaccine

26. Subject has a history of chronic alcohol or drug abuse within the previous 6 months.
27. Subjects has any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.
28. Subject is Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
29. Subject is a UCB employee or is an employee of a third-party organization involved in the study.

6.3 Withdrawal criteria

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

Subjects should be withdrawn from the study and encouraged to come for the SFU Visit (20 weeks after the last received dose of IMP) if any of the following events occur:

1. Subject withdraws his/her consent.
2. The sponsor or a regulatory agency requests withdrawal of the subject.
3. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
4. Subject develops an illness that would interfere with his/her continued participation.

5. Subject considered as having either a suspected new LTBI or who develops active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by interferon-gamma release assay [IGRA] or other diagnostic means) must be immediately discontinued from IMP, and an Early Withdrawal Visit must be scheduled as soon as possible, but not later than the next regular visit.

   Confirmed active TB is a serious adverse event (SAE) and must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements.

   As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.

   Additional information on TB policies are provided Section 12.7.5.

6. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
7. Subject uses prohibited concomitant medications as defined in this protocol (see Section 7.8.2) that may present a risk to the safety of the subject in the opinion of the Investigator and/or the Medical Monitor.
8. Subject develops laboratory abnormalities (with or without clinical symptoms) of ALT or AST as defined in Section Section 6.3.1; neutropenia $<0.5x10^9$/L; lymphopenia $<0.5x10^9$/L. Any laboratory value or change judged to be clinically significant by the Investigator should prompt consideration of whether the subject should continue on IMP. For clarification, laboratory values that are markedly abnormal as per Table 19–2 and Table 19–3 will be flagged to the Investigator and to the medical monitor but do not trigger mandatory withdrawal unless listed above (Refer to Section 6.3.1 for withdrawal criteria in relation to potential drug-induced liver injury [PDILI].)
9. Subject has active suicidal ideation as indicated by a positive response ("Yes") to Questions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
10. Subjects with a Hospital Anxiety and Depression Scale—Depression (HADS-D) score ≥15 must be withdrawn. Any subject who develops a HADS-D score of ≥10 during the study should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.
11. Subjects with newly diagnosed 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 judgement in deciding whether the subject should continue in the study and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.

In an attempt to prevent missing data during the study, efforts will be made to collect data from subjects who withdraw early from the study (NRC, 2010). If a subject withdraws from study treatment for any of the above criteria prior to Week 48, they will be asked to return for the study termination assessments as laid down at the Week 48/WD Visit and for the SFU Visit (20 weeks after final dose administration). 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. If a subject at any time has had an ALT and/or AST >5xULN, additional monitoring of hepatic markers will be performed every week or 2 weeks until resolution of the event, the event is considered stable, or they have reached the end of the SFU Period.

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 eCRF must document the primary reason for withdrawal or discontinuation.

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

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

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

The PDILI criteria below require immediate discontinuation of IMP:

Subjects with either of the following:

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

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

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

Evaluation of PDILI must be initiated as described in Section 12.6.1.

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 eCRF must document the primary reason for IMP discontinuation.

6.4 Study stopping rules

During the study, planned dosing and procedures may be discontinued or suspended for all subjects in any part of the study and appropriate follow-up procedures established. Where it is possible to do so without threatening the safety of subjects, such discontinuation/suspension should be discussed with the UCB Study Physician prior to its implementation.

Possible reasons for discontinuation or suspension of the study include (but are not limited to):

- A pattern of AEs occurs that contraindicates the further dosing of enrolled/additional subjects, including (but not limited to):
  - More than 1 subject meets any individual Withdrawal Criteria #5, #9, ro #10, or (as provided in Section 6.3), regardless of whether they met the same or different criteria.
  - Once a second subject meets any of those criteria, referral to the DMC may not be delayed while awaiting the outcome of either case.

If the above criteria are reached, the DMC will meet as soon as possible to determine whether discontinuation or suspension of the study should occur and to determine what investigations, analyses, procedural amendments, or other actions should occur, before making any recommendation regarding the possibility of recommencing the study. Further details on the role of the DMC are provided in Section 12.5.

- If the Sponsor or designees judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

6.5 Retesting/rescreening

In the event of an isolated laboratory value outside the laboratory's normal range, the evaluation may be repeated on 1 occasion during the Screening Period. If a value from the repeated test is within the screening-specified ranges, the subject maybe enrolled.

Subjects whose Screening Period expires may be rescreened following discussion with the Sponsor.

Subjects who withdraw from the study may be replaced, up to a maximum of 10 subjects.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

The IMPs used in this study are bimekizumab and CZP.

Bimekizumab will be supplied as a vial or in a pre-filled syringe (PFS) form as described below:

- Vial: a clear to opalescent, colorless to slightly brown, sterile, preservative-free solution in 2mL Type I, colorless glass vials (1.0mL extractable volume) closed with a rubber stopper and sealed with an aluminum cap overseal. Each single-use dose vial will contain 160mg/mL bimekizumab in [redacted] mM sodium acetate, [redacted] mM glycine, and [redacted] (w/v) polysorbate 80 at pH [redacted]
- PFS: 1mL PFS at a concentration of 160mg/mL ([redacted] mM sodium acetate, [redacted] mM glycine, [redacted] polysorbate 80 at pH [redacted]) for sc injection.

Certolizumab pegol will be supplied as a sterile, clear, colorless-to-slightly yellow solution at pH [redacted] in 1mL single-use glass PFS for sc injection. Each syringe contains an extractable volume of 1.0mL at a concentration of CZP 200mg/mL in [redacted] mM sodium acetate buffer and [redacted] mM sodium chloride as a tonicity agent. The syringes are stored at 2 to 8ºC, not frozen, and protected from light.

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

Further details of the IMPs and their specifications are provided in the IMP Handling Manual.

7.2 Treatment(s) to be administered

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

The IMP (bimekizumab or CZP) will be administered at time points indicated in Table 5–1.

At Baseline, eligible subjects will be randomized in a 2:1 ratio to the following bimekizumab or CZP treatment arms and will receive IMP as shown in Table 7–1.

Table 7–1: Treatments administered

IMP	Study period	
	Treatment Period	**Treatment Extension Period**
Bimekizumab	160mg sc Q2W[a]	320mg sc Q4W
CZP	Loading doses of 400mg sc Q2W at Weeks 0, 2, and 4 followed by CZP 200mg sc Q2W	400mg sc Q4W

CZP=certolizumab pegol; IMP=investigational medicinal product, Q2W=every 2 weeks; Q4W=every 4 weeks; sc=subcutaneous

[a] In addition, subjects will receive 1 placebo injection at Baseline, Week 2, and Week 4 in order to maintain the blind vs the CZP loading dose at these visits.

The minimum time between doses should be no less than 10 days during the Treatment Period and no less than 22 days during the Treatment Extension Period.

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

7.3 Packaging

Bimekizumab and CZP will be packaged and labeled according to Good Manufacturing Practice (GMP) guidelines and applicable laws or regulations. They 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 according to the storage conditions mentioned on the label.

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

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

7.6 Drug accountability

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

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

The packaging identifies each kit by a unique number. Unblinded study staff will be responsible for preparation (breaking tamper proof sticker on kit, etc) of the clinical trial material, including recording the administration information on source document.

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

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

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

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and destroyed at the site according to local laws, regulations, and UCB standard operating procedures (SOPs). 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 theTreatment Period and the Treatment Extension Period, IMP will be administered in the clinic and compliance will be determined at the visit by study personnel. Drug accountability must be recorded on the Drug Accountability Form.

7.8 Concomitant medication(s)/treatment(s)

All concomitant medications, including over the counter products, herbal, traditional remedies, vitamin/mineral supplements, other dietary supplements, "nutraceuticals," and hormones must be recorded in the subject's source documentation (eg, clinical chart) and on the electronic Case Report Form (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 non-prescription drugs or prescription therapy prescribed by another physician).

7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

Subjects may use NSAIDs under the following conditions:

- Subjects who are already receiving an established NSAID regimen and have been on a stable dose for at least 2 weeks prior to Baseline may continue their use during the study. However, initiation of, or increase in dosage of NSAIDs during the study (especially in subjects with a history of GI intolerance to NSAIDs or a history of GI ulceration) should be done with caution and must not occur until after the Week 12 Visit.

Subjects may use corticosteroids under the following conditions:

- Oral (maximum allowed ≤10mg daily total prednisone equivalent)—subjects are permitted to decrease their oral corticosteroid therapy dose equivalent and/or alter their regimen only after Week 12.

Subjects may use MTX, sulfasalazine (SSZ), or hydroxychloroquine (HCQ) under the following conditions:

- No change in dose or dose regimen of these agents is allowed during the study except for reasons of intolerance/AEs. No increase of the dose is permitted. No change is permitted in the route of administration for MTX (intramuscular [im], sc, or oral). It is strongly recommended that subjects taking MTX are also taking folic acid supplements. No combinations of DMARDs are permitted during the study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

Table 7–2: Prohibited or restricted medications and required wash-out periods prior to Baseline

Drug class	Dose	Exclusion criteria
Analgesics, including opioid analgesics (acetaminophen/paracetamol, etc)	Any dose	Any ad hoc use in the 24 hours prior to any study visit. Stable doses of analgesics permitted.
NSAIDs/COX-2 inhibitors	Any dose regimen	Any change in dose/dose regimen in the 14 days prior to the Baseline Visit
Oral corticosteroids	Any dose regimen	Any change in dose/dose regimen in the 14 days prior to the Baseline Visit
Intramuscular (im)/intravenous (iv)/ intra-articular (ia) corticosteroids/bursal corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit.

Table 7–2: Prohibited or restricted medications and required wash-out periods prior to Baseline

Drug class	Dose	Exclusion criteria
Intra-articular hyaluronic acid	Any dose	Any use in the 6 months prior to the Baseline Visit.
DMARDs: -azathioprine -cyclosporine, -cyclophosphamide, -mycophenolic acid, -mycophenylate mofetil -any other small molecule DMARDs (eg tofacitinib, apremilast)	Any dose	Use within 12 weeks prior to the Baseline Visit.
MTX, SSZ, and HCQ	Maximum allowed: SSZ ≤3g daily HCQ ≤400mg daily MTX ≤25mg weekly	Use initiated and/or any change in the dose regimen in the 28 days prior to the Baseline Visit. No change is permitted in the route of administration for MTX (im, sc, or oral) in the 28 days prior to the Baseline Visit.
DMARDs: -leflunomide	Any dose	Use in the 6 months prior to the Baseline Visit unless a cholestyramine washout has been performed; in which case, use up to 28 days prior to the Baseline Visit is acceptable.
TNF inhibitors -infliximab (IFX) -adalimumab (ADA) -etanercept (ETN) -golimumab (GOL) -certolizumab pegol (CZP)	Any dose	For IFX, ADA, and GOL, any use within the 12 weeks prior to the Baseline Visit For ETN, use within the 28 days prior to the Baseline Visit. For CZP, any previous use This applies to biosimilar versions of any TNF inhibitors.
Any non-TNF biologic medications	Any dose	Any exposure history.

ADA=adalimumab; ia=intra-articular; COX-2=cyclooxygenase 2; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; im=intramuscular; iv=intravenous; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; sc=subcutaneous; SSZ=sulfasalazine; TNF=tumor necrosis factor

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

Subjects who take prohibited medications, except topical therapies, may be withdrawn from study treatment, but followed until the Safety Follow-Up Visit (20 weeks after the final dose of IMP). The decision to withdraw a subject for taking prohibited medications should be made in consultation with the Medical Monitor. As noted above, subjects who use prohibited topical medications will be allowed to stay in the study but will be counseled to not use them further.

Vaccines

Administration of live, attenuated vaccines is not allowed during the conduct of the study or for 20 weeks after the final dose of study drug. Subjects receiving BCG vaccinations within 12 months prior to study drug administration are excluded (see Exclusion Criterion #25, Section 6.2).

7.8.3 Rescue medication

There are no absolute restrictions on the use of concomitant medications to "rescue" subjects whose AS deteriorates during the course of the study. While the objectives of the study should be protected as much as possible through observance of the restrictions detailed in Table 7–2, the wellbeing of the subject will always take priority, and subjects should be managed as deemed appropriate by the Investigator. If use of any prohibited medications is anticipated, this should be discussed with the Sponsor's Study Physician first, wherever possible.

7.9 Blinding

Due to differences in presentation of the IMPs (bimekizumab and CZP), special precautions will be taken to ensure study blinding. Subjects randomized to bimekizumab will receive placebo at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 4) in order to maintain the blind vs the CZP loading dose at these visits.

Investigational medicinal product injections will be prepared at the investigational sites by unblinded, dedicated study personnel. The unblinded personnel will not be involved in the study in any way other than assuring the medication is taken from the correct kit and prepared according to the pharmacy manual instructions, and administering the drug to the subjects.

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

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

7.9.1 Procedures for maintaining and breaking the treatment blind

The IMP handling manual describes the handling of bimekizumab and CZP. Appropriate training will be given to the site personnel to avoid any unblinding. In case the Investigator becomes unblinded for any subject, another assessor will perform the remaining evaluations for that subject.

All Sponsor and Investigator site personnel involved in the study will be blinded to the randomized IMP (bimekizumab or CZP) assignment with the following exceptions:

- Sponsor Clinical Study Supplies manager and qualified personnel
- Sponsor Patient Safety (PS) staff reporting SAEs to the regulatory authorities
- Site pharmacist involved in IMP preparation and dispensing
- Unblinded monitor who reviews the IMP related documentation and drug accountability
- Bioanalytical staff analyzing blood samples for PK and immunogenicity, and biomarkers
- Any Sponsor staff and/or designee who is responsible for data analyses for the unblinded DMC and interim analyses. These individuals will be separate from the main blinded study team.
- Unblinded team at PAREXEL for the purpose of sending unblinded output for the planned interim analyses

If necessary, the results of any planned analysis may be shared with key Sponsor's personnel in order to facilitate additional Clinical Planning or Portfolio Management decisions. Only unblinded summary results will be provided, and individual subject data will be kept blinded. All individuals seeing unblinded summary data will be documented in the Trial Master File (TMF).

7.9.1.1 Maintenance of study treatment blind

All subject treatment details (bimekizumab or CZP) will be allocated and maintained by the interactive response technology (IRT) system.

7.9.1.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the subject has been allocated by contacting the IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

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

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen (as applicable) based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. To enroll a subject at Visit 1, the Investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject at Visit 2, the Investigator or designee will contact the IRT and provide brief details about the subject to be randomized. The IRT will automatically inform the Investigator or designee of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be incorporated into the eCRF.

8 STUDY PROCEDURES BY VISIT

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

- Visit windows of ±3 days on either side of the scheduled dosing are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor.
- For the SFU Visit (20 weeks after the final dose of IMP), 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 to +7 days).

8.1 Screening Visit (Visit 1)

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

Two additional ICFs for substudies will be required:

- Where local regulations permit, subjects will also be given the option to participate in the pharmacogenetic and pharmacogenomic substudy. Subjects agreeing to participate in the substudy will be required to complete a separate ICF. The ICF must be signed prior to collecting any samples for the substudy. The substudy will only be conducted where ethically accepted and authorized by the regulatory agencies. Refusal to participate in the substudy will not affect a subject's ability to participate in the main AS0013 study.
- Subjects will also be given the option to participate in the PET-MRI or PET-CT substudy at selected sites. Subjects who decide to participate in the substudy will need to complete a separate ICF following the same procedure and given the same considerations as the main ICF. Their willingness to participate in the substudy will be independent from their consent to participate in the main AS0013 study.

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

- Obtain written informed consent.
- Collect demographic and Baseline characteristics data (including lifestyle and child bearing potential as applicable).
- Collect AS history.

- Assess if all inclusion criteria and no exclusion criteria are met.
- Collect significant past medical history and concomitant diseases.
- Record prior and concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the Bath Ankylosing Spondylitis Functional Index (BASFI).
- Total and nocturnal spinal pain (NRS).
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB, weight and height.
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Administer the tuberculosis questionnaire.
- Perform an IGRA tuberculosis test (QuantiFERON TB test).
- Perform a serum pregnancy test.
- Collect samples for hematology/biochemistry/urinalysis.
- Collect samples for hs-CRP.
- Collect samples for HIV, hepatitis B and C, and HLA-B27 serology.
- Perform a sacroiliac joint X-ray (if subjects have a previous X-ray documenting AS meeting eligibility criteria, they are eligible for study entry after reconfirming their eligibility by central reading. If no X-ray is available one must be performed at the Screening Visit. If the previous X-ray is more than 1 year old, and central read criteria for randomization are not met, another X-ray may be performed if permitted by local guidelines).
- Perform a PET-MRI or PET-CT scan in approximately 25 subjects at selected sites within 2 weeks prior to Baseline.
- Obtain a chest radiograph or computer tomography (CT) scan, unless one has been obtained within 3 months prior to the Screening Visit.
- Register the subject using the interactive response technology (IRT).

Individual screening tests for which the results are borderline for inclusion in the study may be repeated if necessary without complete rescreening of all tests.

8.2 Baseline (Visit 2, Week 0)

The following procedures or assessments will be performed/recorded prior to administration of the IMP:

- Verify if all inclusion criteria and no exclusion criteria are met.
- Verify significant past medical history and concomitant diseases.
- Record prior and concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the Patient's Global Assessment of Disease Activity (PGADA).
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure) prior to IMP administration and then at 30 minutes and 1 hour after dosing.
- Perform a 12-lead ECG.
- Perform a urine pregnancy test.
- Collect samples for:
  - Hematology/biochemistry/urinalysis.
  - Bimekizumab and CZP plasma concentrations.
  - Anti-bimekizumab and anti-CZP antibody detection.
  - hs-CRP.
- If the respective ICF has been provided collect blood samples for:
  - Cytokines, complement, and biomarker analyses
  - Pharmacogenetic variables.
  - Nonhereditary pharmacogenomic variables.
- Collect urine samples for biomarker research if the respective ICF has been provided.
- Contact the IRT for randomization.
- Administer IMP after all other visit assessments are completed.
- Record visit in the IRT.

8.3 Week 2 (Visit 3)

The following procedures or assessments will be performed/recorded:

- Record concomitant medications.
- Assess adverse events.
- C-SSRS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure).
- Collect samples for hematology/biochemistry/urinalysis.
- Administer IMP.
- Record visit in the IRT.

8.4 Week 4 (Visit 4)

- Record concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Perform a urine pregnancy test.

- Collect samples for:
  - Hematology/biochemistry/urinalysis.
  - Bimekizumab and CZP plasma concentrations.
  - Anti-bimekizumab and anti-CZP antibody detection.
  - hs-CRP.
- If the respective ICF has been provided collect blood samples for:
  - Cytokines, complement, and biomarker analyses.
  - Nonhereditary pharmacogenomic variables.
- Collect urine samples for biomarker research if the respective ICF has been provided.
- Administer IMP.
- Record visit in the IRT.

8.5 Week 6 (Visit 5)

- Record concomitant medications.
- Assess adverse events.
- C-SSRS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure).
- Collect samples for hematology/biochemistry/urinalysis.
- Administer IMP.
- Record visit in the IRT.

8.6 Week 8 (Visit 6)

- Record concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the BASFI.

- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Perform a urine pregnancy test.
- Collect samples for:
  - Hematology/biochemistry/urinalysis.
  - hs-CRP.
- Administer IMP.
- Record visit in the IRT.

8.7 Week 10 (Visit 7)

- Record concomitant medications.
- Assess adverse events.
- C-SSRS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure).
- Collect samples for hematology/biochemistry/urinalysis.
- Administer IMP.
- Record visit in the IRT.

8.8 Week 12 (Visit 8)

- Record concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the BASFI.

- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB and weight.
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Administer the tuberculosis questionnaire.
- Perform a urine pregnancy test.
- Collect samples for:
  - Hematology/biochemistry/urinalysis.
  - Bimekizumab and CZP plasma concentrations.
  - Anti-bimekizumab and anti-CZP antibody detection.
  - hs-CRP.
- If the respective ICF has been provided collect blood samples for:
  - Cytokines, complement, and biomarker analyses.
  - Pharmacogenetic variables.
  - Nonhereditary pharmacogenomic variables.
- Collect urine samples for biomarker research if the respective ICF has been provided.
- Perform a PET-MRI or PET-CT scan in at least 25 subjects at selected sites within 2 weeks after Week 12 Visit if PET-positive lesions were observed in the previous scan.
- Administer IMP.
- Record visit in the IRT.

8.9 Week 16 (Visit 9), Week 20 (Visit 10), Week 28 (Visit 12), Week 32 (Visit 13), Week 40 (Visit 15), and Week 44 (Visit 16)

- Record concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the PGADA.

- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Blood sample for hs-CRP.
- Perform a urine pregnancy test.
- Administer IMP.
- Record visit in the IRT.

8.10 Week 24 (Visit 11) and Week 36 (Visit 14)

- Record prior and concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB.
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Administer the tuberculosis questionnaire.
- Perform a urine pregnancy test.
- Collect samples for:
  - Hematology/biochemistry/urinalysis.
  - Bimekizumab and CZP plasma concentrations.
  - Anti-bimekizumab and anti-CZP antibody detection.
  - hs-CRP.

- If the respective ICF has been provided collect blood samples for:
  - Cytokines, complement, and biomarker analyses.
- Administer IMP.
- Record visit in the IRT.

8.11 Week 48 (Visit 17)/Early Withdrawal Visit

- Record prior and concomitant medications.
- Assess adverse events.
- C-SSRS.
- HADS.
- Determine the BASDAI.
- Determine the BASFI.
- Perform the PGADA.
- Perform the PhGADA.
- Total and nocturnal spinal pain (NRS).
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB and weight.
- Perform a 12-lead ECG.
- Administer the tuberculosis questionnaire.
- Perform an IGRA tuberculosis test (QuantiFERON TB test).
- Perform a urine pregnancy test.
- Collect samples for:
  - Hematology/biochemistry/urinalysis.
  - Bimekizumab and CZP plasma concentrations.
  - Anti-bimekizumab and anti-CZP antibody detection.
  - hs-CRP.
- If the respective ICF has been provided collect blood samples for:
  - Cytokines, complement, and biomarker analyses.
  - Pharmacogenetic variables.
  - Nonhereditary pharmacogenomic variables.

- Collect urine samples for biomarker research if the respective ICF has been provided.
- Obtain a X-ray or CT scan of the chest if the QuantiFERON TB test returned a positive result.
- Perform a PET-MRI or PET-CT scan in at least 25 subjects at selected sites within 2 weeks after the Week 48/WD Visit if PET-positive lesions were observed in the previous scan. At the WD Visit, the PET-MRI or PET-CT must be done only, if the previous imaging evaluation occurred more than 12 weeks ago and if PET-positive lesions were observed in the previous scan.
- Record visit in the IRT.

8.12 Safety Follow-Up Visit (Week 64, Visit 18, 20 weeks after the final dose of IMP)

- Record concomitant medications.
- Assess adverse events.
- Measure vital signs (temperature, pulse, and blood pressure).
- Perform a 12-lead ECG.
- Administer the tuberculosis questionnaire.
- Perform a urine pregnancy test.
- Collect samples for:
  - Hematology/biochemistry/urinalysis.
  - Bimekizumab and CZP plasma concentrations.
  - Anti-bimekizumab and anti-CZP antibody detection.
  - hs-CRP.
- If the respective ICF has been provided collect blood samples for:
  - Cytokines, complement, and biomarker analyses.
  - Nonhereditary pharmacogenomic variables.
- Record visit in the IRT.

8.13 Early Withdrawal Visit

Subjects withdrawing early from the study (see Section 6.3) should undergo the same assessments scheduled for the Week 48 Visit (see Section 8.11) as soon as possible after withdrawal (as an Early Withdrawal Visit) and then enter the SFU Period, completing study participation with the SFU Visit 20 weeks after their final dose of study medication.

8.14 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, a C-SSRS assessment will be performed with the subject during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, repeated collection of a laboratory specimen due to collection or analysis issues), an C-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:

- Vital signs (temperature, pulse, and blood pressure).
- C-SSRS.
- Other patient-reported outcomes (HADS, BASDAI, BASFI, PhGADA, PGADA, total and nocturnal spinal pain) as required.
- Administer the tuberculosis questionnaire.
- Perform a physical examination, including an evaluation for signs and symptoms of active TB and risk for exposure to TB and weight.
- Record 12-lead ECG.
- If medically indicated, obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology, serum chemistry).
  - The blood sample may also be used for PK/PD assessments, if needed.
- Obtain urine sample for standard safety laboratory tests (including urine pregnancy test).
- Record concomitant medication.
- Record AEs.

9 ASSESSMENT OF EFFICACY

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

9.1 ASDAS

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

- 0.121 x Total spinal pain (BASDAI Question 2 result, Section 9.3)
- 0.058 x Duration of morning stiffness (BASDAI Question 6 result, Section 9.3)
- 0.110 x PGADA (Section 9.6)
- 0.073 x Peripheral pain/swelling (BASDAI Question 3 result, Section 9.4)
- 0.579 x (natural logarithm of the CRP [mg/L] + 1)

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

The following definitions apply to ASDAS Disease Activity categories:

- ASDAS-Inactive Disease: ASDAS <1.3
- ASDAS-Moderate Disease activity: ASDAS ≥1.3, <2.1
- ASDAS-High Disease activity: ASDAS ≥2.1; ≤3.5
- ASDAS-Very High Disease activity: ASDAS >3.5

9.2 ASAS20, ASAS40, and ASAS partial remission

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

- PGADA (see Section 9.6)
- Pain assessment (the total spinal pain NRS score; Section 9.8)
- Function (represented by BASFI, Section 9.5)
- Inflammation (the mean of the BASDAI Questions 5 and 6 results, [see Section 9.4] concerning morning stiffness intensity and duration)

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

The ASAS40 response is defined as an improvement of at least 40%, and absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 domains above and no worsening at all in the remaining domain.

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

9.3 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 fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week (van Tubergen et al, 2015). The BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity. Question 2 of the BASDAI asks [redacted] Question 3 of the BASDAI asks [redacted] Question 6 of the BASDAI asks [redacted]

The BASDAI is calculated as follows:

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

Fatigue item of the BASDAI

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

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

Question 5 of the BASDAI (described completely in Section 9.3) measures intensity of morning stiffness. The subject considers the previous week and responds to the question, [redacted]

The response is indicated on a 10-point NRS in which 0=None and 10=Very severe. Question 6 of the BASDAI measures duration of morning stiffness. The subject considers the previous week and responds to the question, [redacted] The response is indicated on a 10-point NRS in which 0=0 hours, 5=1 hour, and 10=2 or more hours. The ratings for each question are summed and divided by 2 to provide the mean of Questions 5 and 6. This is used in the definition of the ASAS response variables defined in Section 9.2.

9.5 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 visual analog scale (VAS) or 17.5% of the Baseline score (Pavy et al, 2005); an MCID of 1 unit will be used for the NRS version. This is used in the definition of the ASAS response variables defined in Section 9.2.

9.6 Patient global assessment (PGADA)

Subjects will provide 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).

This is used in the calculation of ASDAS (Section 9.1) and the definition of the ASAS response variables defined in Section 9.2.

9.7 PhGADA

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

The subject should be asked to consider both joint and skin components in their response to this question.

9.8 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. The total pain score is used in the definition of the ASAS response variables defined in Section 9.2.

9.9 hs-CRP

Blood will be collected for measurement of hs-CRP. After Screening, the hs-CRP data will not be sent to the Investigator to protect the blinded nature of the treatment assignments. The hs-CRP will be used in the calculation of ASDAS (Section 9.1).

9.10 Hospital Anxiety and Depression Scale

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

9.11 PET-MRI or PET-CT scan

High bone turnover assessed by nuclear medicine methods may detect osteoproliferative processes regardless of the inflammatory or noninflammatory origin.

While exact localization of regions of radionuclide uptake is difficult with conventional scintigraphy,18F-fluoride PET-CT or PET-MRI has a much better spatial resolution and sensitivity (Strobel et al, 2010; Even-Sapir et al, 2007). In the present study, UCB will assess the regions of high bone turnover as detected by 18F PET-MRI or 18F PET-CT within the spine and the sacroiliac joints.

The 18F-fluoride PET-MRIs of the whole spine will be performed by using a whole-body PET/MRI system. Alternatively, subjects will be examined in supine position on a combined PET-CT system permitting the acquisition of co-registered CT and PET images in the same session. The PET-MRI or PET-CT scan will be performed at time points provided in Table 5–1 in at least 25 subjects at selected sites.

10 ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC/PHARMACOGENOMIC/ PHARMACOGENETIC VARIABLE(S)

Plasma concentrations of bimekizumab and CZP are the PK variables.

10.1 Pharmacokinetic variables

Blood samples for measurement of PK variables will be collected at the time points specified in the Table 5–1. At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will

be recorded in the eCRF. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analysis will be provided in a bioanalytical report.

10.2 Pharmacodynamic variables

Blood samples for measurement of PD variables will be collected at the time points specified in Table 5–1. Flow cytometry by fluorescence-activated cell sorting (FACS) analysis might include, but is not limited to: cluster of differentiation (CD)3, CD19, CD4, CD8, and CD69. Candidate biomarkers might include, but are not limited to: IL-17A/IL17-F pathway signaling, TNF signaling pathway, bone metabolism and AS (eg, IL-17A, IL-17F, IL-23, IL-6, TNF, DC-STAMP, and circulating osteoclast precursors). At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analysis will be provided in a bioanalytical report.

10.3 Nonhereditary pharmacogenomic variables

Where local regulation permit, blood samples will be drawn for exploratory RNA, proteins and metabolites biomarker analysis at the time points specified in Table 5–1. Where local regulation permit, urine samples will be drawn for exploratory proteins and metabolites biomarker analysis at the time points specified in the schedule of study assessments. Collection of these samples will enable evaluation of biomarkers relative to disease biology and progression, drug treatment, bone metabolism and inflammatory and immune response processes. Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. The nature and format of these tentative analyses will be determined at a later stage. The samples will be stored at the secure long-term storage facility selected by UCB for up to 20 years.

10.4 Pharmacogenetic variables

For individuals consenting to the pharmacogenetic substudy, blood samples will be drawn for exploratory genetic/epigenetic, analyses at the time points specified in Table 5–1. Collection of these samples will enable evaluation of genetics/epigenetics biomarkers relative to disease biology and progression, drug treatment, bone metabolism and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. A separate ICF will be required for those subjects who agree to participate in the pharmacogenetics substudy. The substudy will be conducted only where ethically accepted and authorized by the regulatory agencies. Refusal to participate in the substudy will not affect a subject's ability to participate in the main study. The samples will be stored at -80°C at the central biorepository for up to 20 years.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLE(S)

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

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

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 Adverse event

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

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

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

12.1.1.2 Serious adverse event

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

- Death
- Life-threatening

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

(Important medical events may include, but are not limited to, potential Hy's Law [see Section 12.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

- Initial inpatient hospitalization or prolongation of hospitalization

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

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

12.1.1.2.1 Anticipated serious adverse events

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

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

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

MedDRA system organ class	MedDRA preferred term
Skin and subcutaneous tissue disorders	Psoriasis
Eye disorders	Uveitis
Musculoskeletal and connective tissue disorders	Dactylitis Tendonitis Atlantoaxial instability
Gastrointestinal disorders	Colitis ulcerative Crohn's disease

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

MedDRA system organ class	MedDRA preferred term
Cardiac disorders	Aortic valve incompetence Atrial tachycardia Atrioventricular block Bundle branch block Cardiomyopathy
Vascular disorders	Aortitis
Respiratory, thoracic and mediastinal disorders	Pulmonary fibrosis
Nervous system disorders	Cauda equina syndrome
Injury, poisoning and procedural complications	Spinal cord injury Spinal fracture Cervical Vertebral fracture Lumbar Vertebral fracture Thoracic Vertebral fracture
Immune system disorders	Amyloidosis
Psychiatric disorders	Depression

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

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

12.1.1.3 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound. Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (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.

In addition, events that are considered as Adverse Events of Interest for CZP include:

- Serious infections including opportunistic infections
- Malignancies including lymphoma
- Congestive heart failure
- Demyelinating-like disorders
- Aplastic anaemia, pancytopenia, thrombocytopenia, neutropenia and leucopenia

- Serious bleeding events
- Lupus and lupus-like illness
- Serious skin reactions (e.g. Stevens Johnson syndrome, toxic epidermal necrolysis, and erythema multiforme)

12.1.1.4 Adverse events for special monitoring

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

Adverse events for special monitoring for this study include: infections (serious, opportunistic, fungal, and TB, see Section 12.7.5), neutropenia, hypersensitivity, suicidal ideation and behavior (assessed using the C-SSRS), depression, (assessed using the HADS, see Section 9.10), major cardiovascular events, liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.6.1), malignancies, and inflammatory bowel diseases (with gastroenterology referral as appropriate).

12.1.2 Procedures for reporting and recording adverse events

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

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

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

12.1.2.1 Description of adverse events

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

When recording the intensity of an AE in the eCRF (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 consequency

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

12.1.2.2 Rule for repetition of an adverse event

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

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

12.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site (see contact information for SAE reporting listed in the Serious Adverse Event 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 safety database.

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

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

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

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

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

12.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest; further details regarding follow up of PDILI events is provided in Section 12.6.1.4.

If an AE is ongoing at the end of the study for a subject, follow up should be provided until resolution/stable level of sequelae is achieved, or until the Investigator no longer deems that it is

clinically significant, or until the subject is lost to follow up. If no follow up is provided, the Investigator must provide a justification. The follow up will usually be continued for 20 weeks after the subject has discontinued his/her IMP.

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

12.2 Pregnancy

If an Investigator is notified that a subject has become pregnant after the first intake of any IMP, the Investigator must immediately 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 an early discontinuation visit.
- The subject should immediately stop the intake of the IMP
- A Safety Follow-Up Visit should be scheduled 20 weeks after the subject has discontinued his/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 PS department is the primary contact for any questions related to the data collection for the pregnancy, eventual birth, and follow up.

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/Contract Research Organization (CRO) contract monitor for the study. The Investigator will complete the 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, abortion (elective 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.

12.3 Suspected transmission of an infectious agent

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

12.4 Overdose of investigational medicinal product

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

12.5 Safety signal detection

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

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

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

In addition, an independent DMC will periodically review and monitor the safety data from this study and advise UCB. The DMC membership includes clinicians knowledgeable about the disease or the treatment. All members have experience and expertise in clinical trials. Board members may not participate in the study as principal or co-Investigators, or as study subject care physicians. The duration of membership for the DMC will be inclusive of planned analyses for AS0013. The DMC may also be asked to provide a review of final study results, as deemed appropriate. The DMC procedures will ensure that data remain blind to the study team and Investigators at all times throughout the conduct of the study. The detailed role, scope, responsibilities, and complete procedures, as well as the identity of the DMC members, will be described in a separate charter document. A Cardiovascular and a Neuropsychiatric Adjudication Committee will be in place for this study. Specific procedures will be outlined in the charter, which will be developed by the committee members.

12.6 Laboratory measurements

Clinical laboratory assessments consist of serum chemistry, hematology, and urinalysis, and pregnancy tests (serum or urine) (Table 12–2). A centralized laboratory will be used to supply all laboratory test supplies and analyze all blood and urine samples for hematology, biochemistry and urinalysis measurements. Any unscheduled laboratory testing should also be collected using

the central laboratory. Testing to rule out hepatitis B, hepatitis C, and HIV (see Exclusion Criterion #12, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12–2.

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

The following laboratory parameters will be measured:

Table 12–2: Laboratory measurements

Hematology	Chemistry	Urinalysis	Serology
Basophils	Bicarbonate	Albumin	HIV
Eosinophils	Calcium	Bacteria	HLA-B27
Lymphocytes	Chloride	Crystals	Hepatitis B
Atypical lymphocytes	hs-CRP[a]	Glucose	Hepatitis C
Monocytes	Magnesium	pH	
Neutrophils	Potassium	RBC	
Hematocrit	Sodium	WBC	
Hemoglobin	Glucose	Urine dipstick for pregnancy testing[b]	
MCH	BUN		
MCHC	Creatinine		
MCV	AST		
Platelet count	ALT		
RBC count	ALP		
WBC count	GGT		
	Total bilirubin[c]		
	LDH		
	Uric acid		
	Total cholesterol		
	Serum FSH testing[d]		
	Serum pregnancy testing[b]		

Table 12–2: Laboratory measurements

Hematology	Chemistry	Urinalysis	Serology

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma glutamyltransferase; HIV=human immunodeficiency virus; HLA-B27=human leukocyte antigen B27; hs-CRP=high sensitivity C-reactive protein; IMP=investigational medicinal product; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; ULN=upper limit of normal; WBC=white blood cell

[a] hs-CRP will be tested at specified visits per Table 5–1.

[b] A serum pregnancy test will be conducted at Screening – all other pregnancy tests will be performed on urine. Pregnancy results must be negative prior to administering IMP.

[c] If total bilirubin is >ULN, a direct bilirubin estimation (%) will be performed.

[d] A serum FSH test will be performed at Screening for all female subjects whose last menstrual cycle occurred between 12 and 24 months prior to the Screening Visit.

12.6.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 12.1.1.3), and, if applicable, also reported as an SAE (see Section 12.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12–4 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.6.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 12.6.1.4).

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

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

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

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

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

Table 12–3 summarizes the approach to investigate PDILI.

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate IMP discontinuation[d].	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.6.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[e]
≥3xULN	NA	Yes				
≥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.			Monitoring of liver chemistry values at least twice per week for 2 weeks.[e] • Immediate IMP

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 (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 12.6.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥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 12.6.1.3).	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].

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

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

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

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

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

[c] Details provided in Section 12.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Details are provided in Section 12.6.1.2.1.

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

12.6.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 12.6.1.3) and SAE report (if applicable).

12.6.1.2 Immediate action: Determination of IMP discontinuation

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

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

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

12.6.1.2.1 IMP restart/rechallenge

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

12.6.1.3 Testing: Identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are included but not limited to those listed in Table 12–4 (laboratory measurements) and Table 12–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

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

The following measurements are to be assessed:

Table 12–4: PDILI laboratory measurements

Virology-related	Hepatitis A IgM antibody
	HBsAg
	Hepatitis E IgM antibody
	HBcAb-IgM
	Hepatitis C RNA

Table 12–4: PDILI laboratory measurements

	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
Chemistry	Amylase
	Sodium, potassium, chloride, glucose, BUN, creatinine
	Total bilirubin, ALP, AST, ALT, GGT, total cholesterol, albumin
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[a]
	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] Measured only for subjects with ALT >8xULN, elevations in total bilirubin, and symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia (>5%), rash, and fever (without clear alternative cause).

The following additional information is to be collected:

Table 12–5: PDILI information to be collected

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

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

12.6.1.4 Follow-up evaluation

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

12.7 Other safety measurements

12.7.1 Vital signs

The Investigator or designee should measure all vital signs (systolic and diastolic 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 Baseline/Day 1, pulse and BP should be collected prior to IMP administration and then at 30 minutes and 1 hour after dosing. At all other visits pulse and BP should be collected prior to IMP administration.

12.7.2 Body weight and height

Height is collected at the Screening Visit only. Body weight will be measured by the Investigator or designee at the time points listed in Table 5–1. The Investigator or designee will measure the height of the subject with shoes removed in meters and the weight of the subject in kilograms. The same scale should be utilized throughout the study where possible.

12.7.3 Physical examination

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

12.7.4 12-lead electrocardiogram

The Investigator or designee will perform the ECG at time points specified in Table 5–1. The ECGs will be read locally. The RR, PR, QRS, QT, and QT intervals corrected for heart rate using Fridericia's formula (QTcF) including changes from Baseline ECG variables will be evaluated.

12.7.5 Tuberculosis and TB risk factor assessment and management

All subjects will be assessed for TB at the Screening Visit and at the time points specified in Table 5–1 through physical examination for signs and symptoms of TB, chest X-ray or CT (Section 12.7.5.2), laboratory testing (Section 12.7.5.1), and subject questionnaire (Section 12.7.5.3).

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

Exclusion Criteria at Screening

Subjects with known TB infection, at high risk of acquiring TB infection, with LTBI, or current or history of NTMB infection.

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

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

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

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

c. Latent TB infection is defined as:

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

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

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

Signs and Symptoms

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

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

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

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

Test Conversion

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

Latent TB

In case the evaluation by the appropriate specialist indicates a new LTBI during the study, a prophylactic TB treatment should be initiated and 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 WD Visit, complete all WD Visit assessments, and complete a SFU Visit (20 weeks after the final 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 WD Visit must be scheduled as soon as possible, but no later than the next scheduled visit. The subject should be encouraged to keep the SFU Visit as specified by the protocol. Treatment should be started immediately.

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

12.7.5.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB test is recommended) will be performed at Screening and should be repeated at 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. The retest during Screening must be done during the protocol-defined Screening window.

12.7.5.2 Chest X-ray for tuberculosis

A plain posteroanterior chest X-ray must be performed during the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The chest X-ray (or, if done, Computed Axial Tomography of the Chest) must be clear of signs of TB infection (previous or current) before first IMP administration. All chest imaging (particularly X-rays) should be available for review by the Investigator before randomization of the subject. The chest X-ray should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential lung TB infection (eg, exposure). Radiographic findings suggestive of

inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

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

12.7.5.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed at the Screening Visit, Weeks 12, 24, and 36, and the SFU Visit. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question "Has the subject been in close contact with an individual with active TB, or an individual who has recently been treated for TB?" at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has LTB or active TB (see Exclusion Criterion #13, Section 6.2). A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection.

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

12.7.5.4 Tuberculosis management

LTB infection and active TB identified during study

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

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 WD Visit as soon as possible but no later than the next scheduled study visit and complete all WD Visit assessments.

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

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

12.7.6 Pregnancy testing

A serum human chorionic gonadotropin (hCG) pregnancy test for all women of childbearing potential will be performed at the Screening Visit. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles and women during menopause. Natural menopause is recognized to have occurred after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause (International Menopause Society, 2015).

Pregnancy testing will performed on urine at all other visits. Pregnancy test results (serum and urine) must be negative prior to administering IMP.

12.7.7 Assessment of suicidal ideation and behavior

Suicidal ideation and behavior will be assessed by trained study personnel using the C-SSRS. This scale will be used to assess suicidal ideation and behavior that may occur during the study. The visits at which the C-SSRS assessments will be performed are specified in the schedule of study assessments (Table 5–1).

The C-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 C-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS takes approximately 3 to 10 minutes to complete.

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

13 OTHER STUDY MEASUREMENTS

13.1 Demographic and Baseline characteristics

The Investigator or designee will collect demographic information for all subjects according to local rules and regulations. This will include age, gender, race, and ethnicity. Information will also be collected on Baseline characteristics for subjects including lifestyle, child bearing potential, as applicable, height, weight, and body mass index (BMI). Demographic and baseline characteristics information will be recorded in the eCRF.

13.2 Medical history

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

13.3 Ankylosing spondylitis history

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

13.4 Prior and concomitant medications

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

14 STUDY MANAGEMENT AND ADMINISTRATION

14.1 Adherence to protocol

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

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

14.2 Monitoring

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

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 eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

14.2.1 Definition of source data

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

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

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.

14.2.2 Source data verification

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

14.3 Data handling

14.3.1 Case Report Form completion

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

Any change or correction to the eCRF after saving must be accompanied by a reason for the change.

Corrections made after the Investigator's review and approval (by means of a password/electronic signature) will be reapproved by the Investigator.

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

Serious AE reporting will be done using the SAE Report Form (see Section 12.1.2.3) 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.

Detailed instructions will be provided in the eCRF Completion Guidelines.

14.3.2 Database entry and reconciliation

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

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

14.3.3 Subject Screening and Enrollment log/Subject Identification Code list

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

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

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

14.4 Termination of the study

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

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

14.5 Archiving and data retention

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

14.6 Audit and inspection

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

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

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

14.7 Good Clinical Practice

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

15 STATISTICS

A description of statistical methods follows and will be described in more detail in the SAP. Deviations from the original SAP will be documented in the clinical study report (CSR).

15.1 Definition of analysis sets

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

The Randomized Set (RS) will consist of all randomized subjects.

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

The Full Analysis Set (FAS) will consist of all randomized subjects who receive at least 1 dose of the IMP and have a valid measurement of the primary efficacy variable at Baseline and at least 1 post-baseline efficacy assessment.

The Per-Protocol Set (PPS) will consist of all subjects in the FAS who have no important protocol deviation affecting the primary efficacy variable. The subjects with important protocol deviations will be predefined and evaluated during a data evaluation meeting prior to unblinding of the data.

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized subjects who receive at least 1 dose of the IMP and have at least 1 quantifiable post-dose plasma concentration.

The PET Per-Protocol Set (PET-PPS) will consist of all randomized subjects who receive at least 1 dose of the IMP and have evaluable PET-CT or PET-MRI scan data at Baseline and at at least 1 of the post-Baseline assessments.

Further details of each analysis set along with specifications of analyses by analysis set will be provided in the SAP.

15.2 General statistical considerations

Statistical evaluation will be performed by PAREXEL and supervised by the Exploratory Statistics and Global Statistical Sciences Departments of UCB.

All analyses will be performed using SAS® Version 9.2 or later (SAS Institute, Cary, NC, USA) or R Version 2.10.1 (R Development Core Team) or later, or OpenBUGS Version 3.0.6 or later.

Descriptive statistics will be used to provide an overview of the Baseline, efficacy and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented by treatment group. The denominator for the percentages will be based on the number of subjects appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be expressed to 1 decimal place. For continuous parameters, descriptive statistics will include n, mean, standard deviation (SD), median, minimum, and maximum. Two-

sided 95% confidence intervals, geometric means, and coefficient of variation (CV) will be presented for selected variables as appropriate.

Baseline for each assessment is defined as either the value obtained at Baseline (Visit 2) or the last available value obtained prior to treatment administration at the Screening Visit (Visit 1) (details to be specified in the SAP).

Formal statistical testing will be conducted for this study for the primary efficacy variable. Other efficacy variables will be summarized descriptively by treatment group. Additional exploratory analyses will be conducted as deemed appropriate.

15.3 Subject disposition

The number of subjects who were screened, subjects included in each analysis set, and subjects who completed/prematurely discontinued the study, as well as the primary reason for discontinuation, will be presented by treatment group, and overall using frequency counts and percentages.

15.4 Subject characteristics

The following subject characteristics will summarized and listed as appropriate:

- Demographics (including gender, age, race, and ethnicity)
- Baseline characteristics (including lifestyle, childbearing potential, height, weight, and BMI)
- Medical/procedure history
- Prior and concomitant medications/medical procedures
- Baseline disease characteristics

15.5 Planned efficacy analyses

The primary efficacy analyses will be based on the PPS.

15.5.1 Analysis of the primary efficacy variable

The primary efficacy analysis will be the comparison of the change from Baseline in ASDAS at Week 12 in the bimekizumab treatment group versus the CZP treatment group. Summary statistics will be presented by treatment group for ASDAS at each time point together with the changes from Baseline.

The statistical analysis of the primary efficacy variable will be conducted following a Bayesian paradigm. An informative prior will be used for the model intercept coefficient which in the primary model is equal to the mean change from Baseline in ASDAS in the CZP group when centered Baseline is observed at its mean of zero (βCZP ~ Normal [-1.78, var=0.0605]). Vague priors will be used for all other model coefficients. All priors will be fully documented in the SAP and in the interim analysis SAP.

The Bayesian analysis will employ a linear regression model including treatment group and Baseline ASDAS (mean centered).

The posterior distributions of the mean changes from Baseline in ASDAS in the CZP and bimekizumab groups and of the difference in mean changes from Baseline between the treatment

groups (CZP - bimekizumab) will be summarized with means, standard deviations, 95% credible intervals and 95% Highest Posterior Density intervals. The posterior probability that the difference between treatment groups in the mean change from Baseline in ASDAS is greater than zero will also be presented. The posterior probability that bimekizumab achieves a lower ASDAS score at Week 12 compared to CZP will be derived from this distribution.

The study will be considered a success if the posterior probability of the difference in the mean change from Baseline in ASDAS between the CZP and bimekizumab treatment groups (CZP - bimekizumab) being greater than zero is at least 97.5% (ie, the lower bound of the 95% credible interval of the difference between treatment groups in the mean change from Baseline in ASDAS is zero or greater).

If further information (independent to this study) regarding the CZP treatment group response comes to light subsequent to writing this protocol then this prior may be updated prior to study unblinding, and details of this will be supplied in the SAP and the CSR. Note that the prior will not be updated based upon accrued study data at any time point.

15.5.2 Supportive analysis of the primary efficacy variable

A sensitivity analysis on the choice of the prior distribution for the CZP treatment arm will be conducted by repeating the primary analysis assuming vague priors for all parameters of the model.

Additional sensitivity analyses will assess the primary efficacy for alternative analysis sets.

Further analyses may be performed for the primary efficacy variable adjusting for other Baseline covariates (to be defined in the SAP). Results from any additional analyses will not be used as a substitute for the planned analyses, but may be used as supplemental information for the CSR.

15.5.3 Analysis of the secondary efficacy variables

The secondary efficacy variables are listed in Section 4.1.2.

All secondary efficacy variables will be summarized descriptively by treatment group and time point. Estimated effects relating to the categorical variables ASDAS-MI and ASDAS-ID will be derived from the primary Bayesian analysis. Further details of the analysis methods for secondary efficacy variables will be included in the SAP.

15.5.4 Analysis of the other efficacy variables

The other efficacy variables are listed in Section 4.1.3.

The other efficacy variables will be listed and summarized descriptively by treatment group and time point. Any formal statistical analyses of the other efficacy variables will be described in more detail in the SAP.

Details of the summaries and analyses of efficacy data assessed during the Treatment Extension Period, will be provided in the SAP.

15.6 Pharmacokinetic analyses

Bimekizumab and CZP trough plasma concentrations will be listed and summarized by treatment group at each time point for all subjects in the PK-PPS using descriptive statistics.

15.7 Immunological analyses

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

Anti-bimekizumab and anti-CZP antibody data will be summarized at each scheduled visit, and the rate of ADA positive subjects for each treatment group will be calculated and presented.

15.8 Planned safety and other analyses

15.8.1 Safety analyses

All safety variables will be analyzed for all subjects in the SS.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®, version 19.0). The incidence of treatment-emergent adverse events (TEAEs) will be summarized descriptively by MedDRA system organ class, preferred term, and treatment group. Additional tables will summarize TEAEs by intensity and relationship to IMP, TEAEs leading to withdrawal from the study, serious TEAEs, and deaths. All AE information will be listed.

Laboratory values, ECGs, vital signs, physical examination, and extent of exposure will be presented descriptively by treatment group. The C-SSRS data will be listed only.

15.9 Handling of protocol deviations

After all data have been verified/coded/entered into a database, a data review will be performed. The purpose of this review will be to check all protocol deviations, define the PPS, and check the quality of the data. The review will also help decide how to manage problems in the subjects' data (eg, missing values, withdrawals, dropouts, and protocol deviations).

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the Study Master File. After the pre-analysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

15.10 Handling of dropouts or missing data

Appropriate missing data imputation methods will be used according to the variable being analyzed. Details will be included in the SAP.

15.11 Planned interim analysis and data monitoring

This study will include 3 informal unblinded interim analyses; the first after approximately 45 subjects have completed 4 weeks of the study, the second when the last randomized subject not participating in the PET-MRI or PET-CT substudy has completed the Week 12 Visit at the end of the Treatment Period or has withdrawn prematurely from the study, and the third when the last randomized subject has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely.

The purpose of these interim analyses is for Sponsor key personnel to review results from the primary efficacy analysis and a subset of the analyses of secondary efficacy and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions; consequently, none of the interim analyses will lead to any formal decision to alter or terminate the study.

Interim analyses will be conducted by an unblinded study team and will follow internal SOPs for the formal process to control the unblinding of the study for interim analysis purposes. This process will ensure that no unnecessary or unintentional unblinding occurs. The unblinded team

will not disclose any unblinded information to the blinded study team and the storage of all unblinded documentation will be held securely and separately from the rest of the study documentation and outputs up until the end of the study.

All analyses and unblinding instructions will be prespecified in the interim SAP.

15.12 Determination of sample size

A sufficient number of subjects will be enrolled in order to ensure at least 60 subjects are available at Week 12 to compare the change from Baseline in ASDAS between bimekizumab and CZP and at least 25 subjects will be enrolled into the PET-CT/MRI substudy.

Subjects will be randomized in a 2:1 ratio to receive bimekizumab or CZP respectively.

The sample size was calculated to provide at least 80% power to detect a difference between treatment groups in the mean change from Baseline in ASDAS at Week 12 of 0.89 (group mean change from Baseline for CZP and bimekizumab being -1.78 and -2.67 respectively) with a common standard deviation of 1.17 using frequentist methods for the comparison of the treatment group mean change from Baseline in ASDAS at Week 12 with Baseline ASDAS as a covariate (Overall and Starbuck, 1979). The correlation between Baseline and Week 12 raw ASDAS was assumed to be 0.35. Note that the informative prior for the model intercept to be used in the Bayesian modelling of the primary efficacy variable, given by βCZP ~ Normal (-1.78,var=0.0605), contributes an effective sample size of approximately 20 CZP subjects. A prior data conflict test will be performed and a vague prior will be used for the model intercept coefficient if this test indicates prior data conflict.

16 ETHICS AND REGULATORY REQUIREMENTS

16.1 Informed consent

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

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

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

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

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

Separate ICFs will be required for subjects participating in the pharmacogenetic and pharmacogenomic substudy and in the PET-MRI or PET-CT substudy conducted at selected sites.

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

16.2 Subject identification cards

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

16.3 Institutional Review Boards and Independent Ethics Committees

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

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent form, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

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

UCB (or its representative) will communicate safety information to the appropriate regulatory authorities and all active Investigators in accordance with applicable regulatory requirements.

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

16.4 Subject privacy

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

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

16.5 Protocol amendments

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

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

17 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

18 REFERENCES

Brandt J, Haibel H, Cornely D, Golder W, Gonzalez J, Reddig J, et al. Successful treatment of active ankylosing spondylitis with the anti–tumor necrosis factor α monoclonal antibody infliximab. Arthritis Rheum. 2000;43:1346-52.

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

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

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

Braun J, van der Heijde D. Imaging and scoring in ankylosing spondylitis. Best Pract Res Clin Rheumatol. 2002;16:573-604.

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.

Chabaud M, Lubberts E, Joosten L, van den Berg W, Miossec P. IL-17 derived from juxta-articular bone and synovium contributes to joint degradation in rheumatoid arthritis. Arthritis Res. 2001;3:168–77.

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

CPMP/EWP/556/95. Guideline on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis. Mar 2015.

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.

Davis JC, Mease PJ. Insights into the pathology and treatment of spondyloarthritis: from the bench to the clinic. Semin Arthritis Rheum. 2008;38(2):83-100.

Even-Sapir E, Mishani E, Flusser G, Metser U: 18F-Fluoride positron emission tomography and positron emission tomography/computed tomography. Semin Nucl Med. 2007;37:462–9.

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

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

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

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.

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

Landewé R, Braun J, Deodhar A, Dougados M, Maksymowych WP, Mease PJ, et al. Efficacy of certolizumab pegol on signs and symptoms of axial spondyloarthritis including ankylosing

spondylitis: 24-week results of a double-blind randomised placebo-controlled Phase 3 study. Ann Rheum Dis. 2014;73:39-47.

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.

Lories RJU, Luyten FP, de Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. Arthritis Res Ther. 2009;11:221.

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.

Mease PJ, Fleischmann R, Wollenhaupt J, Deodhar A, Gladman D, Hoepken B, et al. Long-term safety and efficacy of certolizumab pegol in patients with psoriatic arthritis with and without prior anti-tumor necrosis factor exposure: 96-week outcomes from the RAPID-PsA trial. Presented at the European League Against Rheumatism (EULAR) 2014 Congress. Abstract #OP0077.

Miossec P. Update on interleukin-17: a role in the pathogenesis of inflammatory arthritis and implication for clinical practice. RMD Open. 2017;3(1):e000284).

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.

Nam, JM. A simple approximation for calculating sample sizes for detecting linear trend in proportions. Biometrics. 1987;43(3):701-5.

National Research Council Panel on Handling Missing Data in Clinical Trials. The prevention and treatment of missing data in clinical trials. Washington DC: National Academies Press. 2010. Ogdie A, Weiss P. The Epidemiology of Psoriatic Arthritis. Rheum Dis Clin North Am. 2015;41(4):545-68.

Ono T, Okamoto K, Nakashima T, Nitta T, Hori S, Iwakura Y, et al. IL-17-producing γδ T cells enhance bone regeneration. Nat Commun. 2016;11;7:10928.

Osta B, Lavocat F, Eljaafari A, et al. Effects of interleukin-17A on osteogenic differentiation of isolated human mesenchymal stem cells. Front Immunol. 2014;5:425.

Overall J, Starbuck R. Sample size estimation for randomized pre-post designs. Journal of Psychiatric Research. 1979;15(1):51-5.

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.

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

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

Ramiro S, van der Heijde D, van Tubergen A, Stolwijk C, Dougados M, van den Bosch F, et al. Higher disease activity leads to more structural damage in the spine in ankylosing spondylitis: 12-year longitudinal data from the OASIS cohort. Ann Rheum Dis. 2014;73:1455-61.

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

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

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

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

Shah et al. unpublished data/abstract submitted European League Against Rheumatism; 14–17 June 2017.

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.

Sieper J, Kivitz A, van Tubergen A, Deodhar A, Coteur G, Woltering F, et al. Rapid improvements in patient-reported outcomes with certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis: 24-Week results of RAPID-axSpA trial. European League Against Rheumatism (EULAR) 2013b, Congress 2013; Abstract # THU0360.

Sieper J, Rudwaleit M, van der Heijde D. Long-term safety and efficacy of certolizumab pegol in patients with axial spondyloarthritis, including ankylosing spondylitis and non-radiographic axial spondyloarthritis: 96-week outcomes of the RAPID-axSpA trial. Presented at the European League Against Rheumatism (EULAR) 2014 Congress. Abstract #SAT0351.

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

Strobel K, Fischer DR, Tamborrini G, Kyburz D, Stumpe KD, Hesselmann RG, Johayem A, von Schulthess GK, Michel BA, Ciurea A. 18F-fluoride PET/CT for detection of sacroiliitis in ankylosing spondylitis. Eur J Nucl Med Mol Imaging. 2010; 37:1760–65.

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

van der Heijde D, Landewe R, Baraliakos X, Houben H, van Tubergen A, Williamson P, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum. 2008;58:3063-70.

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 Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27:361-68.

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.

Wein MN, Jones DC, Shim JH, et al. Control of bone resorption in mice by Schnurri-3. Proc Natl Acad Sci. 2012;109:8173–8.

19 APPENDICES

19.1 Modified New York (mNY) Classification Criteria for AS

Table 19–1: Modified New York (mNY) Classification Criteria for AS

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

AS=ankylosing spondylitis; mNY=modified New York Criteria

Note: A second grading of "probably ankylosing spondylitis" is part of the modified NY criteria, but it is not applicable for this study. It is included here for completeness. The grading will be probable ankylosing spondylitis if 3 clinical criteria are present and the radiologic criterion is present without any signs or symptoms satisfying the clinical criteria (other causes of sacroiliitis should be considered).

19.2 Markedly abnormal laboratory values

Table 19–2: 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
Data source: modified from Appendix Rheumatology Common Toxicity Criteria v.2.0 presented in Woodworth et al, 2007
[a] Withdrawal criteria for neutrophils is <0.5 (Section 6.3)

Table 19–3: Definitions of markedly abnormal biochemistry values

Parameter (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

19.3 Protocol Amendment 1

Rationale for the amendment

The purpose of this protocol amendment is the following:

- Sections summarizing the use of concomitant DMARDs have been updated for internal consistency.
- hs-CRP was added to the assessments at Screening.

In addition, minor clarifications were made and typographical errors were corrected.

Modifications and changes

Global changes

No global changes have been made.

Specific changes

Change #1

Section 1, Summary, paragraph 8

- Bimekizumab 160mg sc Q2W from Week 0 through Week 10. In addition, subjects will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 3) in order to maintain the blind vs the certolizumab pegol (CZP) loading dose at these visits.

Has been changed to:

- Bimekizumab 160mg sc Q2W from Week 0 through Week 10. In addition, subjects will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit **4**) in order to maintain the blind vs the certolizumab pegol (CZP) loading dose at these visits.

Change #2

Table 5-1, Schedule of assessments, Screening

Study Period	SCr	Treatment Period							Treatment Extension Period									SFU[a]
Visit[b]/Week (Visit window ±3 days)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Procedures	SV	BL W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 / WD	W64
Blood sample for hs-CRP[k]		X		X		X		X	X	X	X	X	X	X	X	X	X	X

Has been changed to:

Study Period	SCr	Treatment Period							Treatment Extension Period									SFU[a]
Visit[b]/Week (Visit window ±3 days)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17	V18
Procedures	SV	BL W0	W2	W4	W6	W8	W10	W12	W16	W20	W24	W28	W32	W36	W40	W44	W48 / WD	W64
Blood sample for hs-CRP[k]	**X**	X		X		X		X	X	X	X	X	X	X	X	X	X	X

Change #3

Table 5-1, Schedule of assessments, footnote g

[g] The physical examination includes the evaluation of signs and symptoms of active TB, risk for exposure to TB, height (Screening only) and weight (Baseline, Week 12 and Week 48/WD only).

Has been changed to:

[g] The physical examination includes the evaluation of signs and symptoms of active TB, risk for exposure to TB, height (Screening only) and weight (**Screening**, Week 12 and Week 48/WD only).

Change #4

Section 7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

Subjects may use NSAIDs under the following conditions:

- Subjects who are already receiving an established NSAID regimen and have been on a stable dose for at least 2 weeks prior to Baseline may continue their use during the study. However, initiation of, or increase in dosage of NSAIDs during the study (especially in subjects with a history of GI intolerance to NSAIDs or a history of GI ulceration) should be done with caution and must not occur until after the Week 12 Visit.

Subjects may use corticosteroids under the following conditions:

- Oral (maximum allowed ≤10mg daily total prednisone equivalent)—subjects are permitted to decrease their oral corticosteroid therapy dose equivalent and/or alter their regimen only after Week 12

Subjects may use sulfasalazine and/or hydroxychloroquine under the following conditions:

- Sulfasalazine (maximum SSZ ≤3g daily) and/or hydroxychloroquine (≤400mg daily) are allowed. No change in dose or dose regimen is allowed during the study except for reasons of intolerance, where the DMARD dose may be reduced or discontinued.

Subjects may use MTX under the following conditions:

- No change in dose or dose regimen of MTX is allowed during the study except for reasons of intolerance/AEs. No increase of the MTX dose is permitted. No change is permitted in the route of administration for MTX (intramuscular [im], sc, or oral). It is strongly recommended that subjects taking MTX are also taking folic acid supplements. No combinations of DMARDs are permitted during the study.

Has been changed to:

The following concomitant medications are permitted during the study:

Subjects may use NSAIDs under the following conditions:

- Subjects who are already receiving an established NSAID regimen and have been on a stable dose for at least 2 weeks prior to Baseline may continue their use during the study. However, initiation of, or increase in dosage of NSAIDs during the study (especially in subjects with a history of GI intolerance to NSAIDs or a history of GI ulceration) should be done with caution and must not occur until after the Week 12 Visit.

Subjects may use corticosteroids under the following conditions:

- Oral (maximum allowed ≤10mg daily total prednisone equivalent)—subjects are permitted to decrease their oral corticosteroid therapy dose equivalent and/or alter their regimen only after Week 12

Subjects may use MTX, sulfasalazine (SSZ), or hydroxychloroquine (HCQ) under the following conditions:

- No change in dose or dose regimen of these agents is allowed during the study except for reasons of intolerance/AEs. No increase of the dose is permitted. No change is permitted in the route of administration for MTX (intramuscular [im], sc, or oral). It is strongly recommended that subjects taking MTX are also taking folic acid supplements. No combinations of DMARDs are permitted during the study.

Change #5

Table 7-2, Prohibited or restricted medications and required wash-out periods prior to Baseline (MTX, SSZ, and HCQ)

Drug class	Dose	Exclusion criteria
…		
MTX	Any dose regimen	Use within 12 weeks prior to the Baseline Visit
SSZ	Any dose	Use within 12 weeks prior to the Baseline Visit
HCQ	Any dose	Use within 12 weeks prior to the Baseline Visit
…		

ADA=adalimumab; COX-2=cyclooxygenase 2; CZP=certolizumab pegol; DMARD=disease modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; ia=intra-articular; im=intramuscular; iv=intravenous; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; sc=subcutaneous; SSZ=sulfasalazine; TNF=tumor necrosis factor

Has been changed to:

Drug class	Dose	Exclusion criteria
…		
~~MTX~~	~~Any dose regimen~~	~~Use within 12 weeks prior to the Baseline Visit~~
~~SSZ~~	~~Any dose~~	~~Use within 12 weeks prior to the Baseline Visit~~
MTX, SSZ, and HCQ	**Maximum allowed:** **SSZ ≤3g daily** **HCQ ≤400mg daily** **MTX ≤25mg weekly**	**Use initiated and/or any change in the dose regimen in the 28 days prior to the Baseline Visit. No change is permitted in the route of administration for MTX (im, sc, or oral) in the 28 days prior to the Baseline Visit.**
~~HCQ~~	~~Any dose~~	~~Use within 12 weeks prior to the Baseline Visit~~
…		

Drug class	Dose	Exclusion criteria

ADA=adalimumab; COX-2=cyclooxygenase 2; CZP=certolizumab pegol; DMARD=disease modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; ia=intra-articular; im=intramuscular; iv=intravenous; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; sc=subcutaneous; SSZ=sulfasalazine; TNF=tumor necrosis factor

Change #6

Section 8.1, Screening Visit (Visit 1)

The following bullet has been added:

- Collect samples for hs-CRP.

Change #7

Section 8.1, Screening Visit (Visit 1)

- Measure vital signs (temperature, pulse, and blood pressure) prior to IMP administration and then at 30 minutes and 1 hour after dosing.

Has been changed to:

- Measure vital signs (temperature, pulse, and blood pressure).

Change #8

Section 8.2, Baseline (Visit 2, Week 0)

- Measure vital signs (temperature, pulse, and blood pressure).

Has been changed to:

- Measure vital signs (temperature, pulse, and blood pressure) prior to IMP administration and then at 30 minutes and 1 hour after dosing.

Change #9

Section 12.7.5, Tuberculosis and TB risk factor assessment and management), latent TB

Latent TB

In case the evaluation by the appropriate specialist indicates a new LTBI during the study, a prophylactic TB treatment should be initiated and 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.

Has been changed to:

Latent TB

In case the evaluation by the appropriate specialist indicates a new LTBI during the study, a prophylactic TB treatment should be initiated and the subject must be withdrawn.

Change #10

Section 12.7.5.4, Tuberculosis management, LTB infection and active TB identified during study, paragraph 2

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.

Has been deleted.

19.4 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment is 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.

In the statistical analysis section of the protocol, text describing the planned analysis of the primary efficacy variable was updated, and text describing the planned interim analyses and sample size re-estimation was revised. The rationale for this is that the observed pattern of subject recruitment is not as expected at the time of study planning. Consequently, an insufficient number of subjects will have completed the Week 12 visit and be evaluable for response at the time of the first interim analysis. The risk of performing an analysis with a very small amount of data is that the estimates obtained from the analysis will be unstable and the risk of committing a Type II error will be inflated. To mitigate these risks it was decided to remove the formal futility and sample size re-estimation aspects from the first interim analysis.

In addition, it was further clarifed that PET-MRI or PET-CT scans for subjects at selected sites participating in the substudy will be performed at Screening and during the study at Week 12 and Week 48/Early Withdrawal Visit if PET positive lesions were observed in the previous scan.

Modifications and changes

Global changes

No global changes have been made.

Specific changes

Change #1

STUDY CONTACT INFORMATION

The Sponsor study physician and Clinical Trial Biostatistician have been changed:

Sponsor Study Physician

Name:	[redacted]
Address:	UCB Celltech, 208 Bath Rd, Slough, Berkshire, SL1 3WE, UK
Phone:	[redacted]
Fax:	[redacted]

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB Celltech, 208 Bath Rd, Slough, Berkshire, SL1 3WE, UK
Phone:	[redacted]
Fax:	[redacted]

Change #2

Section 5.1, Study description

A new paragraph has been added at the end of this section:

In approximately 25 subjects at selected sites, a PET-MRI or PET-CT scan will be performed at Screening and during the study at Week 12 and Week 48/Early Withdrawal Visit if PET positive lesions were observed in the previous scan.

Change #3

Section 5.1.2, Treatment Period (Week 0 to Week 12), bullet #1

Eligible subjects will be randomized in a 2:1 ratio to receive the following blinded study treatments:

- Bimekizumab 160mg sc Q2W from Week 0 through Week 10. In addition, subjects will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 3) in order to maintain the blind vs the CZP loading dose at these visits.
- CZP 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10.

Study treatments will be prepared and administered by appropriately trained unblinded site personnel.

A formal unblinded interim analysis will be conducted when approximately 45 subjects have completed the Week 4 Visit during the Treatment Period. In addition, an informal unblinded interim analysis of the primary efficacy variable is planned when the last randomized subject has completed the Week 12 Visit or the subject has discontinued prematurely from the study. Further details on the interim analyses planned for this study are included in Section 15.11 and in the interim Statistical Analysis Plan (SAP).

Has been changed to:

Eligible subjects will be randomized in a 2:1 ratio to to receive the following blinded study treatments:

- Bimekizumab 160mg sc Q2W from Week 0 through Week 10. In addition, subjects will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit **4**) in order to maintain the blind vs the CZP loading dose at these visits.

- CZP 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10.

Study treatments will be prepared and administered by appropriately trained unblinded site personnel.

Change #4

Section 5.3, Imaging evaluation, paragraph 1

In a subpopulation of AS0013, a PET-MRI or PET-CT scan of the entire spine will be performed at selected sites in approximately 25 subjects at Screening, Week 12, and at Week 48/Early Withdrawal Visit.

Has been changed to:

In a subpopulation of AS0013, a PET-MRI or PET-CT scan of the entire spine will be performed at selected sites in approximately 25 subjects at Screening, and during the study at Week 12 and Week 48/Early Withdrawal Visit if PET positive lesions were observed in the previous scan.

Change #5

Section 5.7, Schedule of assessments, Table 5-1, footnote c

A separate Informed Consent Form is required for subjects participating in the 2 sub-studies:
1) with biomarker, pharmacogenomic and nonhereditary pharmacogenomic blood-samples and
2) PET-MRI or PET-CT scans.

Has been changed to:

A separate Informed Consent Form is required for subjects participating in the 2 sub-studies:
1) with biomarker, pharmacogenetic and nonhereditary pharmacogenomic blood-samples and
2) PET-MRI or PET-CT scans.

Change #6

Section 5.7, Schedule of assessments, Table 5-1, footnote o

A PET-MRI or Pet-CT scan should be done up to 2 weeks before Baseline and within 2 weeks after the W12 and W48/WD Visit. If a subject withdraws from the study early, the PET-MRI or PET-CT scan must be repeated at the WD visit only, if the prior examination was done more than 12 weeks prior to the WD visit.

Has been changed to:

A PET-MRI or P**ET**-CT scan should be done up to 2 weeks before Baseline and within 2 weeks after the W12 and W48/WD Visit **if PET-positive lesions are observed in the previous scan**. If a subject withdraws from the study early, the PET-MRI or PET-CT scan must be repeated at the WD visit only, if the prior examination was done more than 12 weeks prior to the WD visit **and the previous PET-scan showed positive lesions**.

Change #7

Section 5.7, Table 5-1 Schedule of assessments, footnote p

CZP 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10 and 400mg Q4W from Week 12 to Week 44. Bimekizumab will be administered at a dose of 160mg sc Q2W from Week 0 through Week 10 and 320mg sc Q4W from Week 12 to Week 44. The IMP will be administered at the end of the visit after all assessments have been completed. Subjects randomized to bimekizumab will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 3).

Has been changed to:

CZP 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by CZP 200mg sc Q2W in Weeks 6 to 10 and 400mg Q4W from Week 12 to Week 44. Bimekizumab will be administered at a dose of 160mg sc Q2W from Week 0 through Week 10 and 320mg sc Q4W from Week 12 to Week 44. The IMP will be administered at the end of the visit after all assessments have been completed. Subjects randomized to bimekizumab will receive 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit **4**).

Change #8

Section 6.3, Withdrawal criteria

The following was added to the withdrawal criteria:

11. 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 judgement 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 #9

Section 7.2, Treatments to be administered, paragraph 1

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

Has been changed to:

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

Change #10

Section 7.9, Blinding, paragraph 1

Due to differences in presentation of the IMPs (bimekizumab and CZP), special precautions will be taken to ensure study blinding. Subjects randomized to bimekizumab will receive placebo at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 3) in order to maintain the blind vs the CZP loading dose at these visits.

Has been changed to:

Due to differences in presentation of the IMPs (bimekizumab and CZP), special precautions will be taken to ensure study blinding. Subjects randomized to bimekizumab will receive placebo at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit **4**) in order to maintain the blind vs the CZP loading dose at these visits.

Change #11

Section 7.9.1, Procedures for maintaining and breaking the treatment blind, last 2 paragraphs

- Any Sponsor staff and/or designee who is responsible for data analyses for the unblinded DMC and interim analysis. These individuals will be separate from the main blinded study team.
- Unblinded programming team at PAREXEL for the purpose of sending unblinded data cuts

Has been changed to:

- Any Sponsor staff and/or designee who is responsible for data analyses for the unblinded DMC and interim analyses. These individuals will be separate from the main blinded study team.
- Unblinded team at PAREXEL for the purpose of sending unblinded output for the planned interim analyses

Change #12

Section 8.8, Week 12 (Visit 8), bullet #18

- Perform a PET-MRI or PET-CT scan in approximately 25 subjects at selected sites within 2 weeks after Week 12 Visit.

Has been changed to:

- Perform a PET-MRI or PET-CT scan in approximately 25 subjects at selected sites within 2 weeks after Week 12 Visit **if PET positive lesions were observed in the previous scan**.

Change #13

Section 8.11, Week 48 (Visit 17)/Early Withdrawal Visit, bullet #21

- Perform a PET-MRI or PET-CT scan in approximately 25 subjects at selected sites within 2 weeks after the Week 48/WD Visit. At the WD Visit, the PET-MRI or PET-CT must be done only, if the previous imaging evaluation occurred more than 12 weeks ago

Has been changed to:

- Perform a PET-MRI or PET-CT scan in approximately 25 subjects at selected sites within 2 weeks after the Week 48/WD Visit **if PET positive lesions were observed in the previous scan.** At the WD Visit, the PET-MRI or PET-CT must be done only, if the previous imaging evaluation occurred more than 12 weeks ago **and if PET positive lesions were observed in the previous scan**.

Change #14

Section 9.7, PhGADA, paragraph 1

The Investigator will assess the overall status of the subject with respect to their AS signs and symptoms and functional capacity (considering both joint and skin components) using an NRS in which 0=very good, asymptomatic and no limitations of normal activities and 10=very poor, very severe symptoms which are intolerable and inability to carry out normal activities. This assessment by the Investigator should be made blind to the PGADA.

Has been changed to:

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

Change #15

Section 10, ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC/PHARMACOGENOMIC VARIABLE(S)

Has been changed to:

Section 10, ASSESSMENT OF PHARMACOKINETIC/ PHARMACODYNAMIC/PHARMACOGENOMIC/PHARMACOGENETIC VARIABLE(S)

Change #16

Section 12.6.1.3, Table 12-4 PDILI laboratory measurements

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

Has been changed to:

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

And the following was added to the list of abbreviations:

AST=aspartate aminotransferase;

Change #17

Section 15.5.1, Analysis of the primary efficacy variable

The primary efficacy analysis will be the comparison of the change from Baseline in ASDAS at Week 12 in the bimekizumab treatment group versus the CZP treatment group. Summary statistics will be presented by treatment group for ASDAS at each time point together with the changes from Baseline.

The statistical analysis of the primary efficacy variable will be conducted following a Bayesian paradigm. Informative priors will be assumed for the mean change from Baseline in ASDAS in the CZP treatment arm and for the effect of Baseline ASDAS. These will be derived from an internal UCB study (AS0001). A vague prior will be applied to the mean change from Baseline in ASDAS in the bimekizumab treatment group. All priors will be fully documented in the SAP and in the interim analysis SAP.

The Bayesian analysis will employ a linear regression model including treatment group and adjusting for Baseline ASDAS.

The posterior distributions of the mean changes from Baseline in ASDAS in the CZP and bimekizumab groups and of the difference in mean changes from Baseline between the treatment groups (CZP - bimekizumab) will be summarized with means, standard deviations, 95% credible intervals and 95% Highest Posterior Density intervals. The posterior probability that the difference between treatment groups in the mean change from Baseline in ASDAS is greater than zero will also be presented. The posterior probability that bimekizumab achieves a lower ASDAS score at Week 12 compared to CZP will be derived from this distribution.

The study will be considered a success if this posterior probability is at least 97.5% (ie, the lower bound of the 95% credible interval of the difference between treatment groups in the mean change from Baseline in ASDAS is greater than zero).

If further information (independent to this study) regarding the CZP treatment group response comes to light subsequent to writing this protocol then this prior may be updated prior to study unblinding, and details of this will be supplied in the SAP and the CSR. Note that the prior will not be updated based upon accrued study data at any time point.

Has been changed to:

The primary efficacy analysis will be the comparison of the change from Baseline in ASDAS at Week 12 in the bimekizumab treatment group versus the CZP treatment group. Summary statistics will be presented by treatment group for ASDAS at each time point together with the changes from Baseline.

The statistical analysis of the primary efficacy variable will be conducted following a Bayesian paradigm. An informative prior will be used for the model intercept coefficient which in the primary model is equal to the mean change from Baseline in ASDAS in the CZP group when centered Baseline is observed at its mean of zero ($\beta CZP \sim Normal [-1.78, var=0.0605)$). Vague priors will be used for all other model coefficients. All priors will be fully documented in the SAP and in the interim analysis SAP.

The Bayesian analysis will employ a linear regression model including treatment group and Baseline ASDAS (mean centered).

The posterior distributions of the mean changes from Baseline in ASDAS in the CZP and bimekizumab groups and of the difference in mean changes from Baseline between the treatment groups (CZP - bimekizumab) will be summarized with means, standard deviations, 95% credible intervals and 95% Highest Posterior Density intervals. The posterior probability that the difference between treatment groups in the mean change from Baseline in ASDAS is greater than zero will also be presented. The posterior probability that bimekizumab achieves a lower ASDAS score at Week 12 compared to CZP will be derived from this distribution.

The study will be considered a success if the posterior probability of the difference in the mean change from Baseline in ASDAS between the CZP and bimekizumab treatment groups (CZP - bimekizumab) being greater than zero is at least 97.5% (ie, the lower bound of the 95% credible interval of the difference between treatment groups in the mean change from Baseline in ASDAS is zero or greater).

If further information (independent to this study) regarding the CZP treatment group response comes to light subsequent to writing this protocol then this prior may be updated prior to study unblinding, and details of this will be supplied in the SAP and the CSR. Note that the prior will not be updated based upon accrued study data at any time point.

Change #18

Section 15.11, Planned interim analysis and data monitoring

A formal unblinded interim analysis will be conducted after approximately 45 subjects have completed 4 weeks of the study. During this interim analysis, the sample size assumptions will be checked and the final sample size may be modified.

The study may be stopped for futility. Futility rules and operating characteristics will be detailed in the interim SAP. The futility rule will be chosen such that the overall power of the study remains high.

An informal unblinded interim analysis will be performed when the last randomized subject for this study has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely. The purpose of this informal interim analysis is for the Sponsor key personnel to review results from the primary efficacy analysis and a subset of the analyses of secondary efficacy and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions.

All analyses and unblinding instructions will be prespecified in the interim SAP.

Has been changed to:

This study will include two unblinded interim analyses, the first after approximately 45 subjects have completed 4 weeks of the study and the second when the last randomized subject for this study has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely. The purpose of these interim analyses is for Sponsor key personnel to review results from the primary efficacy analysis and a subset of the analyses of secondary efficacy and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions; consequently, neither analysis and will lead to any formal decision to alter or terminate the trial. Interim analyses will be conducted by an unblinded study team and will follow internal SOPs for the formal process to control the unblinding of the study for interim analysis purposes. This process will ensure that no unnecessary or unintentional unblinding occurs. The unblinded team will not disclose any unblinded information to the blinded study team and the storage of all unblinded documentation will be held securely and separately from the rest of the study documentation and outputs up until the end of the study.

All analyses and unblinding instructions will be prespecified in the interim SAP.

Change #19

Section 15.12, Determination of sample size, paragraph 3

The sample size was calculated to provide at least 80% power to detect a difference between treatment groups in the mean change from Baseline in ASDAS at Week 12 of 0.89 (group means for CZP and bimekizumab change from baseline being -1.78 and -2.67 respectively) with a common standard deviation of 1.17 using frequentist methods for the comparison of group means with baseline as covariate (Overall and Starbuck, 1979). The correlation between Baseline and Week 12 raw ASDAS was assumed to be 0.35. UCB considers this sample size conservative

as the Bayesian analysis with the informative priors described in Section 15.5.1 will improve the probability of study success for an effective drug.

Has been changed to:

The sample size was calculated to provide at least 80% power to detect a difference between treatment groups in the mean change from Baseline in ASDAS at Week 12 of 0.89 (group mean change from Baseline for CZP and bimekizumab being -1.78 and -2.67 respectively) with a common standard deviation of 1.17 using frequentist methods for the comparison of the treatment group mean change from Baseline in ASDAS at Week 12 with Baseline ASDAS as a covariate (Overall and Starbuck, 1979). The correlation between Baseline and Week 12 raw ASDAS was assumed to be 0.35. Note that the informative prior for the model intercept to be used in the Bayesian modelling of the primary efficacy variable, given by βCZP ~ Normal (-1.78,var=0.0605), contributes an effective sample size of approximately 20 CZP subjects. A prior data conflict test will be performed and a vague prior will be used for the model intercept coefficient if this test indicates prior data conflict.

19.5 Protocol Amendment 3

Rationale for the amendment

The major purpose of this protocol amendment is the following:

- Secondary and other study objectives and variables have been updated to evaluate the effect of bimekizumab or CZP on changes in bone formation as an "other" exploratory variable.

  It is convention that clinical study research is divided into 2 broad areas of evaluations: 1) prospectively declared analyses and 2) hypothesis-generating or exploratory analyses. Prospectively declared evaluations are partitioned into primary analyses (where type I error is conserved) and secondary analyses that are prospectively declared in order to offer unambiguous interpretation. Owing to the novelty of PET-CT/MRI assessments within this disease indication, it is not possible to prospectively define the analyses as we are continuing to develop UCB's understanding of the specific data and endpoints yielded from the imaging software, the distribution and covariance of these endpoints and the hypothesized difference owing to treatment. As a result, the analyses of the PET-CT/MRI data in this study will primarily be descriptive and exploratory and this is now updated in the study objectives, ie, the evaluation of the effect of bimekizumab or CZP on changes in bone formation is now an other exploratory objective or variable instead of a secondary objective or variable.

- A clarification regarding the sample size is required in this protocol amendment. The planned sample size of 60 subjects provides sufficient power to detect meaningful treatment differences in the primary efficacy variable whilst also providing at least 25 subjects for the PET-CT/MRI substudy. However, due to complexities in the initiation of sites capable of performing PET-CT or PET-MRI scans, more than the planned 35 non-PET-CT/MRI substudy subjects were screened and randomized before it was possible to close enrolment at the sites not participating in the substudy. Owing to the novelty of the PET-CT/MRI outcomes within this disease area, it is considered important to ensure at least 25 evaluable subjects are included in the assessment of this exploratory objective to maximize the possibility of identifying the salient factors or variables that might differ between the treatment groups and, therefore, the total sample size is increased to at least 72 subjects. This sample size increase will not negatively impact the power to detect a difference in the primary efficacy variable at Week 12 (ie, it will remain >80%), but will ensure that the target number of subjects are included in the exploratory analysis of changes in bone formation at Week 12 and Week 48. Since the analyses of PET-CT/MRI data are exploratory and treatment effect sizes are unknown, formal power calculations were not performed. Clinical expertise does, however, indicate that a sample size of at least 25 subjects in the substudy will characterize broad differences between treatment groups.

- Objectives related to PK and immunogenicity were downgraded from "secondary" objectives to "other" objectives for consistency with the classification of the corresponding variables.

- Nonhereditary pharmacogenomic variables and pharmacogenetic variables are considered exploratory in nature and have been labelled as "other".

- A PFS as described in Section 7.1 is available for administration in addition to the vial and corresponding text has been added. The PFS use is expected to improve the subject experience.

- The section describing AEs of special monitoring have been updated to reflect the development process and to maintain consistency with other protocols.
- A third informal unblinded interim analysis when the last randomized subject has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely, has been added to facilitate additional Clinical Planning or Portfolio Management decisions.
- Study contact details have been updated.

In addition, a few minor updates including consistency changes for PDILI-related text and a few clarifications and corrections of typographical errors have been made. The occurrence of abbreviations was updated.

Modifications and changes

Global changes

The specification of the IGRA TB test has been changed from "QuantiFERON TB GOLD test" to "QuantiFERON TB test".

Specific changes

Change #1

Sponsor Study Physician

Name:	[redacted]
Address:	UCB Celltech, 208 Bath Rd, Slough, Berkshire, SL1 3WE, UK
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Name:	[redacted]
Address:	UCB Celltech, 208 Bath Rd, Slough, Berkshire, SL1 3WE, UK
Phone:	[redacted]
Fax:	[redacted]

Change #2

Section 1, Summary, paragraphs 3, 4, and 5

The primary objective of the study is to evaluate the efficacy of bimekizumab administered subcutaneously (sc) every 2 weeks (Q2W) for 12 weeks compared to CZP in the treatment of subjects with active AS. The primary efficacy variable is the change from Baseline in

Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 12. The secondary objectives of the study are to evaluate the effect of bimekizumab or CZP on changes in osteoblastic activity, to assess the safety and tolerability of bimekizumab, and to assess the pharmacokinetics (PK) and immunogenicity of bimekizumab. The secondary efficacy variables include the determination of ASDAS inactive disease (ASDAS-ID) at Week 12, ASDAS major improvement (ASDAS-MI) at Week 12, and osteoblastic activity as detected by positron-emission tomography-magnetic resonance imaging (PET-MRI) or positron-emission tomography computed tomography (PET-CT) at Week 12 and Week 48. Primary safety variables include the incidence of adverse events (AEs), serious adverse events (SAEs), and withdrawal due to AEs.

Other objectives of the study are to obtain additional biomarkers and clinical and imaging data as applicable and to assess the efficacy and safety of bimekizumab or CZP during the Treatment Extension Period.

Multiple sites in North America, Europe, and the Asian-Pacific (APAC) region will randomize approximately 60 subjects in a 2:1 ratio to receive either bimekizumab or CZP.

Has been changed to:

The primary objective of the study is to evaluate the efficacy of bimekizumab administered subcutaneously (sc) every 2 weeks (Q2W) for 12 weeks compared to CZP in the treatment of subjects with active AS. The primary efficacy variable is the change from Baseline in Ankylosing Spondylitis Disease Activity Score (ASDAS) at Week 12. The secondary objective of the study **is** to assess the safety and tolerability of bimekizumab. The secondary efficacy variables include the determination of ASDAS inactive disease (ASDAS-ID) **and** ASDAS major improvement (ASDAS-MI) at Week 12. Primary safety variables include the incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to withdrawal from **investigational medicinal product (IMP).**

Other **exploratory** objectives of the study are **to evaluate the effect of bimekizumab or CZP on changes in bone formation, to assess the pharmacokinetics (PK) and immunogenicity of bimekizumab, to** obtain additional biomarkers and clinical and imaging data as applicable, and to assess the efficacy and safety of bimekizumab or CZP during the Treatment **Period and the Treatment** Extension Period.

Multiple sites in North America, Europe, and the Asian-Pacific (APAC) region will randomize at **least 60** subjects in a 2:1 ratio to receive either bimekizumab or CZP.

Change #3

Section 3.2, Secondary objectives

The secondary objectives of the study are as follows:

- To evaluate the effect of bimekizumab or CZP on changes in osteoblastic activity
- To assess the safety and tolerability of bimekizumab
- To assess the PK and immunogenicity of bimekizumab

Has been changed to:

Section 3.2, Secondary objective

The secondary objective of the study **is** as follows:

- To assess the safety and tolerability of bimekizumab

Change #4

Section 3.3, Other objectives

The other objectives of the study are as follows:

- To assess additional biomarker, clinical, and imaging data as available
- To assess the efficacy and safety of bimekizumab or CZP during the Treatment Extension Period

Has been changed to:

Section 3.3, Other exploratory objectives

The other **exploratory** objectives of the study are as follows:

- **To evaluate the effect of bimekizumab or CZP on changes in bone formation**
- **To assess the PK and immunogenicity of bimekizumab**
- To assess additional biomarker, clinical, and imaging data as available
- To assess the efficacy and safety of bimekizumab or CZP during the Treatment Extension Period

Change #5

Section 4.1.2, Secondary efficacy variables

The secondary efficacy variables for this study are as follows:

- ASDAS-ID at Week 12
- ASDAS-MI at Week 12
- Osteoblastic activity as detected by PET-MRI or PET-CT at Week 12 and Week 48

Has been changed to:

The secondary efficacy variables for this study are as follows:

- ASDAS-ID at Week 12
- ASDAS-MI at Week 12

Change #6

Section 4.1.3, Other efficacy variables

Assessment time points for the other efficacy variables are specified in Table 5–1. Other efficacy variables are as follows:

- Change from Baseline in ASDAS
- ASAS20 response
- ASAS40 response
- Time to ASAS20 response
- Time to ASAS40 response
- ASAS partial remission
- Change from Baseline in BASDAI

Has been changed to:

Section 4.1.3, Other efficacy variables

Assessment time points for the other efficacy variables are specified in Table 5–1. **The following efficacy variables are exploratory and are assessed over the Treatment Period and Treatment Extension Period, as applicable:**

- Change from Baseline in ASDAS
- ASAS20 response
- ASAS40 response
- Time to ASAS20 response
- Time to ASAS40 response
- ASAS partial remission
- Change from Baseline in BASDAI
- **Changes in bone formation as measured by standardized uptake value by area under the curve (SUV_{AUC}) and derived from PET-MRI or PET-CT at Baseline, Week 12, and Week 48**

Change #7, Primary safety variables

The primary safety variables for this study are as follows:

- Incidence of AEs and SAEs
- Withdrawal due to AEs

Has been changed to:

The primary safety variables for this study are as follows:

- Incidence of AEs and SAEs
- **Adverse events leading to withdrawal from IMP**

Change #8, Section header

4.5 Nonhereditary pharmacogenomic variables

Has been changed to:

4.5 Other nonhereditary pharmacogenomic variables

Change #9, Section header

4.6 Pharmacogenetic variables

Has been changed to:

4.6 Other pharmacogenetic variables

Change #10

Section 5.1, Study description, paragraph 3

Approximately 60 subjects will be randomized to 1 of 2 treatment arms in a 2:1 ratio and will receive either bimekizumab or CZP up to Week 44 (final dose of IMP).

Has been changed to:

At least 60 subjects will be randomized to 1 of 2 treatment arms in a 2:1 ratio and will receive either bimekizumab or CZP up to Week 44 (final dose of IMP).

Change #11

Section 5.5, Planned number of subjects and site(s)

It is anticipated that approximately 120 subjects will be screened in order to enroll approximately 60 subjects at multiple sites.

Has been changed to:

It is anticipated that approximately 120 subjects will be screened in order to enroll **at least** 60 subjects **in the main study and at least 25 subjects in the PET-CT or PET-MRI substudy** at multiple sites.

Change #12

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:

Subjects with either of the following:

- ALT or AST ≥5ULN
- 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%).

Has been changed to:

The PDILI criteria below require immediate discontinuation of IMP:

Subjects with either of the following:

- ALT or AST ≥5ULN
- 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%).

Change #13

Section 7.1, Description of investigational medicinal product(s), paragraphs 1 and 2

The IMPs used in this study are bimekizumab and CZP.

Bimekizumab will be supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative-free solution in 2mL Type I, colorless glass vials (1.0mL extractable volume) closed with a rubber stopper and sealed with an aluminum cap overseal. Each single-use dose vial will contain 160mg/mL bimekizumab in [redacted]mM sodium acetate, [redacted]mM glycine and [redacted] (w/v) polysorbate 80 at pH[redacted].

Has been changed to:

The IMPs used in this study are bimekizumab and CZP.

Bimekizumab will be supplied **as a vial or in a pre-filled syringe (PFS) form as described below:**

- **Vial:** a clear to opalescent, colorless to slightly brown, sterile, preservative-free solution in 2mL Type I, colorless glass vials (1.0mL extractable volume) closed with a rubber stopper and sealed with an aluminum cap overseal. Each single-use dose vial will contain 160mg/mL bimekizumab in [redacted] mM sodium acetate, [redacted] mM glycine, and [redacted] (w/v) polysorbate 80 at pH [redacted]
- **PFS: 1mL PFS at a concentration of 160mg/mL [redacted] mM sodium acetate, [redacted] mM glycine, [redacted] polysorbate 80 at pH [redacted]) for sc injection.**

Change #14

Section 8.8, Week 12 (Visit 8), PET-MRI/PET-CT scan bullet

- Perform a PET-MRI or PET-CT scan in approximately 25 subjects at selected sites within 2 weeks after Week 12 Visit if PET positive lesions were observed in the previous scan.

Has been changed to:

- Perform a PET-MRI or PET-CT scan in **at least** 25 subjects at selected sites within 2 weeks after Week 12 Visit if PET-positive lesions were observed in the previous scan.

Change #15

Section 8.11, Week 48 (Visit 17), PET-MRI/PET-CT scan bullet

- Perform a PET-MRI or PET-CT scan in approximately 25 subjects at selected sites within 2 weeks after the Week 48/WD Visit if PET positive lesions were observed in the previous scan. At the WD Visit, the PET-MRI or PET-CT must be done only, if the previous imaging evaluation occurred more than 12 weeks ago and if PET positive lesions were observed in the previous scan.

Has been changed to:

- Perform a PET-MRI or PET-CT scan in **at least** 25 subjects at selected sites within 2 weeks after the Week 48/WD Visit if PET-positive lesions were observed in the previous scan. At the WD Visit, the PET-MRI or PET-CT must be done only, if the previous imaging evaluation occurred more than 12 weeks ago and if PET-positive lesions were observed in the previous scan.

Change #16

Section 9.11, PET-MRI or PET-CT scan, last paragraph

The 18F-fluoride PET-MRIs of the whole spines will be performed by using a whole-body PET/MRI system. Alternatively, subjects will be examined in supine position on a combined PET-CT system permitting the acquisition of co-registered CT and PET images in the same

session. The PET-MRI or PET-CT scan will be performed at time points provided in Table 5–1 in approximately 25 subjects at selected sites.

Has been changed to:

The 18F-fluoride PET-MRIs of the whole spine will be performed by using a whole-body PET/MRI system. Alternatively, subjects will be examined in supine position on a combined PET-CT system permitting the acquisition of co-registered CT and PET images in the same session. The PET-MRI or PET-CT scan will be performed at time points provided in Table 5–1 in **at least** 25 subjects at selected sites.

Change #17

Section 12.1.14, Adverse events for special monitoring, section header and paragraph 2

12.1.1.4 Adverse events for special monitoring

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB, see Section 12.7.5), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the C-SSRS), depression and anxiety (assessed using the HADS, see Section 9.10), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.6.1), malignancies, and inflammatory bowel diseases.

Has been changed to:

12.1.1.4 Adverse events for special monitoring

Adverse events for special monitoring for this study include: infections (**serious**, opportunistic, **fungal**, and TB, see Section 12.7.5), **neutropenia,** hypersensitivity, suicid**al** ideation **and** behavior (assessed using the C-SSRS), depression, (assessed using the HADS, see Section 9.10), major cardiovascular events, liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.6.1), malignancies, and inflammatory bowel diseases **(with gastroenterology referral as appropriate).**

Change #18

Section 12.6.1, Evaluation of PDILI, Table 12-3

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult.[b] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.6.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[b]
≥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		Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver chemistry values

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 (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 12.6.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥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 12.6.1.3).	continue to increase. After 2 weeks of monitoring liver chemistry values: • Discontinue IMP if levels remain ≥3xULN (and ≥2x baseline) without evidence of resolutiond Continue to monitor until values normalize, stabilize, or return to within baseline valuesd.

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

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

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

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

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

[c] Details provided in Section 12.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] 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:

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	≥2xULNb	NA	Hepatology consult.c Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate IMP discontinuation[d].	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.6.1.3); recommended to occur at the site	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[e]
≥3xULN	NA	Yes				

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis or hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN	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.		with HCP.	Monitoring of liver chemistry values at least twice per week for 2 weeks.e • Immediate IMP

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 (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 12.6.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥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 12.6.1.3).	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].

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

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

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

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

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

[c] Details provided in Section 12.6.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] **Details are provided in Section 12.6.1.2.1.**

[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 #19

Section 12.6.1.2, 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 12–3 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 discontinuation (see Section 6.3.1 and Table 12–3 for details).

Change #20

Section 12.6.1.3, Testing: Identification/exclusion of alternative etiology, Table 12-4, chemistry

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

Has been changed to:

Chemistry	Amylase
	Sodium, potassium, chloride, glucose, BUN, creatinine
	Total bilirubin, ALP, AST, ALT, GGT, total cholesterol, albumin
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation

Change #21

Section 15.1, Definition of analysis sets

The following analysis set has been added:

The PET Per-Protocol Set (PET-PPS) will consist of all randomized subjects who receive at least 1 dose of the IMP and have evaluable PET-CT or PET-MRI scan data at Baseline and at at least 1 of the post-Baseline assessments.

Change #22

Section 15.8.1, Safety analyses, paragraph 2

Adverse events will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA®). The incidence of treatment-emergent adverse events

(TEAEs) will be summarized descriptively by MedDRA system organ class, preferred term, and treatment group. Additional tables will summarize TEAEs by intensity and relationship to IMP, TEAEs leading to withdrawal from the study, serious TEAEs, and deaths. All AE information will be listed.

Has been changed to:

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®, **version 19.0**). The incidence of treatment-emergent adverse events (TEAEs) will be summarized descriptively by MedDRA system organ class, preferred term, and treatment group. Additional tables will summarize TEAEs by intensity and relationship to IMP, TEAEs leading to withdrawal from the study, serious TEAEs, and deaths. All AE information will be listed.

Change #23

Section 15.11, Planned interim analysis and data monitoring

This study will include two unblinded interim analyses, the first after approximately 45 subjects have completed 4 weeks of the study and the second when the last randomized subject for this study has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely. The purpose of these interim analyses is for Sponsor key personnel to review results from the primary efficacy analysis and a subset of the analyses of secondary efficacy and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions; consequently, neither analysis and will lead to any formal decision to alter or terminate the trial. Interim analyses will be conducted by an unblinded study team and will follow internal SOPs for the formal process to control the unblinding of the study for interim analysis purposes. This process will ensure that no unnecessary or unintentional unblinding occurs. The unblinded team will not disclose any unblinded information to the blinded study team and the storage of all unblinded documentation will be held securely and separately from the rest of the study documentation and outputs up until the end of the study.

All analyses and unblinding instructions will be prespecified in the interim SAP.

Has been changed to:

This study will include **3 informal** unblinded interim analyses; the first after approximately 45 subjects have completed 4 weeks of the study, the second when the last randomized subject **not participating in the PET-MRI or PET-CT substudy** has completed the Week 12 Visit at the end of the Treatment Period or **has withdrawn prematurely from the study, and the third when the last randomized subject has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely.**

The purpose of these interim analyses is for Sponsor key personnel to review results from the primary efficacy analysis and a subset of the analyses of secondary efficacy and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions; consequently, **none of the interim analyses** will lead to any formal decision to alter or terminate the **study**.

Interim analyses will be conducted by an unblinded study team and will follow internal SOPs for the formal process to control the unblinding of the study for interim analysis purposes. This process will ensure that no unnecessary or unintentional unblinding occurs. The unblinded team will not disclose any unblinded information to the blinded study team and the storage of all

unblinded documentation will be held securely and separately from the rest of the study documentation and outputs up until the end of the study.

All analyses and unblinding instructions will be prespecified in the interim SAP.

Change #24

Section 15.12, Determination of sample size, first paragraph

A sufficient number of subjects will be enrolled in order to ensure 60 subjects are available at Week 12 to compare the change from Baseline in ASDAS between bimekizumab and CZP.

Has been changed to:

A sufficient number of subjects will be enrolled in order to ensure **at least** 60 subjects are available at Week 12 to compare the change from Baseline in ASDAS between bimekizumab and CZP **and at least 25 subjects will be enrolled into the PET-CT/MRI substudy.**

20 DECLARATION AND SIGNATURE OF INVESTIGATOR

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

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

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

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

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

Investigator:

Printed name	Date/Signature

21 SPONSOR DECLARATION

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

Approval Signatures

Name: as0013-protocol-amend-3

Version: 1.0

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Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 05-Mar-2019 09:01:24 GMT+0000
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