PROTOCOL PA0010 AMENDMENT 2

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, ACTIVE REFERENCE (ADALIMUMAB) STUDY EVALUATING THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN THE TREATMENT OF SUBJECTS WITH ACTIVE PSORIATIC ARTHRITIS

PHASE 3

EudraCT Number: 2017-002322-20

IND Number: 128708

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

Protocol/Amendment number	Date	Type of amendment
Final Protocol	28 Nov 2018	Not applicable
Protocol Amendment 0.1 (Japan)	05 Feb 2019	Not applicable
Protocol Amendment 1	10 Jan 2020	Substantial
Protocol Amendment 1.1 (Japan)	04 Feb 2020	Substantial
Protocol Amendment 2	22 Feb 2021	Substantial

STUDY CONTACT INFORMATION

Sponsor

UCB Biopharma SRL

Allée de la Recherche 60

1070 Brussels

BELGIUM

Sponsor Study Physician

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

Clinical Project Manager

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

Clinical Trial Biostatistician

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

Clinical Monitoring Contract Research Organization

Name:	PAREXEL International (IRL) Limited-Ireland
Address:	Ireland Limited at 70 Sir John Rogerson’s Quay, Dublin 2, Ireland
Phone:	+353 (1) 477-3171
Fax:	+353 (1) 477-3308

SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
All serious adverse events will be reported and transmitted to Patient Safety through the eCRF system. The numbers below are to be used to send ancillary documentation only (discharge summaries, death certificates, etc) or in the event that the electronic reporting (eCRF) is not available.	
Fax	**Europe and Rest of the World:** +32-2-386-24-21 **USA and Canada:** +1-800-880-6949 or +1-866-890-3175
Email	**Global:** DS_ICT@ucb.com

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMS	Active Medication Set
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
AST	aspartate aminotransferase
ATS	Active Treatment-Blind Set
BA	bioavailability
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease modifying antirheumatic drug
BP	blood pressure
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CCP	cyclic citrullinated peptide
CD	cluster of differentiation
cDMARD	conventional disease-modifying antirheumatic drug
CDMS	clinical data management system
CI	confidence interval
COX-2	cyclooxygenase-2
CPM	Clinical Project Manager
CRO	contract research organization
CRP	C-reactive protein
CSR	Clinical Study Report
CZP	certolizumab pegol
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAS28(CRP)	Disease Activity Score-28 based on C-reactive protein
DIP	distal interphalangeal
DMARD	disease modifying antirheumatic drug
DMC	Data Monitoring Committee

ECG	electrocardiogram
eCRF	electronic Case Report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EDC	electronic data capture
ePRO	Electronic Patient-Reported Outcome
EQ-5D-3L	EuroQol-5 Dimensions-3 Level
ES	Enrolled Set
ET	Early Termination
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	gastrointestinal
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCQ	hydroxychloroquine
HCV	hepatitis C virus
HDL	high density lipoprotein
HIV	human immunodeficiency virus
HLA-B27	human leukocyte antigen B27
HRQoL	Health-Related Quality of Life
HS	hidradenitis suppurativa
hs-CRP	high sensitivity C-reactive protein
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IGRA	interferon gamma release assay
IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board

iv	intravenous
IXRS	interactive voice or web response system
LDI	Leeds Dactylitis Index
LDL	low density lipoprotein
LEF	leflunomide
LEI	Leeds Enthesitis Index
LN	natural logarithm
LS	least squares
LTB	latent tuberculosis
MAR	missing at random
MCMC	Markov-Chain Monte Carlo
MCS	Mental Component Summary
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mNAPSI	modified Nail Psoriasis Severity Index
MTX	methotrexate
NHP	nonhuman primate
NRI	nonresponder imputation
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacteria
OC	observed case
PASI	Psoriasis Area and Severity Index
PASDAS	Psoriatic Arthritis Disease Activity Score
PCS	Physical Component Summary
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PFS	prefilled syringe
PGADA	Patient’s Global Assessment of Disease Activity
PGA-Arthritis	Patient’s Global Assessment of Arthritis
PGA-PsA	Patient’s Global Assessment of Psoriatic Arthritis
PhGADA	Physician’s Global Assessment of Disease Activity

PhGA-Arthritis	Physician's Global Assessment of Arthritis
PhGA-PsA	Physician's Global Assessment of Psoriatic Arthritis
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PK-PPS	Pharmacokinetics Per-Protocol Set
PPS	Per-Protocol Set
PS	Patient Safety
PsA	psoriatic arthritis
PsAID-12	Psoriatic Arthritis Impact of Disease-12
PsARC	Psoriatic Arthritis Response Criteria
PsAQoL	Psoriatic Arthritis Quality of Life
PSO	psoriasis
PtAAP	Patient's Assessment of Arthritis Pain
Q2W	every 2 weeks
Q4W	every 4 weeks
R/L	right/left
RA	rheumatoid arthritis
RNA	ribonucleic acid
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SD	standard deviation
SF-36	Short-Form 36-item Health Survey
SFU	Safety Follow-up
SJC	swollen joint count
SOP	standard operating procedure
SPARCC	Spondyloarthritis Research Consortium of Canada
SS	Safety Set
SSZ	sulfasalazine
TB	tuberculosis
TEAE	treatment-emergent adverse event

TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
ULN	upper normal limit
VAS	Visual Analog Scale
vdHmTSS	van der Heijde modified Total Sharp Score
VLDA	Very Low Disease Activity
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire–Specific Health Problem

1 SUMMARY

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, noninferential active reference study to evaluate the efficacy and safety of bimekizumab in subjects with active psoriatic arthritis (PsA) who are biologic disease-modifying antirheumatic drug (bDMARD) naïve. To be eligible to participate in this study, subjects must be adults with a diagnosis of active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and have disease with tender joint count (TJC) ≥3 and swollen joint count (SJC) ≥3. In addition, subjects should not have been previously exposed to any bDMARD for PsA or psoriasis (PSO) to be eligible for the study.

The primary objective is to demonstrate the efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) for 16 weeks compared with placebo in the treatment of subjects with active PsA as assessed by the American College of Rheumatology (ACR) 50% response. The secondary efficacy and safety objectives of the study are listed in Section 3.2, and other objectives are listed in Section 3.3. In this study, the efficacy of bimekizumab will be assessed with reference to the active-reference drug, adalimumab (HUMIRA®; AbbVie Pharmaceuticals, North Chicago, IL); however, no formal statistical comparisons of adalimumab to bimekizumab or placebo are planned.

The primary efficacy variable for this study is the ACR50 at Week 16. The secondary and other efficacy variables are listed in Section 4.2.1 and Section 4.3.1, respectively.

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

PA0010 will evaluate the efficacy and safety of bimekizumab 160mg sc Q4W in adult subjects with active PsA. The dose regimens were selected based on currently available safety and efficacy data from a Phase 2b study, and PK/pharmacodynamics (PD) modeling.

The overall study design consists of a Screening Period (≥14 days to ≤35 days), a 16-week placebo-controlled Double-Blind Treatment Period, a 36-week Active Treatment-Blind Period, and a Safety Follow-Up (SFU) Visit 20 weeks after the final dose of investigational medicinal product (IMP) (for subjects not entering the extension study or who discontinue early, including those withdrawn from IMP). The maximum study duration per subject will be up to 73 weeks.

It is planned to enroll a minimum of 45% of subjects who are positive for elevated high sensitivity C-reactive protein (hs-CRP ≥6mg/L) and/or who have at least 1 bone erosion at Screening.

During the Double-Blind Treatment and Active Treatment-Blind Periods, permitted rescue therapy after Week 16 is described in Section 5.4. Subjects' permitted background medications may be changed if the subject is not responding as per Investigator assessment.

Subjects completing Week 52 are eligible for enrollment in an extension study where all subjects will receive bimekizumab.

Approximately 840 subjects will be randomly assigned in a 3:2:1 ratio (stratified by region and bone erosion [0, ≥1]) to the following treatment groups: bimekizumab 160mg sc Q4W (420 subjects), placebo (280 subjects), and adalimumab sc 40mg every 2 weeks (Q2W) (140 subjects). The planned number of study sites is approximately 150.

2 INTRODUCTION

2.1 Psoriatic arthritis

Psoriatic arthritis is a chronic inflammatory musculoskeletal disorder, which occurs in approximately 6% to 41% of people affected by PSO (Ogdie and Weiss, 2015). A substantial proportion of subjects have polyarthritis (McHugh et al, 2003). These disorders are distinct from rheumatoid arthritis (RA), the prototypical inflammatory arthritis, and generally have an earlier onset, distal interphalangeal (DIP) joint involvement, asymmetric distribution, dactylitis (inflammation of the whole digit), enthesitis (inflammation at the site of tendon insertion into bone), spinal involvement, and an association with the human leukocyte antigen (HLA)-B27 allele.

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

2.1.1 Psoriatic arthritis epidemiology

Psoriatic arthritis is usually diagnosed years after PSO appears. A substantial proportion of subjects have polyarthritis (Gladman 2015; McHugh et al, 2003). More than 50% of patients with PsA experience progressive, erosive arthritis that is often accompanied by pain, fatigue, and functional impairment. The combination of joint and skin manifestations of PsA can have a profound impact on patient function, well-being, and Health-Related Quality of Life (HRQoL). The functional impairments are also associated with significant direct health care costs and substantial work-related disability, including a lower rate of employment (Lee et al, 2010; Salaffi et al, 2009).

2.1.2 Current treatments for psoriatic arthritis

Disease-modifying antirheumatic drugs (DMARDs) and biological agents targeting tumor necrosis factor alpha (TNFα), IL-17, and IL-12/23 are effective for the treatment of PsA (Kavanaugh et al, 2012; Kavanaugh et al, 2009; Gottlieb et al, 2009; Gladman et al, 2007;

Genovese et al, 2007; Kavanaugh et al, 2006; Antoni et al, 2005a; Antoni et al, 2005b; Mease et al, 2005; Mease et al, 2004; McInnes et al, 2015; Mease et al, 2015). Current treatments include DMARDs (hydroxychloroquine, azathioprine, cyclosporine, cyclophosphamide, mycophenolic acid, mycophenolate mofetil, sulfasalazine [SSZ], tofacitinib, apremilast, abatacept, methotrexate [MTX], and leflunomide [LEF]), IL-17A inhibitor (secukinumab, and ixekizumab) and TNFα inhibitors (infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol [CZP]). However, some subjects are not responsive to these treatments (defined as achieving ACR20 response criteria), do not maintain a clinical response, or have contraindications or intolerance to these agents. The long-term goals of therapy include improvement in symptoms of the disease, psoriatic plaque clearance, inhibition of disease progression, and prevention of bone destruction.

2.2 Bimekizumab

Bimekizumab (UCB4940) is an engineered, humanized full-length monoclonal antibody of immunoglobin G1 (IgG1) subclass of approximately 150,000 Dalton, which is expressed in a genetically engineered Chinese Hamster Ovarian (CHO) cell line. Bimekizumab has high affinity for human IL-17A and human IL-17F, and selectively and potently inhibits the activity of both isoforms in vitro. Interleukin-17A and IL-17F are key proinflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases. Interleukin-17A has been shown to have a role in pathogenesis of several autoimmune disorders and IL-17F has been increasingly recognized to contribute to the pathogenesis of a number of inflammatory diseases, including PSO, ulcerative colitis, asthma, AS, PsA, and RA (Raychaudhuri et al, 2012; Fujishima et al, 2010; Watanabe et al, 2009).

While anti-IL-17A antibodies have demonstrated efficacy in subjects with PSO, PsA, and AS, there is currently no therapeutic approach available that fully inhibits the activity of IL-17F. Bimekizumab selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro. Therefore, it permits an evaluation of the potential for additional efficacy, which may be conferred by dual inhibition of both cytokines in patients with diseases in which both cytokines are active. Furthermore, a proof-of-concept study (PA0007) with bimekizumab in subjects with moderate to severe PsA demonstrated a strong efficacy signal that warrants further exploration of bimekizumab in this indication. A Phase 2b, dose-ranging study (PA0008) was designed to investigate the efficacy and safety of various bimekizumab dose regimens in subjects with active PsA. The current Phase 3, randomized, double-blind, placebo-controlled, and active-controlled confirmatory study (PA0010) is designed to investigate the efficacy and safety of bimekizumab in subjects with active PsA.

2.2.1 Nonclinical

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

dermatitis associated with increased bacterial load on the skin (mainly gram-positive cocci, including *Staphylococcus aureus*), and abscesses.

Infection-related safety findings in a nonhuman primate can be highly variable from study to study and have limited ability to accurately predict the incidence and type of infection that can be expected in humans, especially because nonhuman primates bear different commensal flora and show different sensitivity to different pathogens. Immunomodulators can increase the susceptibility of monkeys to potential pathogens that are endemic in nonhuman primate populations and usually remain clinically undetectable or are mild and self-limiting in immunocompetent animals. Moreover, infections associated with the gastrointestinal (GI) tract that result in chronic enterocolitis are a persistent and widespread colony problem in nonhuman primates, often multifactorial in origin.

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

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

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

2.2.2 Clinical

2.2.2.1 Completed studies

In the overall bimekizumab development program, the following clinical studies in healthy volunteers and subjects with PSO, RA, PsA, AS, ulcerative colitis (UC), and hidradenitis suppurativa (HS) have been completed:

- UP0008 was a Phase 1, first-in-human study in subjects with mild to moderate PSO.
- RA0124 and UP0031 were 2 Phase 1, bioavailability studies in healthy subjects.
- UP0033 was a Phase 1, open-label, multicenter, randomized, parallel-group, 3-arm, single-dose bioequivalence study of bimekizumab injected sc either by a prefilled syringe (PFS) or by an auto-injector in adult healthy subjects.
- UP0034 is a Phase 1, open-label, randomized, parallel-group, single-dose study to evaluate the antibody response of influenza vaccination following concomitant exposure to bimekizumab in adult healthy subjects.
- UP0074 was a Phase 1, open-label, randomized, parallel-group, single-dose study to evaluate the PK, safety, and tolerability of bimekizumab given as 2x1mL or 1x2mL sc administration in healthy subjects.
- PA0007 was a Phase 1b study in subjects with moderate to severe PsA.

- UP0042 was a Phase 1, PK study in healthy Japanese and Caucasian subjects.
- RA0123 was a Phase 2a study evaluating safety, PK, PD, and efficacy in subjects with moderate to severe RA who received bimekizumab as an add-on therapy to CZP.
- UC0011 was a Phase 2a, multinational, multicenter, subject- and Investigator-blind, randomized, placebo-controlled study to evaluate the efficacy, safety, tolerability, and PK of bimekizumab in adult subjects with moderate to severe active UC (discontinued study).
- PS0016 was a Phase 2a study evaluating the time course of Psoriasis Area and Severity Index (PASI) response, safety, and PK in subjects with moderate to severe chronic plaque PSO. PS0018 was the corresponding Phase 2 extension study.
- PS0018 was a Phase 2 OLE study evaluating the long-term safety, tolerability, and efficacy of bimekizumab in subjects who completed PS0016.
- PS0010 was a Phase 2b placebo-controlled dose-ranging study evaluating safety, efficacy, PK, and PD in subjects with moderate to severe PSO.
- PS0011 was a Phase 2b, multicenter, 48-week, double-blind, parallel-group, extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult subjects with moderate to severe chronic plaque PSO who completed PS0010.
- PS0008 is a Phase 3, multicenter, randomized, double-blind, parallel-group, active-comparator-controlled study to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PS0009 is a Phase 3 randomized, double-blind, placebo- and active comparator-controlled study to evaluate the efficacy and safety of bimekizumab administered sc to adult subjects with moderate to severe plaque PSO.
- PS0013 is a Phase 3, multicenter, randomized withdrawal, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PA0008 was a Phase 2b study evaluating the efficacy and safety in subjects with active PsA.
- AS0008 was a Phase 2b, placebo-controlled study evaluating the efficacy and safety of bimekizumab in subjects with active AS.
- HS0001 was a Phase 2 study to evaluate the safety, efficacy, and PK of bimekizumab in subjects with moderate to severe HS.

To evaluate treatment in subjects with PsA, bimekizumab has been investigated in a Phase 1b, proof-of-concept, randomized, placebo-controlled, multiple-dose study (PA0007). The primary objective of PA0007 was to assess the safety and PK of multiple dose administration of iv bimekizumab in subjects with PsA. Four active doses and a placebo were tested. Drug was administered as a loading dose at Week 1, and 2 additional doses were administered at Week 4 and Week 7. In each treatment group, subjects received a total of 3 doses of bimekizumab, administered every 3 weeks as shown below:

- 80mg loading dose followed by 40mg at Weeks 4 and 7
- 160mg loading dose followed by 80mg at Weeks 4 and 7

- 240mg loading dose followed by 160mg at Weeks 4 and 7
- 560mg loading dose followed by 320mg at Weeks 4 and 7

The results of this study demonstrated that all doses of bimekizumab were well tolerated and there were no unexpected clinically relevant safety findings.

Infections (mostly nasopharyngitis) were the most commonly reported events in both the active treatment and the placebo group. None of the infections were considered serious or required treatment with antibiotics. Two subjects in the active treatment group experienced one local candida infection each (oropharyngitis and vulvovaginitis, respectively) that were nonserious and resolved with topical therapy. There was a potential reduction in mean neutrophil count in the active treatment group, although this drop was not clinically relevant and a clear relationship with dose or time was not evident. Some increases in liver function tests were reported, but none had a clear relationship to exposure to IMP. The exploratory analysis showed clinically relevant improvement in activity of PsA and in skin involvement in those subjects with concomitant active psoriatic lesions.

PA0008 was a Phase 2b, placebo-controlled study to evaluate the efficacy, safety, tolerability, PK, PD, and immunogenicity of bimekizumab in subjects with active PsA. The primary objective of PA0008 was to assess the dose response based on the efficacy of bimekizumab administered sc Q4W (monthly) for 12 weeks in the treatment of subjects with active PsA.

During the 12-week Double-Blind Period, subjects were randomized 1:1:1:1:1 (stratified by region and prior tumor necrosis factor [TNF] inhibitor exposure) to receive the following blinded IMP regimens. The enrollment of TNF inhibitor-experienced subjects was planned to be limited to approximately 30% of the total study population (actual enrollment was 18.9% of all subjects).

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

After the 12-week Double-Blind Period, subjects entered the 36-week Dose-Blind Period. At the Week 12 Visit, subjects were allocated to bimekizumab treatment regimens: 160mg Q4W or 320mg Q4W.

The results of this study demonstrated a statistically significant dose response in the primary efficacy variable (ACR50 response at Week 12), and the dose response was linear for bimekizumab doses up to 160mg. The results of all secondary efficacy endpoints (ACR20, ACR70, PASI75, and PASI90 response at Week 12) were consistent with and supported the findings of the primary endpoint. All bimekizumab doses were associated with a greater response compared with placebo.

In PA0008, all doses of bimekizumab were well tolerated, and there were no unexpected clinically relevant safety findings. During the overall study, the most commonly reported adverse events (AEs) in subjects treated with bimekizumab were nasopharyngitis (12.3%), upper

respiratory tract infection (10.3%), respiratory tract infection (5.9%), and pharyngitis (5.4%); all other AEs were reported by <5.0% of subjects. There was no apparent relationship to bimekizumab dose with regard to the incidence of treatment-emergent adverse events (TEAEs). Eight participants (3.9%) had serious adverse events (SAEs) in bimekizumab arms, and no SAE (by preferred term) was reported by more than 1 subject. Eight participants (3.9%) discontinued due to a TEAE.

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

2.2.2.2 Ongoing studies

The following studies of bimekizumab are ongoing:

- PS0014 is a Phase 3, long-term extension study for eligible subjects from the Phase 3 PSO feeder studies to assess the safety, tolerability, and efficacy of bimekizumab.
  - DV0002 and DV0006 are multicenter, randomized, open-label studies to evaluate the safe and effective use of the prefilled safety syringe or the auto-injector for the sc self-injection of bimekizumab solution by subjects with moderate to severe PSO. DV0002 and DV0006 are substudies of PS0014; DV0002 is being conducted in North America, and DV0006 is being conducted in the EU and Japan.
- PS0015 is a Phase 3b, randomized, double-blind, secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab administered sc to subjects with moderate to severe chronic plaque PSO.
- PA0009 is a Phase 2b, long-term extension study for eligible subjects from PA0008 to assess the safety, tolerability, and efficacy of bimekizumab.
- PA0011 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in the treatment of subjects with active PsA.
- PA0012 is a Phase 3, multicenter, OLE study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of subjects with active PsA who complete PA0010 or PA0011.
  - DV0004 is a multicenter, randomized, open-label study to evaluate the safe and effective use of the prefilled safety syringe or auto-injector for the sc self-injection of bimekizumab solution by subjects with active PsA. DV0004 is a substudy of PA0012.
- AS0009 is a Phase 2b, long-term extension study for eligible subjects from AS0008 to assess the safety, tolerability, and efficacy of bimekizumab.
- AS0010 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in subjects with active nonradiographic axial spondyloarthritis.
- AS0011 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in subjects with active AS.

- AS0014 is a Phase 3, multicenter, OLE study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of subjects who complete AS0010 or AS0011.
- AS0013 is a Phase 2a, active-controlled study evaluating the efficacy and safety of bimekizumab compared with CZP in subjects with active AS.
- HS0003 and HS0004 are Phase 3, multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of bimekizumab in subjects with moderate to severe HS.
- HS0005 is a Phase 3, multicenter, OLE study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of subjects who complete HS0003 or HS0004.

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

2.3 Adalimumab

In this study, the efficacy of bimekizumab will be assessed with reference to the active-reference drug, adalimumab. Adalimumab's mechanism of action occurs through TNFα inhibition compared with bimekizumab's inhibition of IL-17A and IL-17F (HUMIRA®, 2016). Adalimumab has been approved for the treatment of several auto-immune diseases such as PsA, RA, AS, Crohn's disease, HS, and plaque PSO in the US and EU, as well as in many other countries globally, and is among the first line standard of care biologic therapy for patients not responding to conventional disease-modifying antirheumatic drugs (cDMARDs).

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective is to demonstrate the clinical efficacy of bimekizumab administered sc Q4W for 16 weeks compared with placebo in the treatment of subjects with active PsA, as assessed by the ACR50 response.

3.2 Secondary objectives

The secondary objectives of the study are as follows:

- To assess the efficacy of bimekizumab compared with placebo
- To assess the safety and tolerability of bimekizumab
- To assess the impact of bimekizumab on patient-reported quality of life
- To assess the impact of bimekizumab on skin PSO in the subgroup of affected subjects at Baseline
- To assess the impact of bimekizumab on functional improvement
- To assess the impact of bimekizumab on radiographic changes in the hands and feet
- To assess the impact of bimekizumab on extra-articular disease manifestations (dactylitis, enthesitis)

3.3 Other objectives

Other objectives are as follows:

- To descriptively assess the efficacy of bimekizumab with reference to adalimumab
- To assess the immunogenicity of bimekizumab
- To assess the impact of bimekizumab treatment on axial disease
- To assess the maintenance of treatment effect
- To assess nail PSO in the subgroup of affected subjects at Baseline
- To explore the exposure response relationship of bimekizumab
- To assess the effect of bimekizumab on gene and protein expression, and explore the relationship between genomic, genetic, and proteomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (from consenting subjects who agree to participate in the biomarker substudy)
- To assess the impact of bimekizumab on social life and work productivity

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable for this study is the ACR50 response at Week 16.

4.2 Secondary variables

4.2.1 Secondary efficacy variables

The secondary efficacy variables for this study are as follows:

- Change from Baseline in Health Assessment Questionnaire—Disability Index (HAQ-DI) at Week 16
- PASI90 response at Week 4 and Week 16 in the subgroup of subjects with PSO involving at least 3% BSA at Baseline
- Change from Baseline in the Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Week 16
- Minimal Disease Activity (MDA) response at Week 16
- Change from Baseline in Van der Heijde modified Total Sharp Score (vdHmTSS) in subjects with elevated hs-CRP and/or at least 1 bone erosion at Baseline at Week 16
- Enthesitis-free state in the Leeds Enthesitis Index (LEI) at Week 16 in the subgroup of subjects with enthesitis at Baseline in the pooled population of PA0010 and PA0011
- Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of subjects with dactylitis at Baseline in the pooled population of PA0010 and PA0011
- Change from Baseline in vdHmTSS in the overall population at Week 16

- ACR20 response at Week 16
- ACR70 response at Week 16
- Proportion of subjects with an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) AND at least a 2-grade reduction from Baseline at Week 4 and Week 16 in the subset of subjects with psoriatic skin lesions at Baseline
- Change from Baseline in the Patient's Assessment of Arthritis Pain (PtAAP) at Week 16
- Enthesitis-free state based on the Spondyloarthritis Research Consortium of Canada (SPARCC) index at Week 16 in the subgroup of subjects with enthesitis at Baseline
- Change from Baseline in Psoriatic Arthritis Impact of Disease-12 (PsAID-12) total score at Week 16

4.2.2 Secondary safety variables

Secondary safety variables to be assessed are as follows:

- Incidence of TEAEs
- Incidence of treatment-emergent SAEs
- TEAEs leading to withdrawal from IMP

4.3 Other variables

4.3.1 Other efficacy variables

Other efficacy variables will be assessed as specified in Table 5-1 (all time points not specified in Section 4.1.1 or Section 4.2.1 are exploratory):

- Time to ACR20, ACR50, and ACR70 response from Baseline (Day 1)
- ACR20, ACR50, and ACR70 response
- PASI75, PASI90, and PASI100 response in the subgroup of subjects with PSO involving at least 3% BSA at Baseline
- Composite endpoint composed of ACR50 and PASI90 response in subjects with PSO involving at least 3% BSA at Baseline
- Composite endpoint composed of ACR50 and PASI100 response in subjects with PSO involving at least 3% BSA at Baseline
- Proportion of Psoriatic Arthritis Response Criteria (PsARC) responders
- Psoriatic Arthritis Disease Activity Score (PASDAS) categories
- Change from Baseline in the PASDAS
- The proportion of ACR50 responders at Week 16 and maintaining response at Week 52
- MDA response
- Very Low Disease Activity (VLDA) response

- Proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) AND at least a 2-grade reduction from Baseline in the subset of subjects with psoriatic skin lesions at Baseline
- Disease Activity Index for Psoriatic Arthritis (DAPSA) score categories
- Change from Baseline in DAPSA score
- Change from Baseline in the Disease Activity Score-28 based on C-reactive protein (DAS28[CRP])
- Change from Baseline in all individual ACR core components:
  - SJC
  - TJC
  - HAQ-DI
  - PtAAP
  - Physician's Global Assessment of Psoriatic Arthritis (PhGA-PsA)
  - Patient's Global Assessment of Psoriatic Arthritis (PGA-PsA)
  - hs-CRP
- Change from Baseline in vdHmTSS total score and in erosion and joint space narrowing (subscores) in subjects with elevated hs-CRP and/or with at least 1 bone erosion at Baseline
- Change from Baseline in vdHmTSS total score and in erosion and joint space narrowing (subscores) in the overall population
- Proportion of subjects with no radiographic joint damage progression (change from Baseline vdHmTSS of ≤0.5)
- Dactylitis-free state based on the LDI in the subgroup of subjects with dactylitis at Baseline in the pooled population of PA0010 and PA0011, as well as for PA0010 alone
- Enthesitis-free state based on the LEI in the subgroup of subjects with enthesitis at Baseline in the pooled population of PA0010 and PA0011, as well as for PA0010 alone
- Enthesitis-free state based on the SPARCC index in the subgroup of subjects with enthesitis at Baseline in the pooled population of PA0010 and PA0011, as well as for PA0010 alone
- Proportion of subjects with a decrease of HAQ-DI from Baseline of at least 0.35 in those subjects with HAQ-DI>0.35 at Baseline
- Change from Baseline in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in the subgroup of subjects with axial involvement defined by a score of ≥4 at Baseline
- Change from Baseline in the modified Nail Psoriasis Severity Index (mNAPSI) score in the subgroup of subjects with psoriatic nail disease at Baseline
- Change from Baseline in the LEI in the subgroup of subjects with enthesitis at Baseline in the pooled population of PA0010 and PA0011, as well as for PA0010 alone

- Change from Baseline in the SPARCC index in the subgroup of subjects with enthesitis at Baseline in the pooled population of PA0010 and PA0011, as well as for PA0010 alone
- Change from Baseline in the LDI in the subgroup of subjects with dactylitis at Baseline in the pooled population of PA0010 and PA0011, as well as for PA0010 alone
- Change from Baseline in PsAID-12 total score, as well as the individual domain scores
- Proportion of subjects achieving PsAID-12 total score ≤4
- Proportion of PsAID-12 responders (decrease from Baseline in PsAID-12 total score ≥3 in subjects with PsAID-12 total score >3 at Baseline)
- Change from Baseline in the Psoriatic Arthritis Quality of Life (PsAQoL) total score
- Change from Baseline in the SF-36 PCS and Mental Component Summary (MCS), as well as the 8 domain scores (Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health)
- Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale score
- Proportion of FACIT-Fatigue subscale responders (subjects with a minimum clinically-important difference for FACIT-Fatigue subscale score, defined as an increase of ≥4)
- Change from Baseline in Work Productivity and Activity Impairment Questionnaire-Specific Health Problem (WPAI-SHP) v2.0 adapted to PsA scores
- Responses to the EuroQol-5 Dimensions-3 Level (EQ-5D-3L)
- Change from Baseline in EQ-5D-3L Visual Analog Scale (VAS) scores
- Change from Baseline in Physician's Global Assessment of Arthritis (PhGA-Arthritis)
- Change from Baseline in Patient's Global Assessment of Arthritis (PGA-Arthritis)

4.3.2 Other safety variables

Other safety variables to be assessed are:

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

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

4.3.3 Pharmacokinetic variable

The PK variable is the plasma concentration of bimekizumab.

4.3.4 Pharmacogenomic variables

Additional blood samples will be collected from subjects who consent to participate in the substudy at specific time points. If the collected samples are not used immediately, they will be stored at -80°C for up to 20 years until the completion of bimekizumab development program.

Genomic, genetic, epigenetic, proteins, and metabolite biomarkers may be measured to evaluate the relationship with response to treatment with bimekizumab, psoriatic arthritis disease biology, and inflammatory and immune response processes. The nature and format of these tentative substudy analyses will be determined when the results of the main study are made available.

The candidate exploratory variables are the blood or blood derivative (eg, serum) concentrations of cytokines and chemokines of relevance to IL-17A/F signaling pathway and psoriatic arthritis biology. Additional variables may include but will not be limited to serum complement concentrations. Where local regulations permit, additional blood samples will be collected at time points specified in Table 5-1. They may be used to allow for potential exploratory analyses of ribonucleic acid (RNA), proteins, lipids, and metabolite biomarkers relevant to disease biology and progression, response to therapy, the inflammatory and immune response processes, and cardiovascular risk in PsA.

4.3.5 Immunological variables

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

5 STUDY DESIGN

5.1 Study description

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-reference study to evaluate the efficacy and safety of bimekizumab in subjects with active PsA. To be eligible to participate in this study, subjects must be adults with a diagnosis of active PsA based on the CASPAR criteria and have active disease with TJC ≥3 and SJC ≥3. It is planned to enroll a minimum of 45% of subjects who are positive for elevated hs-CRP (hs-CRP ≥6mg/L) and/or who have at least 1 bone erosion at Screening.

Subjects should not have previously been treated with any biologic drugs for PsA or PSO. Detailed inclusion and exclusion criteria are presented in Section 6.1 and Section 6.2, respectively.

The study will include 3 periods: a Screening Period (≥14 days to ≤35 days), a Treatment Period (52 weeks), and a Safety Follow-up Period (20 weeks after the final dose of IMP). The Treatment Period will consist of a 16-week Double-Blind Treatment Period followed by a 36-week Active Treatment-Blind Period. Permitted rescue therapy changes after Week 16 are described in Section 5.4. The maximum study duration per subject will be up to 73 weeks.

Eligible subjects will be randomized 3:2:1 (stratified by region and bone erosion [0, ≥1]) to receive 1 of 3 blinded treatments (bimekizumab 160mg sc Q4W, placebo, or active-reference [adalimumab 40mg sc Q2W]) and will remain on their allowable background medication. Details of the Treatment Period are provided in Section 5.3.

Subjects completing Week 52 and meeting eligibility criteria are eligible for enrollment in an extension study to continue to receive bimekizumab.

An interim analysis of all available data (including efficacy, safety, and PK) will be undertaken after all randomized subjects have completed 24 weeks of treatment or have withdrawn from IMP or the study. The purpose of this analysis is to perform a comprehensive evaluation of all available data for the 3 treatment arms to prepare a regulatory submission for a marketing authorization application based on this analysis.

A second interim analysis of all available data will be undertaken after all randomized subjects have completed 52 weeks of treatment or have withdrawn from IMP or the study. The purpose of this analysis is to demonstrate the long-term efficacy and safety of bimekizumab. For subjects who are ineligible for the open-label extension study at Week 52, a final analysis will be undertaken after the SFU Visit.

Additional details for the interim analyses and data monitoring in this study are provided in Section 14.8.1. A detailed schedule of study assessments is presented in Table 5-1 and a study schematic diagram is presented in Figure 5-1.

5.2 Screening Period/Baseline

The Screening Period will last for a minimum duration of 14 days and a maximum duration of 35 days and will involve obtaining laboratory data and verifying that the doses of nonsteroidal anti-inflammatory drugs (NSAIDs), or permitted DMARDs, if used to treat PsA, are stable. The Screening Period will also enable washout of any medications not permitted for use during the study.

During the Screening Period, X-rays of hands and feet will be assessed for bone erosion and used for the stratification of subjects at Baseline (Day 1).

5.2.1 Within-study rescreening/retesting requirements

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

- Subjects who fail to meet the eligibility criteria for PHQ-9, electronic Columbia-Suicide Severity Rating Scale (eC-SSRS), or the tuberculosis (TB) questionnaire **are not allowed** to be rescreened.

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

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

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

5.3 Treatment Period

5.3.1 Double-Blind Treatment Period

During the Double-Blind Treatment Period, subjects will be randomized 3:2:1 (stratified by region and bone erosion [0, ≥1]) to 1 of 3 blinded treatments.

Investigational medicinal product treatment details are provided in Section 7.2. Visit windows of ±2 days are allowed for all visits through Week 16. The visit window is relative to the Day 1 (Baseline) Visit.

Bimekizumab, adalimumab, and placebo will be administered sc by unblinded study personnel at the clinical site.

The time between IMP doses should be ≥12 days and ≤16 days during the Double-Blind Treatment Period. The Double-Blind Period is 16 weeks in duration. At Week 16, subjects will transition from the double-blind, placebo-controlled treatment into the 36-week Active Treatment-Blind Period, as discussed in Section 5.3.2.

Subjects withdrawing early from the study will undergo the Early Termination (ET) Visit assessments and will enter the SFU Period. Subjects who withdraw from IMP during the Double-Blind Period will be encouraged to return for all scheduled visits up to Week 52 and for the SFU Visit (20 weeks after their final dose of IMP), as applicable.

5.3.2 Active Treatment-Blind Period

After the 16-week Double-Blind Treatment Period, subjects will enter the 36-week Active Treatment-Blind Period. At the Week 16 Visit, subjects will be allocated to treatment regimens as follows:

- Subjects in the bimekizumab 160mg sc Q4W group will continue to receive bimekizumab 160mg Q4W
- Subjects in the adalimumab 40mg sc Q2W group will continue to receive adalimumab 40mg sc Q2W
- Subjects in the placebo group will be reallocated to bimekizumab 160mg sc Q4W

Bimekizumab and adalimumab will be administered sc by unblinded study personnel at the clinical site. The first dose in the Active Treatment-Blind Period will be administered at Week 16 after all assessments have been completed. After Week 16, if the subjects are not responding adequately as per Investigators' judgement, rescue therapy will be allowed as described in Section 5.4.

Visit windows of ±3 days are allowed for all visits after Week 16.

The time between doses during the Active Treatment-Blind Period should be ≥11 days and ≤17 days.

Subjects who withdraw early from the study will undergo the ET Visit assessments and will enter the SFU Period. Subjects who withdraw from IMP during the Active-Treatment-Blind Period will be encouraged to return for all remaining scheduled visits up to Week 52 and the SFU Visit (20 weeks after their final dose of IMP), as applicable.

At the completion of the Active Treatment-Blind Period, Investigators should discuss treatment options with the subject. Subjects who complete PA0010 will be given the opportunity to enter an extension study at Week 52.

5.4 Permitted rescue therapy after Week 16

After Week 16, subjects may be rescued by changes to their permitted background medications, if the subject is not responding as per Investigator assessment. Permitted rescue therapy changes are listed below. Any other changes should be discussed with the Medical Monitor prior to the change.

Subjects who are rescued will remain on IMP. Permitted rescue therapy for eligible subjects will be at the Investigator's discretion, with the following options:

- Nonsteroidal anti-inflammatory drugs, DMARDs (MTX, SSZ, LEF, hydroxychloroquine [HCQ], apremilast), and/or joint injections may be given as permitted rescue therapy if deemed appropriate by the Investigator as outlined below. Subjects may receive these add-on therapies while continuing to receive their randomized dose of IMP.
  - For subjects taking NSAID/cyclooxygenase 2 (COX-2) inhibitors at Baseline, a change can be made to a different NSAID/COX-2 inhibitor. Changes from an NSAID to a COX-2 inhibitor or from a COX-2 inhibitor to an NSAID are permitted up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 inhibitor may be taken at a given time.
  - For subjects not taking NSAID/COX-2 inhibitors at Baseline, either an NSAID or COX-2 inhibitor can be initiated, up to the maximum approved or tolerated dose, whichever is lower. Only 1 NSAID/COX-2 inhibitor may be taken at a given time.
  - Methotrexate may be added or increased to a maximum dose of 25mg/week, or the maximum tolerated dose, whichever is lower. The route of administration may be changed from oral to sc.
  - Sulfasalazine may be given up to a maximum dose of 3g/day or 4g/day if in accordance with local standard of care, or the maximum tolerated dose, whichever is lower.
  - Leflunomide may be given at a maximum dose of 20mg/day (or an average of 20mg/day if not dosed daily), or the maximum tolerated dose, whichever is lower.
  - Hydroxychloroquine may be added or increased to a maximum dose of 400mg/day or the maximum tolerated dose, whichever is lower.
  - Apremilast may be given at a maximum dose of 30mg twice daily, or the maximum tolerated dose, whichever is lower.
  - Combination DMARDs are allowed except that LEF and MTX may not be given together.
  - Up to 2 joints (up to a total dose of 80mg methylprednisolone or equivalent) may be injected at or after Week 16; however, the same joint should not be injected more than once during the study.

- A decrease in dose or dosing frequency of any agent for the treatment of PsA is permitted for reasons of intolerance/AEs/side-effects at any time.
- Any medication not listed in the protocol for rescue must be approved by the Medical Monitor prior to starting that medication.
- If, in the judgment of the Investigator, the options outlined above are not considered appropriate for the subject, or the subject does not achieve sufficient response to these options, biologics may be considered. Subjects must discontinue IMP prior to use of another biologic therapy and follow the withdrawal criteria and follow-up as outlined in Section 6.3.
- Permitted rescue therapy will be determined by the Investigator taking into account the half-life of bimekizumab (27.8 days).

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

Subjects may be withdrawn from IMP at any time if they are judged to be not responding and continue treatment per the Investigator's discretion, as described in the Withdrawal Section (Section 6.3).

5.5 Safety Follow-Up Visit

All subjects who complete the study and do not enter the extension study will have an SFU Visit, 20 weeks after their final dose of IMP.

Any subjects who discontinue early, including those withdrawn from IMP, will be asked to attend all scheduled visits and will have an SFU Visit, 20 weeks after their final dose of IMP.

5.6 Study duration per subject

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

- ≥14 days to ≤35 days in the Screening Period
- 16 weeks in the placebo-controlled, Double-Blind Treatment Period
- 36 weeks in the Active Treatment-Blind Period
- An SFU Visit 20 weeks after the final dose of IMP (for subjects not entering the extension study or who discontinue early, including those withdrawn from IMP)

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

5.7 Planned number of subjects and sites

Approximately 840 subjects will be randomly assigned in a 3:2:1 ratio (stratified by region and bone erosion [0, ≥1]) to the following treatment groups: bimekizumab 160mg sc Q4W (420 subjects), placebo (280 subjects), and adalimumab 40mg sc Q2W (140 subjects). The planned number of study sites is approximately 150.

5.7.1 Enrollment of hs-CRP/bone erosion positive subjects

It is planned to enroll a minimum of 45% of subjects who are positive for elevated hs-CRP (hs-CRP ≥6mg/L) and/or who have at least 1 bone erosion at Screening.

5.8 Anticipated regions and countries

This will be a multicenter, international study. Enrollment will be competitive among study sites and may be capped at sites.

5.9 Schedule of study assessments

The schedule of study assessments is presented in Table 5-1.

Table 5-1: Schedule of study assessments

Visit [a]/ Week / Protocol activity	Screening (V1)	Baseline (Day 1) (first dose) (V2)	Double-Blind Treatment Period (weeks after first dose)								Active Treatment-Blind Period (weeks after first dose)																			ET	SFU [b]
			3/ 2	4/ 4	5/ 6	6/ 8	7/ 10	8/ 12	9/ 14	10/ 16	11/ 18	12/ 20	13/ 22	14/ 24	15/ 26	16/ 28	17/ 30	18/ 32	19/ 34	20/ 36	21/ 38	22/ 40	23/ 42	24/ 44	25/ 46	26/ 48	27/ 50	28/ 52		
Written Informed consent	X																														
Inclusion/ exclusion	X	X																													
Demographic data [c]	X																														
Psoriatic arthritis history	X																														
Significant past medical history and concomitant diseases	X	X [d]																													
Prior medication	X																														
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-9	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X
eC-SSRS	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X
Height [e]		X																													
Weight [e]		X						X						X						X									X	X	X
Vital signs [f]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X
ECG by central reader	X									X																			X	X	X
Hematology/ biochemistry [g]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X

Table 5-1: Schedule of study assessments

Visit [a]/ Week / Protocol activity	Screening (V1)	Baseline (Day 1) (first dose) (V2)	Double-Blind Treatment Period (weeks after first dose)								Active Treatment-Blind Period (weeks after first dose)																		ET	SFU [b]
			3/ 2	4/ 4	5/ 6	6/ 8	7/ 10	8/ 12	9/ 14	10/ 16	11/ 18	12/ 20	13/ 22	14/ 24	15/ 26	16/ 28	17/ 30	18/ 32	19/ 34	20/ 36	21/ 38	22/ 40	23/ 42	24/ 44	25/ 46	26/ 48	27/ 50	28/ 52		
hs-CRP [h]	X	X	X	X		X		X		X		X		X		X		X		X				X				X	X	X
Pregnancy testing[i]	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	X
Urinalysis	X	X								X				X				X				X				X		X	X	X
Urine drug screen	X																													
Hepatitis B and C testing	X																													
HIV testing	X																													
HLA-B27		X																												
RF and anti-CCP antibodies	X																													
Blood sample for bimekizumab plasma concentrations[j]		X	X	X		X		X		X		X		X						X								X	X	X
Anti-bimekizumab antibody detection[j]		X		X		X		X		X		X		X						X								X	X	X
Serum and plasma blood samples for exploratory biomarkers[j]		X								X																				
RNA blood samples for exploratory biomarkers[j]		X								X																				

Table 5-1: Schedule of study assessments

Visit [a]/ Week / Protocol activity	Screening (V1)	Baseline (Day 1) (first dose) (V2)	Double-Blind Treatment Period (weeks after first dose)								Active Treatment-Blind Period (weeks after first dose)																		ET	SFU [b]
			3/ 2	4/ 4	5/ 6	6/ 8	7/ 10	8/ 12	9/ 14	10/ 16	11/ 18	12/ 20	13/ 22	14/ 24	15/ 26	16/ 28	17/ 30	18/ 32	19/ 34	20/ 36	21/ 38	22/ 40	23/ 42	24/ 44	25/ 46	26/ 48	27/ 50	28/ 52		
Blood samples for genetic/ epigenetic analysis [j]		X								X																				
IGRA tuberculosis test	X																								X					
Tuberculosis questionnaire	X	X						X						X						X								X	X	X
Physical examination[k]	X	X						X		X				X						X								X	X	X
BSA affected by PSO [l]	X	X	X	X		X		X		X		X		X						X								X	X	X
PASI[m]	X	X	X	X		X		X		X		X		X						X								X	X	X
IGA[m]	X	X	X	X		X		X		X		X		X						X								X	X	X
TJC and SJC	X	X	X	X		X		X		X		X		X		X		X		X		X		X				X	X	X
HAQ-DI		X	X	X		X		X		X		X		X		X		X		X				X				X	X	X
PtAAP		X	X	X		X		X		X		X		X		X		X		X				X				X	X	X
PhGA-PsA		X	X	X		X		X		X		X		X		X		X		X				X				X	X	X
PhGA-Arthritis		X	X	X		X		X		X		X		X		X		X		X				X				X	X	X
PGA-PsA		X	X	X		X		X		X		X		X		X		X		X				X				X	X	X
PGA-Arthritis		X	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
mNAPSI[n]		X		X		X		X		X				X						X								X	X	

Table 5-1: Schedule of study assessments

Visit [a]/ Week / Protocol activity	Screening (V1)	Baseline (Day 1) (first dose) (V2)	Double-Blind Treatment Period (weeks after first dose)								Active Treatment-Blind Period (weeks after first dose)																			ET	SFU [b]
			3/ 2	4/ 4	5/ 6	6/ 8	7/ 10	8/ 12	9/ 14	10/ 16	11/ 18	12/ 20	13/ 22	14/ 24	15/ 26	16/ 28	17/ 30	18/ 32	19/ 34	20/ 36	21/ 38	22/ 40	23/ 42	24/ 44	25/ 46	26/ 48	27/ 50	28/ 52		
LEI		X		X		X		X		X		X		X						X								X	X	X
SPARCC		X		X		X		X		X		X		X						X								X	X	X
LDI[o]		X		X		X		X		X		X		X						X								X	X	X
PsAQoL		X		X						X				X						X								X	X	X
PsAID-12		X		X						X				X						X								X	X	
FACIT-Fatigue subscale		X		X						X				X						X								X	X	
SF-36		X		X						X				X						X								X	X	X
EQ-5D-3L		X		X						X				X						X								X	X	
WPAI-SHP		X								X				X														X	X	
Chest x-ray[p]	X																													
X-ray of hands and feet[q]	X									X																		X	X	
Adverse events[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IXRS[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP administration[t,u]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Table 5-1: Schedule of study assessments

Visit [a]/ Week / Protocol activity	Screening (V1)	Baseline (Day 1) (first dose) (V2)	Double-Blind Treatment Period (weeks after first dose)								Active Treatment-Blind Period (weeks after first dose)																ET	SFU [b]
			3/ 2	4/ 4	5/ 6	6/ 8	7/ 10	8/ 12	9/ 14	10/ 16	11/ 18	12/ 20	13/ 22	14/ 24	15/ 26	16/ 28	17/ 30	18/ 32	19/ 34	20/ 36	21/ 38	22/ 40	23/ 42	24/ 44	25/ 46	26/ 48	27/ 50	28/ 52		

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BP=blood pressure; BSA=body surface area; CASPAR=Classification Criteria for Psoriatic Arthritis; CCP=cyclic citrullinated peptide; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; EQ-5D-3L=EuroQol-5-Dimensions-3 Level; ET=Early Termination; FACIT=Functional Assessment of Chronic Illness Therapy; HAQ-DI=Health Assessment Questionnaire—Disability Index; HDL=high density lipoprotein; HIV=human immunodeficiency virus; HLA-27=human leukocyte antigen B27; hs-CRP=high sensitivity C-reactive protein; IGA=Investigator's Global Assessment; IGRA=interferon gamma release assay; IMP=investigational medicinal product; IXRS=interactive voice or web response system; LDI=Leeds Dactylitis Index; LDL=low density lipoprotein; LEI=Leeds Enthesitis Index; mNAPSI=modified Nail Psoriasis Severity Index; PASI=Psoriasis Area and Severity Index; PGA-Arthritis=Patient's Global Assessment of Arthritis; PGA-PsA=Patient's Global Assessment of Psoriatic Arthritis; PhGA-Arthritis=Physician's Global Assessment of Arthritis; PhGA-PsA=Physician's Global Assessment of Psoriatic Arthritis; PHQ-9=Patient Health Questionnaire-9; PsA=psoriatic arthritis; PsAID-12=Psoriatic Arthritis Impact of Disease-12; PsAQoL=Psoriatic Arthritis Quality of Life; PSO=psoriasis; PtAAP=Patient's Assessment of Arthritis Pain; Q2W=every 2 weeks; Q4W=every 4 weeks; RF=rheumatoid factor; RNA=ribonucleic acid; SF-36= Short-Form 36-item Health Survey; SFU=Safety Follow-Up; SJC=swollen joint count; SPARCC= Spondyloarthritis Research Consortium of Canada; TB=tuberculosis; TJC=tender joint count; vdHmTSS=Van der Heijde modified Total Sharp Score; V=Visit; WPAI-SHP=Work Productivity and Activity Impairment Questionnaire–Specific Health Problem

[a] Visit windows of ±2 days are allowed for all visits up to Week 16 and ±3 days are allowed for all visits after Week 16. The time between study treatment doses should be ≥12 days and ≤16 days or ≥11 days and ≤17 days, respectively. For the SFU Visit, the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

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

[c] A complete history of lifestyle (alcohol, drug, and nicotine consumption at the time of Screening) and infections (fungal skin infections within 12 months prior to Screening).

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

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

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

[g] Biochemistry testing will include triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol at Baseline, Weeks 12 and 24, and at the ET Visit.

[h] After Baseline, the hs-CRP data will not be sent to the Investigator to protect the blinded nature of the treatment assignments.

[i] Pregnancy testing will consist of serum testing at Screening for all women of childbearing potential. The pregnancy test will be urine at all other visits.

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

Table 5-1: Schedule of study assessments

Visit [a]/ Week / Protocol activity	Screening (V1)	Baseline (Day 1) (first dose) (V2)	Double-Blind Treatment Period (weeks after first dose)								Active Treatment-Blind Period (weeks after first dose)																	ET	SFU [b]
			3/ 2	4/ 4	5/ 6	6/ 8	7/ 10	8/ 12	9/ 14	10/ 16	11/ 18	12/ 20	13/ 22	14/ 24	15/ 26	16/ 28	17/ 30	18/ 32	19/ 34	20/ 36	21/ 38	22/ 40	23/ 42	24/ 44	25/ 46	26/ 48	27/ 50	28/ 52		

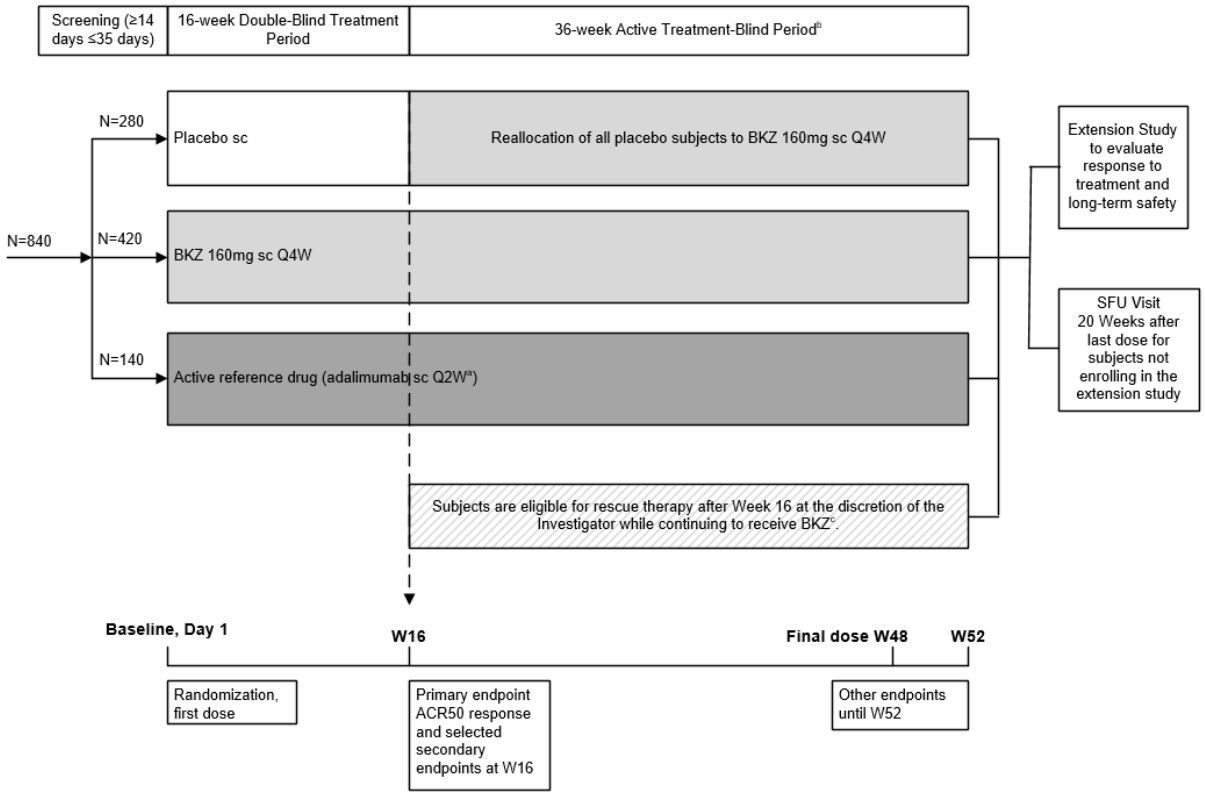
[k] Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.
[l] Any subject with PSO lesions at Baseline will have a BSA-PSO assessment (Section 9.8.1) at each scheduled visit.
[m] Only subjects with a BSA of ≥3% at Baseline will be required to have the PASI and IGA assessed at selected visits post Baseline (Day 1).
[n] Only for subjects who have nail PSO at Baseline.
[o] Circumference measured in millimeters.
[p] If a subject has had a radiograph of the chest within 3 months prior to the Screening Visit, it may be used as the Screening chest x-ray.
[q] The x-ray at Screening will be used for CASPAR classification (for inclusion) and will serve as the Baseline x-ray for assessment of the degree of joint damage, which will be assessed using the vdHmTSS (Van der Heijde et al, 2005).
[r] Adverse events are to be collected beginning at the signing of the Informed Consent form.
[s] The IXRS will be used to register subjects at Screening, to randomize eligible subjects to treatment groups at Baseline (Day 1), to reallocate subjects (at Week 16) in the placebo group, and to register visits.
[t] Bimekizumab subjects will be administered bimekizumab at Baseline, Week 4, and Q4W thereafter. The subjects will also receive dummy treatments at Week 2, and Q4W thereafter, in order to preserve the blind. Adalimumab subjects will be administered with adalimumab at Baseline, Week 2, and Q2W thereafter. Placebo will be administered at Baseline, Week 2, and Q2W thereafter to preserve blinding and correspond to the dosing schedule for adalimumab. For details of bimekizumab and adalimumab doses, see Section 7.2.
[u] At Week 16 after all assessments are complete, the Active Treatment-Blind Period dosing will start as detailed in Section 5.3.2, at which point no subjects will be in the placebo group, but will still be administered placebo to maintain blind.

.

5.10 Schematic diagram

The study schematic PA0010 is presented in Figure 5-1.

Figure 5-1: Study schematic diagram



ACR50=American College of Rheumatology 50% response criteria; BKZ=bimekizumab; PsA=psoriatic arthritis; Q2W=every 2 weeks; Q4W=every 4 weeks; sc=subcutaneous; SFU=Safety Follow-Up; W=week

[a] Adalimumab dosing is presented in Section 7.2.

[b] After 16 weeks of double-blind treatment, subjects will enter the Active Treatment-Blind Period. All subjects randomized to placebo will be reallocated to receive bimekizumab 160mg Q4W. Subjects randomized to bimekizumab 160mg Q4W will continue to receive their originally randomized dose. Subjects randomized to active-reference (adalimumab) will continue with their active treatment.

[c] Permitted rescue therapy is defined in Section 5.4.

5.11 Rationale for study design and selection of dose

Bimekizumab

Bimekizumab doses of 16mg, 160mg, 160mg with an initial 320mg dose, and 320mg were evaluated in PA0008, a Phase 2b multicenter, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study. In this study, doses up to 320mg were well tolerated by subjects and found to have acceptable safety profile.

PA0010 will evaluate the efficacy and safety of bimekizumab 160mg sc Q4W in adult subjects with active PsA. The dose was selected based on the data from Phase 2b study. In PA0008, both ACR50 and PASI90 responder rates saturate at bimekizumab 160mg Q4W, further increase in dose does not provide a significant benefit on either ACR50 or PASI90 responder rates. This

plateau at bimekizumab 160mg was further confirmed based on the observed noncontrolled Week 48 data, which demonstrated a similar ACR50 and PASI90 response between 160mg and 320mg Q4W at Week 48. An exposure-response analysis was performed on both endpoints which also indicated that bimekizumab 160mg Q4W is the optimal dose for these patients.

There were no dose-related safety concerns or changes in laboratory values in the preliminary data review up to 48 weeks that preclude the use of any of the tested doses in PA0008 for the Phase 3 program in PsA.

Adalimumab

Adalimumab is approved and indicated for the treatment of active and progressive PsA in adults when the response to previous DMARD therapy has been inadequate. The recommended dose of adalimumab for patients with PsA is 40mg adalimumab administered Q2W as a single dose via sc injection. Available data suggest that the clinical response is usually achieved within 12 weeks of treatment. Adalimumab dosing schedules are provided in Section 7.2.

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 at Screening and be reconfirmed at the Baseline Visit:

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

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

3. Subject is male or female at least 18 years of age.

4. Female subjects must be:

   – postmenopausal (menopause is defined as 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause),

   – permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy),

   – or, if of childbearing potential (and engaged in sexual activity that could result in procreation), must be willing to use a highly effective method of contraception throughout the duration of the study until 20 weeks after last administration of IMP, and have a negative pregnancy test at Screening and immediately prior to the 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, or implantable)

   – intrauterine device

- intrauterine hormone-releasing system
- vasectomized partner
- Abstinence as a form of birth control is generally not allowed in the study unless abstinence is in accordance with a subject's preferred and common lifestyle. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.

5. Subject has a documented diagnosis of adult-onset PsA classified and meets the CASPAR classification criteria (Table 18-1) for at least 6 months prior to Screening with active PsA and must have at Baseline TJC ≥3 out of 68 and SJC ≥3 out of 66 (dactylitis of a digit counts as 1 joint each).
6. Subject must be negative for rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies.
7. Subject must have at least 1 active psoriatic lesion(s) and/or a documented history of PSO.
8. Subject must be considered, in the opinion of the Investigator, to be a suitable candidate for treatment with adalimumab per regional labeling and has no contraindications to receive adalimumab as per the local label.
9. Subjects who are regularly taking NSAIDs/COX-2 inhibitors or analgesics (including mild opioids) as part of their PsA therapy are required to be on a stable dose/dose regimen for at least 14 days before Baseline and should remain on a stable dose until Week 16.
10. Subjects taking oral corticosteroids must be on an average daily dose of ≤10mg/day prednisone or equivalent for at least 14 days before Baseline and should remain on a stable dose until Week 16.
11. Subjects taking MTX (≤25mg/week) are allowed to continue their medication if started at least 12 weeks prior to Baseline, with a stable dose for at least 8 weeks before randomization. Dose, dosing schedule and route of administration (oral or sc) should remain stable until Week 16. It is strongly recommended that subjects taking MTX are also taking folic acid supplementation.
12. Subjects taking LEF (≤20mg/day or an average of 20mg/day if not dosed daily) are allowed to continue their medication if started at least 12 weeks prior to Baseline, with a stable dose for at least 8 weeks before randomization. Dose and dosing schedule should remain stable until Week 16.
13. Subjects taking SSZ (up to 3g/day, for arthritis or 4g/day if in accordance with local standard of care, HCQ (up to 400mg/day), or apremilast (up to 60mg/day and dosed as per local label) are allowed to continue their medication if started 8 weeks prior Baseline, with a stable dose for at least 4 weeks before randomization. Dose and dosing schedule should remain stable until Week 16.

6.2 Exclusion criteria

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

1. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 20 weeks following last dose of IMP.

2. Subjects with current or prior exposure to any biologics for the treatment of PsA or PSO, including participation in a bimekizumab clinical study who received at least 1 dose of IMP (including placebo).
3. Subject previously participated in another study of a medication (systemic) under investigation. Subject must be washed out of the medication for 12 weeks or at least 5 half-lives prior to the Baseline Visit, whichever is greater, or is currently participating in another study of a medication (systemic) under investigation, with the exception of subjects who were screen failures in PA0011.
4. Subject previously participated in another study of a medical device under investigation within the 4 weeks prior to the Screening Visit or is currently participating in another study of a medical device under investigation.
5. Subject has a known hypersensitivity to any excipients of bimekizumab or adalimumab.
6. Subject is taking or has taken prohibited PsA or PSO medications without meeting the mandatory wash-out period relative to the Baseline Visit (Table 7-2 and Table 7-3).
7. Subject has an active infection or history of infections as follows:
   - Any active infection (except common cold) within 14 days prior to Baseline.
   - A serious infection, defined as requiring hospitalization or iv anti-infectives within 2 months prior to Baseline.
   - A history of opportunistic, recurrent or chronic infections that, in the opinion of the Investigator, might cause this study to be detrimental to the subject. Opportunistic infections are infections caused by uncommon pathogens (eg, pneumocystis jirovicii, cryptococcosis) or unusually severe infections caused by common pathogens (eg, cytomegalovirus, herpes zoster).
8. Subject has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Subjects who have evidence of or tested positive for hepatitis B or hepatitis C are excluded.

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

   - positive for hepatitis B surface antigen; or,
   - positive for anti-hepatitis B core antibody

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

   - positive for hepatitis C antibody (anti-HCV antibody), and
   - positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction)
9. Subject has received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted).
10. Subject has received Bacillus Calmette-Guerin (BCG) vaccinations within 1 year prior to the Baseline Visit.

11. Subject has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection. A subject with latent tuberculosis (LTB) (a positive interferon gamma release assay [IGRA] and diagnosis confirmed by TB specialist) may be rescreened once and enrolled after receiving at least 4 weeks of appropriate LTB infection (LTBI) therapy and if no evidence of therapy-related hepatotoxicity has occurred prior to the first injection (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] remain ≤3 times upper limit of normal [ULN]).

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

    Refer to Section 12.3.5 for details on determining full TB exclusion criteria.

12. Subject has a history of a lymphoproliferative disorder including lymphoma and/or current signs and symptoms suggestive of lymphoproliferative disease.
13. Subject has a diagnosis of inflammatory conditions other than PSO or PsA including, but not limited to RA, sarcoidosis, systemic lupus erythematosus, and reactive arthritis. Subjects with a diagnosis of Crohn's disease, ulcerative colitis, or other inflammatory bowel disease (IBD) are allowed as long as they have no active symptomatic disease at Screening or Baseline.
14. Subject had acute anterior uveitis within 6 weeks of Baseline.
15. Subjects with fibromyalgia or osteoarthritis symptoms that in the Investigator's opinion would have potential to interfere with efficacy assessments.
16. Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer.
17. Subject has a form of PSO other than chronic plaque-type (eg, pustular, erythrodermic and guttate PSO, or drug-induced PSO).
18. Subject has had major surgery (including joint surgery) within the 3 months prior to Baseline, or planned surgery within 6 months after entering the study.
19. Subject has any systemic disease (ie, cardiovascular, neurological, renal, liver, metabolic, GI, hematological, immunological, etc) considered by the Investigator to be uncontrolled, unstable or likely to progress to a clinically significant degree during the course of the study.
20. Subject has had myocardial infarction or stroke within the 6 months prior to the Screening Visit.
21. Subject has laboratory abnormalities at Screening, including any of the following:
    a. ≥3x ULN of any of the following: ALT, AST, alkaline phosphatase (ALP); or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome)
    b. White blood cell count $<3.0x10^3/\mu L$
    c. Absolute neutrophil count $<1.5x10^3/\mu L$
    d. Lymphocyte count <500 cells/μL

e. Hemoglobin <8.5g/dL

f. Creatinine >2mg/dL

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

Individual screening tests for which the results are in error, borderline, or indeterminate for inclusion in the study, can be repeated once for confirmation during the Screening Period. Upon retesting, subjects whose results remain outside this threshold should not be randomized.

22. Subject has any other condition including medical or psychiatric which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.
23. Presence of active suicidal ideation, or positive suicide behavior using the "Screening" version of the electronic Columbia-Suicide Severity Rating Scale (eC-SSRS) with either of the following criteria:
    - Subject has a history of a suicide attempt within the 5 years prior to the Screening Visit. Subjects with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare professional (eg, locally licensed psychiatrist, psychologist, or master's level therapist) before enrolling into the study.
    - Subject has suicidal ideation in the past month prior to the Screening Visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening" version of the eC-SSRS
24. Subject has presence of moderately severe major depression, or severe major depression, indicated by a Score ≥15 using the screening PHQ-9. Medication used to treat depression should be stable for 8 weeks prior to Baseline.
25. Subjects taking PsA medications other than MTX, SSZ, apremilast, HCQ, LEF, NSAIDs/COX-2 inhibitors, and oral corticosteroids as outlined in the Inclusion criteria (Section 6.1). Stable doses/regimens of analgesics are also permitted.
26. Subject has a history of chronic alcohol or drug abuse within 6 months prior to Screening evaluated by the Investigator based on medical history, site interview, and results of the specified urine drug screen.
27. Subject is a member of Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
28. Subject is a UCB employee or is an employee of third-party organizations involved in the study.

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Subjects who withdraw from the study should complete the Early Termination Visit (see Section 8.3).

Subjects should be withdrawn from the study and will be asked to come back for the SFU Visit 20 weeks after the final dose of IMP if the subject withdraws his/her consent.

Subjects should be withdrawn from IMP and will be asked to come back for all scheduled visits (up to Week 52) and the SFU Visit 20 weeks after the final dose of IMP if any of the following events occur:

1. The Sponsor or a regulatory agency requests withdrawal of the subject.
2. Subject develops an illness that, in the opinion of the Investigator, would interfere with his/her continued participation, if the risk of continuing with IMP outweighs the potential benefit.
3. Subject is noncompliant with the study procedures or medications, which may present a risk to the safety of the subject, in the opinion of the Investigator.
4. Subject uses prohibited concomitant medications, as defined in Section 7.8.2, that may present a risk to the safety of the subject in the opinion of the Investigator and the Medical Monitor.
5. Subject has a clinical laboratory value meeting any of the following criteria:
   a. Hepatotoxicity as described in Section 6.3.1.
   b. A laboratory value meeting any of the following criteria:
   – Absolute neutrophil count $<1.0x10^3/\mu L$
   – Absolute lymphocyte count $<0.2x10^3/\mu L$

   Subjects may remain on IMP if the result is transient. A retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat absolute neutrophil count or absolute lymphocyte count is still below the allowable values, the subject must be withdrawn from the IMP. If the repeat absolute neutrophil count or absolute lymphocyte count is above the allowable values, the subject may continue to receive IMP.
6. The subject experiences a severe AE, SAE, or a clinically significant change in a laboratory value occurs that, in the opinion of the Investigator, merits the discontinuation of the IMP and appropriate measures being taken.
7. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test (see Section 12.1.4 for more information regarding pregnancies).
8. Subject develops erythrodermic, guttate or generalized pustular form of PSO.
9. A 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 IGRA or other diagnostic means) must be immediately discontinued from IMP, and an ET Visit must be scheduled as soon as possible, but not later than the next regular visit.

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

Confirmed active TB is an SAE and must be captured in the electronic Case Report form (eCRF) in the SAE Report Form section. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.

Additional information on TB policies is provided in Section 12.3.5.

10. Subjects with newly diagnosed IBD or with IBD flares during the study must:
    - Be referred, as appropriate, to a health care professional treating IBD, such as a gastroenterologist
    - Discontinue IMP and be followed-up until resolution of active IBD symptoms

    If IBD flares increase in severity or frequency during the study, the Investigator should use clinical judgment in deciding whether the subject should continue on IMP and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.
11. Subjects **must be referred** immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk for:
    a. Active suicidal ideation as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the eC-SSRS.
    b. Moderately severe major depression as indicated by a PHQ-9 score of 15 to 19 if this represents an increase of 3 points compared to last visit.

    The mental health consultation must be recorded in the subject's source documentation.
12. Subjects **must be referred** immediately to a mental health care professional and must be withdrawn from the study:
    a. Active suicidal ideation as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the eC-SSRS.
    b. Any suicidal behavior since the last visit.
    c. Severe major depression as indicated by a PHQ-9 score ≥20.

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

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

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

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

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 ≥8xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN
  - Subjects with ALT or AST ≥3xULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, right upper quadrant pain or tenderness. Hypersensitivity symptoms include fever (without clear alternative cause), rash, or eosinophilia (ie, >5%).

If a nondrug-related cause for the symptoms can be confirmed, these subjects may resume IMP administration after discussion with the responsible UCB physician, but only when the requirements for rechallenge with IMP as provided in Section 12.2.1.2.1 are followed.

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

- Subjects with ALT or AST ≥5xULN and <8xULN, total bilirubin <2xULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

Evaluation of PDILI must be initiated as described in Section 12.2.1 with repeat tests performed in 2 weeks. Upon retest, if ALT or AST values have reduced to <5xULN, the subject can continue with the study. However, if ALT or AST remains ≥5xULN <8xULN after retest, IMP should be temporarily withheld and subject should undergo a repeat test in 2 weeks. The subject will continue to be monitored at least twice per week until values normalize, stabilize, or return to within baseline values. If ALT or AST values remain ≥5xULN even after the second retest, then the subject should be permanently withdrawn from the study and should be followed for possible PDILI.

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

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

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

The IMPs used in this study are bimekizumab, adalimumab, and placebo.

- Bimekizumab will be supplied in a 1mL PFS. Each single-use syringe contains bimekizumab drug substance at a nominal formulation of 160mg/mL in [redacted]mM sodium acetate, [redacted]mM glycine, and [redacted]% polysorbate 80 at pH [redacted] for sc injection.
- [redacted]
- Placebo will be supplied as 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (US Pharmacopoeia/European Pharmacopoeia) quality in a 1mL PFS for sc injection.

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

7.2 Treatments to be administered

The IMPs are to be administered in the clinic by unblinded study site staff. At all visits, only a single sc injection would be administered. Suitable areas for sc injections are the lateral abdominal wall and upper outer thigh. Injection sites should be rotated and injections should not be given in areas where the skin is tender, bruised, red, or hard.

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

The IMP dosing scheme is presented in Table 7-1.

Table 7-1: Dosing scheme

Protocol activity \ Week	Baseline (first dose)	Double-Blind Treatment Period								Active Treatment-Blind Period																
		2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50
Bimekizumab 160mg sc Q4W	●	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○[a]
Adalimumab 40mg	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲ a
Placebo	○	○	○	○	○	○	○	○	●[b]	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○	●	○[a]

Note: A bimekizumab 160mg Q4W dose injection is depicted by a black circle (●). A placebo injection is depicted by a white circle (○). An adalimumab 40mg injection is depicted by a black triangle (▲).

[a] Subjects that continue to the extension study will receive their final dose of IMP.

[b] Placebo subjects reallocated to bimekizumab 160mg sc Q4W (follow applicable schedules noted above).

7.3 Packaging

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

7.4 Labeling

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

7.5 Handling and storage requirements

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

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

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

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

7.6 Drug accountability

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

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

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

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

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

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either

destroyed at the site according to local laws, regulations, and UCB standard operating procedures (SOPs), or returned to UCB (or designee). 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

Bimekizumab, adalimumab, and placebo will be administered in the clinic and compliance will be determined at the visit by unblinded study personnel. Drug accountability must be recorded by unblinded study personnel on the Drug Accountability form.

7.8 Concomitant medications/treatments

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

7.8.1 Permitted concomitant treatments (medications and therapies)

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

After Week 16, background medication changes are permitted at the Investigator's discretion if the subject is considered to be not responding adequately. Permitted rescue therapy is described in Section 5.4.

Subjects are allowed to use acetaminophen/paracetamol and mild opioids as needed, except within 24 hours of a visit with disease activity assessment.

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

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

7.8.1.1 Psoriasis treatments

For treatment of PSO, subjects may continue to use topical moisturizers, emollients, salicylic acid preparations, bath oils, and oatmeal bath preparations for skin conditions during the study, as needed. Over-the-counter shampoos for the treatment of PSO of the scalp are also permitted. Additionally, mild topical steroids are permitted for use limited to the face, axillae, and/or genitalia, as needed. Subjects who use prohibited topical medications will be allowed to stay in the study but will counseled to not use them further. No other topical preparations are allowed in the 2 weeks prior to randomization or during the study unless medically required to treat an AE. See Table 7-3 for prohibited PSO medications.

After the Week 16 Visit, the addition of topical retinoids, vitamin D analogues, coal tar preparations, and more potent topical steroids may be used as medically required to treat a flare but are not permitted to be used within 24 hours prior to a study visit. Use of psoralen and

ultraviolet A light (PUVA/UVA) therapy for the treatment of PSO is not permitted for the first 16 weeks of the study and is discouraged through the duration of the study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Prohibited and/or restricted medications are summarized in Table 7-2 and Table 7-3.

Table 7-2: Prohibited or restricted medications and required wash-out periods

Drug class	Dose	Exclusion/Washout
Analgesics, including mild opioid analgesics, acetaminophen/paracetamol, etc.	Any dose	Any ad hoc use in the 24 hours prior to any study visit. Stable doses of analgesics are 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/intravenous /intra-articular corticosteroids	Any dose	Use in the 28 days prior to the Baseline Visit and during the study.
Intra-articular hyaluronic acid	Any dose	Use in the 6 months prior to the Baseline Visit.
DMARDs: -azathioprine, -cyclosporine, -cyclophosphamide, -mycophenolic acid -mycophenolate mofetil -any other nonpermitted small molecule DMARDs (eg, tofacitinib)	Any dose	Use within 8 weeks prior to the Baseline Visit and during the study.
-apremilast [a]	Any dose	Use within 8 weeks prior to the Baseline Visit unless Inclusion Criterion #13 is met.
-hydroxychloroquine [a]	Any dose	Use within 8 weeks prior to the Baseline Visit unless Inclusion Criterion #13 is met.
-sulfasalazine [a]	Any dose	Use within 8 weeks prior to the Baseline Visit unless Inclusion Criterion #13 is met.

Table 7-2: Prohibited or restricted medications and required wash-out periods

Drug class	Dose	Exclusion/Washout
-methotrexate [a]	Any dose regimen	Initiation less than 12 weeks prior to the Baseline Visit unless Inclusion Criterion #11 is met. Administration of LEF and MTX together is not permitted at any time during the study.
-leflunomide [a]	Any dose	Use in the 6 months prior to the Baseline Visit, unless (1) a cholestyramine washout has been performed, in which case, use up to 28 days prior to the Baseline Visit is acceptable or (2) Inclusion Criterion #12 is met.
Any bDMARDs	Any dose	Any exposure history.

COX-2=cyclooxygenase-2; CZP=certolizumab pegol; bDMARD=biological disease modifying antirheumatic drug; DMARD=disease modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; LEF=leflunomide; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; SSZ=sulfasalazine

[a] Permitted as per Section 5.4.

Table 7-3 Additional prohibited psoriasis treatments

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

7.8.3 Vaccines

Administration of live (including attenuated) vaccines is not allowed during the conduct of the study and for 20 weeks after the final dose IMP (see exclusion criteria, Section 6.2). Administration of inactivated vaccines is allowed during the study at the discretion of the Investigator.

7.9 Blinding

Due to differences in presentation between the bimekizumab, adalimumab, and placebo treatments, special precautions will be taken to ensure study blinding and study sites will have blinded and unblinded personnel.

As per dosing schedule for adalimumab (see Section 7.2), all subjects must come to the study center for IMP administration at Baseline, Week 2, Week 4, and then Q2W thereafter.

For subjects receiving bimekizumab, bimekizumab will be administered at Baseline and Q4W thereafter; dummy/placebo treatments at Week 2 and Q4W thereafter to preserve blinding and correspond to the dosing schedule for adalimumab. Adalimumab subjects will receive adalimumab at Baseline and Q2W thereafter. Details of the interim sensitivity analysis to examine any treatment biases are provided in Section 14.3.2.

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

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

Additional information on procedures to maintain the treatment blind after the 24-week and 52-week interim analyses is provided in Section 14.8.1.

7.9.1.2 Breaking the treatment blind in an emergency situation

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

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

7.10 Randomization and numbering of subjects

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IXRS vendor. The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject, the Investigator or designee will contact the IXRS 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 IXRS regarding a particular subject. Subject numbers and kit numbers will be tracked via the IXRS.

Eligible subjects will be randomized to treatment groups at Baseline (Day 1). To randomize a subject, the Investigator or designee will contact the IXRS and provide brief details about the subject to be randomized. The IXRS will automatically inform the Investigator or designee of the subject's randomization number. The IXRS will allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be documented into the eCRF.

After 16 weeks of double-blind treatment, subjects who were randomized to placebo will be reallocated to bimekizumab 160mg sc Q4W. Subjects randomized to bimekizumab160mg sc Q4W will continue to receive their originally randomized dose. Subjects randomized to adalimumab 40mg Q2W will continue with their reference treatment.

8 STUDY PROCEDURES BY VISIT

The schedule of study assessments (Table 5-1) provides an overview of study assessments. A list of procedures to be completed at each visit is described below. Visit windows of ±2 days are allowed from the first dose at all visits through to Week 16. During the 16-week Double-Blind Period, the time between doses should be ≥12 days and ≤16 days. Visit windows of ±3 days are allowed for all visits after Week 16. The time between doses during the Active Treatment-Blind Period should be ≥11 days and ≤17 days. 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/+7 days).

Where local regulations permit, subjects will also be given the option to participate in the genomics, genetics, and proteomics substudy. Subjects agreeing to participate in the substudy will be required to complete a separate Informed Consent form (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 PA0010 study.

8.1 Screening Period/Baseline

8.1.1 Screening

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

Prior to any study-specific activities, subjects will be asked to read, sign, and date an Informed Consent form that has been approved by the Sponsor and an IRB/IEC, 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.

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

- Obtain written informed consent
- Assessment of inclusion and exclusion criteria
- Collect demographic data
- Collect PsA history
- Collect significant past medical history and concomitant diseases
- Record prior medications
- Record concomitant medications
- PHQ-9
- eC-SSRS

- Vital signs
- ECG by central reader
- Collect samples for hematology and biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (serum)
- Urinalysis
- Urine drug screen
- Collect samples for Hepatitis B and Hepatitis C testing
- Collect samples for HIV testing
- Collect samples for rheumatoid factor, anti-CCP antibodies
- IGRA TB test
- TB questionnaire
- Physical examination
- BSA affected by PSO
- PASI (if the BSA affected by PSO is ≥3%)
- Investigator's Global Assessment (IGA)
- Perform TJC and SJC
- Chest x-ray
- X-ray of hands and feet
- AEs
- IXRS

8.1.2 Baseline (Day 1)

- Assessment of inclusion and exclusion criteria
- Collect significant past medical history and concomitant diseases
- Record concomitant medications
- PHQ-9
- eC-SSRS
- Weight
- Height
- Vital signs
- Collect samples for hematology and biochemistry (including triglycerides, cholesterol, high density lipoprotein [HDL] cholesterol, and low-density lipoprotein [LDL] cholesterol)

- Collect samples for hs-CRP
- Collect sample for HLA-B27
- Pregnancy testing (urine)
- Urinalysis
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- Serum and plasma blood samples for exploratory biomarkers (participating subjects only)
- RNA blood samples for exploratory biomarkers (participating subjects only)
- Blood samples for genetic/epigenetic analysis (participating subjects only)
- TB questionnaire
- Physical examination
- BSA affected by PSO using the BSA palm method
- PASI (if the BSA affected by PSO is ≥3%)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI
- LEI
- SPARCC
- LDI
- PsAQoL
- PsAID-12
- FACIT-Fatigue subscale
- SF-36
- EQ-5D-3L

- WPAI-SHP
- AEs
- IXRS (randomization)
- IMP administration

8.2 Treatment Period

8.2.1 Double-Blind Treatment Period

8.2.1.1 Week 2

- Record concomitant medications
- Vital signs
- Collect samples for hematology and biochemistry
- Collect samples for hs-CRP
- Blood sample for bimekizumab plasma concentrations
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- AEs
- IXRS
- IMP administration

8.2.1.2 Week 4

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology and biochemistry

- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI
- LEI
- SPARCC
- LDI
- PsAQoL
- PsAID-12
- FACIT-Fatigue subscale
- SF-36
- EQ-5D-3L
- AEs
- IXRS
- IMP administration

8.2.1.3 Weeks 6, 10, and 14

- Record concomitant medications
- IXRS
- AEs
- IMP administration

8.2.1.4 Week 8

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology and biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI
- LEI
- SPARCC
- LDI
- AEs

- IXRS
- IMP administration

8.2.1.5 Week 12

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Weight
- Vital signs
- Collect samples for hematology and biochemistry (including triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol)
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- TB questionnaire
- Physical examination
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI
- LEI
- SPARCC
- LDI
- AEs

- IXRS
- IMP administration

8.2.1.6 Week 16

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- ECG by central reader
- Collect samples for hematology and biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Urinalysis
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- Serum and plasma blood samples for exploratory biomarkers (participating subjects only)
- RNA blood samples for exploratory biomarkers (participating subjects only)
- Blood samples for genetic/epigenetic analysis (participating subjects only)
- Physical examination
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI
- LEI

- SPARCC
- LDI
- PsAQoL
- PsAID-12
- FACIT-Fatigue subscale
- SF-36
- EQ-5D-3L
- WPAI-SHP
- X-ray of hands and feet
- AEs
- IXRS
- IMP administration

8.2.2 Active Treatment-Blind Period

After 16 weeks of double-blind treatment, subjects will enter the Active Treatment-Blind Period. Subjects in the placebo group will be reallocated to bimekizumab 160mg sc Q4W. Subjects randomized to receive bimekizumab or adalimumab during the Double-Blind Treatment Period will continue their Double-Blind Treatment Period regimen in the Active Treatment-Blind Period. After Week 16, rescue therapy will be permitted for all subjects at the Investigator's discretion if the subject is judged to be not responding adequately.

8.2.2.1 Weeks 18 and 22

- Record concomitant medications
- IXRS
- AEs
- IMP administration

8.2.2.2 Week 20

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology and biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Blood sample for bimekizumab plasma concentrations

- Blood sample for anti-bimekizumab antibody detection
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- LEI
- SPARCC
- LDI
- AEs
- IXRS
- IMP administration

8.2.2.3 Week 24

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Weight
- Vital signs
- Collect samples for hematology and biochemistry (including triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol)
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Urinalysis
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- TB questionnaire
- Physical examination

- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC/SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI
- LEI
- SPARCC
- LDI
- PsAQoL
- PsAID-12
- FACIT-Fatigue subscale
- SF-36
- EQ-5D-3L
- WPAI-SHP
- AEs
- IXRS
- IMP administration

8.2.2.4 Weeks 26, 30, 34, 38, 42, 46, and 50

- Record concomitant medications
- IXRS
- AEs
- IMP administration

8.2.2.5 Week 28

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology/biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- AEs
- IXRS
- IMP administration

8.2.2.6 Week 32

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology/biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Urinalysis
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA

- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- AEs
- IXRS
- IMP administration

8.2.2.7 Week 36

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Weight
- Vital signs
- Collect samples for hematology/biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- TB questionnaire
- Physical examination
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI

- LEI
- SPARCC
- LDI
- PsAQoL
- PsAID-12
- FACIT-Fatigue subscale
- SF-36
- EQ-5D-3L
- AEs
- IXRS
- IMP administration

8.2.2.8 Week 40

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology/biochemistry
- Pregnancy testing (urine)
- Urinalysis
- Perform TJC and SJC
- AEs
- IXRS
- IMP administration

8.2.2.9 Week 44

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology/biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)

- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- AEs
- IXRS
- IMP administration

8.2.2.10 Week 48

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Vital signs
- Collect samples for hematology/biochemistry
- Pregnancy testing (urine)
- Urinalysis
- IGRA TB test
- AEs
- IXRS
- IMP administration

8.2.2.11 Week 52

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Weight
- Vital signs
- ECG by central reader
- Collect samples for hematology/biochemistry
- Collect samples for hs-CRP

- Pregnancy testing (urine)
- Urinalysis
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- TB questionnaire
- Physical examination
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- mNAPSI
- LEI
- SPARCC
- LDI
- PsAQoL
- PsAID-12
- FACIT-Fatigue subscale
- SF-36
- EQ-5D-3L
- WPAI-SHP
- X-ray of hands and feet
- AEs
- IXRS

At the completion of the Active Treatment-Blind Period, Investigators should discuss treatment options with the subject. Subjects will be given the opportunity to enter an extension study at Week 52.

8.3 Early Termination Visit

Subjects withdrawing early from the study will undergo the following ET Visit assessments and will enter the SFU Period:

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Weight
- Vital signs
- ECG by central reader
- Collect samples for hematology/biochemistry (including triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol)
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Urinalysis
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- TB questionnaire
- Physical examination
- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI

- mNAPSI
- LEI
- SPARCC
- LDI
- PsAQoL
- PsAID-12
- FACIT-Fatigue subscale
- SF-36
- EQ-5D-3L
- WPAI-SHP
- X-ray of hands and feet
- AEs
- IXRS

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

All subjects who complete the study and do not enter the extension study or who discontinue early, including those withdrawn from IMP, will have an SFU Visit 20 weeks after their final dose of IMP with the following assessments:

- Record concomitant medications
- PHQ-9
- eC-SSRS
- Weight
- Vital signs
- ECG by central reader
- Collect samples for hematology/biochemistry
- Collect samples for hs-CRP
- Pregnancy testing (urine)
- Urinalysis
- Blood sample for bimekizumab plasma concentrations
- Blood sample for anti-bimekizumab antibody detection
- TB questionnaire
- Physical examination

- BSA affected by PSO
- PASI (if BSA affected by PSO is ≥3% at the Baseline [Day 1] visit)
- IGA
- Perform TJC and SJC
- HAQ-DI
- PtAAP
- PhGA-PsA
- PhGA-Arthritis
- PGA-PsA
- PGA-Arthritis
- BASDAI
- LEI
- SPARCC
- LDI
- PsAQoL
- SF-36
- AEs
- IXRS

8.5 Unscheduled Visits

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 wellbeing.

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

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

- Record concomitant medication
- eC-SSRS
- Vital signs
- ECG
- Obtain urine sample for urine pregnancy test

- If indicated, obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology/biochemistry)
  - Bimekizumab plasma concentrations and anti-bimekizumab antibody detection
- An IGRA TB test
- Physical examination
- AEs

9 ASSESSMENT OF EFFICACY

The ACR50 response at Week 16 is the primary efficacy variable. In addition, the ACR20 and ACR70 responses are secondary or other efficacy variables. Several assessments must be completed in order to determine the ACR response. These include the TJC and SJC based on 68 and 66 joints, respectively, PGA-PsA, PhGA-PsA, PtAAP, HAQ-DI and hs-CRP. The methods for the component measures will be described first, followed by ACR response and assessments used in secondary and other efficacy variables.

The timing for all assessments is specified in the schedule of study assessments (Table 5-1).

9.1 Joint assessments

9.1.1 68/66 joint evaluation for ACR response and verification of Inclusion Criterion 5

The TJC/SJC, as recommended by ACR in RA, is the 68/66 count and it has since also been used in PsA studies; therefore, it will be utilized in this study.

All joint assessments will be performed by an experienced independent evaluator who has had documented training on how to perform these assessments correctly. Preferably, the same evaluator should perform these assessment at all visits, as indicated in Table 5-1. The independent evaluator will not be involved in any other assessments. The following joints will be assessed for tenderness:

- Upper body (6) - bilateral temporomandibular, sternoclavicular, and acromioclavicular joints
- Upper extremity (34) - bilateral shoulders, elbows, wrists (includes radiocarpal, and carpal and carpometacarpal bones considered as a single unit), metacarpophalangeal (I, II, III, IV, and V), thumb interphalangeals, proximal interphalangeal (II, III, IV, and V), and distal interphalangeals (II, III, IV, and V).
- Lower extremity (28) - bilateral hips, knees, ankles, tarsi (includes subtalar, transverse tarsal, and tarsometatarsal considered as a single unit), metatarsophalangeals (I, II, III, IV, and V), great toe interphalangeals, and proximal interphalangeals (II, III, IV, and V).

All of these except for the hips are assessed for swelling.

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

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

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

Table 9-1: Swelling and tenderness grading

Grade	Tenderness response (68)	Swelling response (66)
0	Not tender	None
1	Tenderness present	Detectable synovial thickening

Data mapping from collected data to the grades listed in Table 9-1 will be described in the Statistical Analysis Plan (SAP).

9.1.2 28 joint evaluation for determination of DAS28(CRP)

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

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

9.2 ACR20, ACR50, and ACR70 response

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

- TJC based on 68 joints
- SJC based on 66 joints
- 3 of the 5 remaining core set measures:
  - PGA-PsA
  - PhGA-PsA
  - PtAAP
  - HAQ-DI
  - hs-CRP

9.3 Patient's Global Assessments

9.3.1 Patient's Global Assessment of Psoriatic Arthritis (PGA-PsA)

The subject's global assessment of PsA will be performed using a 100mm VAS scale where 0 is "very good, no symptoms" and 100 is "very poor, severe symptoms." The subject will be asked the following question:

"Considering all the ways your psoriatic arthritis affects you, please mark a vertical line on the scale below to show how well you are doing today."

The subject should be asked to consider all aspects of their disease (including joint and skin components) in their response to this question.

9.3.2 Patient's Global Assessment of Arthritis (PGA-arthritis)

The subject's global assessment of arthritis will be performed using a 100mm VAS scale where 0 is "very good, no symptoms" and 100 is "very poor, severe symptoms." The subject will be asked the following question:

"**Considering all the ways your arthritis affects you, please mark a vertical line on the scale below to show how you are feeling today."**

The subject should be asked to consider their arthritis symptoms and functional capacity in their response to this question.

9.4 Physician's Global Assessments

These assessments will be performed by the Principal Investigator, another delegated physician or an appropriately trained medical professional (based on local requirements) who has documented training on how to perform these assessments correctly. The assessments should be made blind to the PGA-PsA and PGA-Arthritis assessments.

9.4.1 Physician's Global Assessment of Psoriatic Arthritis (PhGA-PsA)

The Investigator or delegate will assess the overall status of the subject with respect to their PsA, which may include any element of the disease and may include arthritis, PSO, enthesitis, dactylitis, or spondylitis. This will be assessed using a 100mm VAS scale where 0 is "very good, asymptomatic and no limitation of normal activities" and 100 is "very poor, very severe symptoms which are intolerable and inability to carry out all normal activities". The Investigator or delegate will be asked the following question:

"Considering all the ways the disease affects your patient, mark a vertical line on the scale for how well his or her condition is today."

9.4.2 Physician's Global Assessment of Arthritis (PhGA-Arthritis)

The Physician or delegate will assess how the subject's overall arthritis appears at the time of the visit. This is an evaluation based on the subject's disease signs, functional capacity, and physical examination using a 100mm VAS scale where 0 is "very good" and 100 is "very poor". The physician will be asked to mark the Patient's arthritis:

The Patient's arthritis at this time is:

"Please mark a vertical line on the scale below to assess the overall status of the subject's arthritis signs and symptoms and the functional capacity of the subject."

Very Good----------Very Poor

9.5 Patient's Assessment of Arthritis Pain (PtAAP)

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

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

The HAQ-DI contains 20 items divided into 8 domains that measure: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and common daily activities. Subjects are required to indicate the degree of difficulty they have experienced in each domain in the past week on a 4-point scale that ranges from 0 (without difficulty) to 3 (unable to do). Any individual score of less than 2 is adjusted to 2 if the activity requires assistance from another individual or the use of an assistive device. The highest score in each category is then summed (0 to 24) and divided by the number of categories scored to give a score that ranges from 0 to 3.

9.7 High sensitivity C-reactive protein levels (hs-CRP)

High sensitivity CRP levels will be analyzed by the central laboratory according to Table 5-1.

After Baseline, the hs-CRP data will not be sent to the Investigator in order to protect the blinded nature of the treatment assignments and response.

9.8 Evaluation of psoriasis

9.8.1 Body surface area-psoriasis (BSA-PSO)

In the BSA-PSO assessment, the subject's hand (including the palm, fingers, and thumb) is used as the reference point for measuring how much of their skin is affected by PSO, representing roughly 1% of the body's surface.

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

- Head and neck=10% (10 palms)
- Upper extremities=20% (20 palms)
- Trunk=30% (30 palms)
- Lower extremities=40% (40 palms)
- Total BSA=100%

9.8.2 Psoriasis Area and Severity Index (PASI)

The PASI will be assessed in all subjects with Baseline/Day 1 BSA affected by PSO ≥3% determined by the method described in Section 9.8.1 (ie, the BSA palm method).

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

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

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

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

Table 9-2: Body areas for calculation of percent BSA for PASI

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

BSA=body surface area; PASI=Psoriasis Area and Severity Index
[a] Where 0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected

The PASI75, PASI90, and PASI100 responses are based on at least 75%, 90%, and 100% improvement in the PASI score. The PASI will be assessed at Screening and at Baseline/Day 1. Thereafter, the PASI will be assessed for the purposes of determining response only in subjects with PSO involving at ≥3% of BSA at Baseline/Day 1.

9.8.3 Investigator's Global Assessment (IGA)

A static IGA for PSO will be used to assess disease severity in all subjects during the study. The IGA will completed at the visits specified in Table 5-1.

The Investigator will assess the overall severity of PSO using the following 5-point scale presented in Table 9-3.

Table 9-3: Five-point IGA

Score	Short Descriptor	Detailed Descriptor
0	Clear	No signs of PSO; post-inflammatory hyperpigmentation may be present
1	Almost Clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominantly fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration severe/coarse scaling covering almost all or all lesions

IGA=Investigator's Global Assessment; PSO=psoriasis

The IGA response is defined as a clear [0] or almost clear [1] assessment with at least a 2-category improvement from Baseline, meaning that this parameter will be evaluable only for subjects with psoriatic skin lesions (IGA score ≥2) at Baseline.

In this study, only subjects with BSA ≥ 3% at Baseline will have IGA assessed at post-Baseline Visits.

9.8.4 Modified Nail Psoriasis Severity Index (mNAPSI)

Subjects with psoriatic nail disease will have a target nail selected at the Baseline Visit for evaluation using the mNAPSI. The nail selected should be the most affected nail observed at Baseline and should be the only one assessed throughout the study. The target nail will be scored (0 to 3) for onycholysis/oil drop dyschromia, nail plate crumbling, and pitting and will be scored (0 for "no" or 1 for "yes") for leukonychia, nail bed hyperkeratosis, splinter hemorrhages, and red spots in the lunula.

9.9 Minimal Disease Activity (MDA) and Very Low Disease Activity (VLDA)

Minimal Disease Activity and VLDA are states of disease activity deemed useful targets of treatment by both the subject and physician, given current treatment possibilities and limitations. Criteria covering all domains of the disease have been developed to determine whether or not a subject has reached MDA or VLDA based on key outcome measures in PsA (Mease, 2011; Coates et al, 2010).

A subject is considered as having MDA if 5 or more of the following 7 criteria are fulfilled:

- Tender joint count ≤1
- Swollen joint count ≤1
- PASI ≤1 or BSA ≤3
- Patients' pain VAS ≤15
- PGA-PsA-VAS ≤20
- HAQ-DI ≤0.5
- Tender enthesial points ≤1

A subject is considered as having VLDA if all 7 of the above criteria are fulfilled.

9.10 Disease Activity Index for Psoriatic Arthritis (DAPSA)

Disease Activity Index for Psoriatic Arthritis (DAPSA) is a composite score of patient global and pain VAS, TJC/SJC, and hs-CRP that incorporates a pattern of peripheral arthritis that often is encountered in PsA, and is calculated as follows:

DAPSA=SJC (range 0-66) + TJC (range 0-68) + PGA-Arthritis (VAS range 0-10cm; 0=best, 10=worst) + PtAAP (VAS range 0-10cm) + hs-CRP.

9.11 Van der Heijde modified Total Sharp Score (vdHmTSS)

The degree of joint damage is to be assessed using the vdHmTSS as used in the evaluation of PsA (Van der Heijde et al, 2005). This methodology quantifies the extent of bone erosions and joint space narrowing for 64 and 52 joints, respectively, with higher scores representing greater damage.

Radiographs of the hands and feet are to be taken using standardized imaging methodology, which is defined in the Hand and Foot Radiography Manual that will be provided as part of the Study Manual.

All enrolled subjects are required to have radiographs taken of both hands and both feet (a single posteroanterior view of each hand and a single dorsoplantar of each foot). Radiographs are to be read centrally and independently by 2 experienced readers. Readers will be blind to treatment assignment and time course of the films.

9.12 Disease Activity Score-28 based on C-reactive protein (DAS28[CRP])

The components for DAS28(CRP) include the TJC and SJC based on 28 joints (Section 9.1.2), hs-CRP (Section 9.7) and the PGA-Arthritis (Section 9.5). The DAS28(CRP) is calculated as follows:

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

9.13 Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

The BASDAI is the most common instrument used to measure the disease activity of ankylosing spondylitis from the subject's perspective (Garrett et al, 1994) and is considered useful for evaluating axial involvement in subjects with PsA (Fernandez-Sueiro et al, 2009). The BASDAI is a validated self-reported instrument which consists of six 10-unit horizontal numeric rating scales to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week (van Tubergen et al, 2015). The final BASDAI score ranges from 0 to 10, with lower scores indicating lower disease activity.

The BASDAI is calculated as follows:

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

9.14 Leeds Enthesitis Index (LEI)

Enthesitis, the inflammation at the bone insertion of tendon, ligament, or joint capsule, is common in PsA. The LEI is a new enthesitis index designed for use in PsA (Healy and Helliwell, 2007) adopted for use in randomized controlled studies involving subjects with PsA. Enthesitis will be assessed by palpation on the lateral epicondyles of the humerus (elbows), medial femoral epicondyles (knees), and Achilles tendons (heels) bilaterally and scored as 0=no pain and 1=painful.

9.15 Spondyloarthritis Research Consortium of Canada (SPARCC)

The SPARCC is an index that measures the severity of enthesitis through the assessment of 16 sites (the greater trochanter (right/left [R/L]), quadriceps tendon insertion into the patella (R/L), patellar ligament insertion into the patella and tibial tuberosity (R/L), Achilles tendon insertion (R/L), plantar fascia insertion (R/L), medial and lateral epicondyles (R/L) and the supraspinatus insertion [R/L]) (Maksymowych et al, 2009). Tenderness on examination is recorded as either present (1) or absent (0) for each of the 16 sites, for an overall score range of 0 to 16.

9.16 Leeds Dactylitis Index (LDI)

Dactylitis, the swelling of an entire digit related to articular and periarticular inflammation is a characteristic of inflammatory spondyloarthropathies, including PsA. Presence of dactylitis will be assessed using the LDI basic. It measures the ratio of the circumference of the affected digit to the circumference of the digit on the contralateral hand or foot (millimeters): a minimum difference of 10% is used to define a dactylitic digit (Healy and Helliwell, 2007; Helliwell et al, 2005). If the contralateral digit is also dactylitic, a table of normative values based on population averages is used to provide the comparison. The ratio is then multiplied by the tenderness score, using a simple grading system (0=absent, 1=present). The results from each digit with dactylitis are then summed to produce a final score. The digits involved and the matching contralateral digit will also be recorded at the same visits.

9.17 Psoriatic Arthritis Quality of Life (PsAQoL)

The use of the PsAQoL is recommended by the health regulatory authorities as 1 of the disease-specific HRQoL measures in PsA (CHMP/EWP/438/04). The PsAQoL comprises 20 items so that the score ranges from 0 to 20 with higher scores indicating worse HRQoL.

9.18 Psoriatic Arthritis Impact of Disease-12 (PsAID-12)

The PsAID-12 is a patient-reported outcome measure for assessing the impact of PsA in 12 physical and psychological domains, including pain, fatigue, skin problems, work and/or leisure activities, functional capacity, discomfort, sleep disturbance, coping, anxiety/fear/uncertainty, embarrassment and/or shame, social participation, and depression. Each domain is assessed with a single question using a 0 to 10 numerical rating scale. Each domain score is multiplied by a weighting factor and the results are then summed to provide the total score. The total score ranges from 0 to 10, with higher scores indicating a worse status. The PsAID-12 demonstrated satisfactory psychometric properties in an international validation study; however, further validation is needed (Gossec et al, 2014). A score below 4 out of 10 is considered a patient-acceptable status. A change of 3 or more points is considered relevant absolute change.

9.19 Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale

The FACIT-Fatigue is a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function over the past 7 days (FACIT.org). The scale consists of 5 subscales (physical well-being, social/family well-being, emotional well-being, functional well-being, and fatigue). The fatigue subscale is the only one used in this study . It is composed of 13 items, all scored from 0 (Not at all) to 4 (Very much). The FACIT-Fatigue subscale score ranges from 0 to

52 with 0 being the worst possible score and 52 being the best possible score. To obtain a score from 0 to 52, all negatively worded questions have to be recoded, so that responses range from worst (0) to the best (4) outcome.

The FACIT-Fatigue subscale has been validated in patients with PsA. The minimum clinically important difference for FACIT-Fatigue subscale in patients with PsA was determined to be a 4-point change (Cella et al, 2019).

9.20 Short-Form 36-item Health Survey (SF-36)

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

In addition to domain scores, the PCS and MCS scores are calculated from the 8 domains (excluding the Health Transition item). Component scores reflect the impact of each domain on physical and mental health status. The norm-based T-scores for the 2 SF-36 component summary (PCS and MCS) and the 8 domains are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general US population (Maruish, 2011). An individual respondent's score that falls outside the T-score range of 45 to 55 should be considered outside the average range for the US general population. When considering group-level data, a score below 47 should be considered indicative of impaired functioning within that health domain or dimension. Similar to individual respondent data, group mean scores of 47 or greater should be considered average or above average as compared to the general US population. Higher scores indicate a better health status.

9.21 Euro Quality of life 5-Dimensions-3 Level (EQ-5D-3L)

The EQ-5D-3L is comprised of a 5-item health status dimension and a VAS. The response to each of the 5 health status dimensions is divided into 3 levels (no problem, some or moderate problems, or extreme problems) and is scored as 1, 2, and 3, respectively. The EQ-5D-3L VAS records the respondent's self-rated health status on a vertical 20cm scale, 0 to 100 graduated (0=worst imaginable health status, 100=best imaginable health status).

9.22 Work Productivity and Activity Impairment Questionnaire– Specific Health Problem (WPAI-SHP)

The WPAI-SHP v2.0 is a patient-reported questionnaire that assesses subject's employment status, work absenteeism, work impairment while working (presenteeism), overall work, and daily activity impairment attributable to a specific health problem (Reilly et al, 1993).

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

9.23 Psoriatic Arthritis Response Criteria (PsARC)

The PsARC is based on the TJC (68 joints) and SJC (66 joints), the PGA-PsA and PhGA-PsA VAS.

The PsARC response is defined as improvement from Baseline in at least 2 of the 4 measures (TJC, SJC, PGA-PsA, PhGA-PsA) 1 of which must be TJC or SJC and no worsening from Baseline in any of the 4 measures. Improvement for TJC and SJC is defined as a reduction of ≥30% and worsening is defined as an increase of ≥30%. Improvement of PGA-PsA and PhGA-PsA is defined as a reduction of the 100-point VAS of ≥20 points and worsening is defined as an increase of the 100-point VAS of ≥20.

9.24 Psoriatic Arthritis Disease Activity Score (PASDAS)

The PASDAS (Coates et al, 2014) is a composite score that includes patient and physician global scores of skin and joint disease, SJC, TJC, LEI, tender dactylitis count, the physical component of the SF-36 Health Survey, and level of CRP. It was developed by the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and the European League Against Rheumatism. PASDAS is calculated using the following equation:

PASDAS = (((0.18 × √Physician global VAS) + (0.159 × √Patient global VAS) − (0.253 × √SF36 − PCS) + (0.101 × LN (SJC + 1)) + (0.048 × LN (TJC + 1)) + (0.23 × LN (LEI + 1)) + (0.377 LN (tender Dactylitis count + 1)) + (0.102 × LN (CRPmg/dL + 1)) +2)*1.5.

Note: LN=natural logarithm

The following categories are used to define the level of disease activity (Coates et al, 2018):

- Remission: PASDAS ≤1.9
- Low disease activity: PASDAS 1.9 to <3.2
- Moderate disease activity: PASDAS 3.2 to <5.4
- High disease activity: PASDAS ≥5.4

10 ASSESSMENT OF PHARMACOKINETIC AND PHARMACOGENOMIC VARIABLES

10.1 Pharmacokinetic variable

The PK variable is the plasma concentrations of bimekizumab.

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

10.2 Pharmacogenomic variables

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

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

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

Collection of these samples will occur at the time points specified in the schedule of study assessments (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. The samples will be stored at -80°C at the central biorepository for up to 20 years.

Detailed information on the collection, storage, preparation, and shipping of samples for potential RNA, proteins, lipids, and metabolites analysis will be presented in a Laboratory Manual.

The nature and format of these tentative analyses will be determined at a later date.

Results for the exploratory parameters obtained from potential RNA, lipids, proteins and metabolites analysis will be described in a separate report.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLES

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

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

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

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 Adverse event

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

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

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

12.1.1.2 Serious adverse event

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

- Death
- Life-threatening

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

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

  (A patient admitted to a hospital, even if he/she is released on the same day, meets the criteria for the initial inpatient hospitalization. An emergency room visit that results in

admission to the hospital would also qualify for the initial inpatient hospitalization criteria. However, emergency room visits that do not result in admission to the hospital would not qualify for this criteria and, instead, should be evaluated for 1 of the other criteria in the definition of serious [eg, life-threatening adverse experience, important medical event].

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

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

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

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

Table 12-1: Anticipated SAEs for the population of subjects with PsA

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

MedDRA=Medical Dictionary for Regulatory Activities; PsA=psoriatic arthritis; 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 (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

12.1.1.4 Other safety topics of interest

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

This is based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related

mechanism of action. There are no specific AE reporting requirements for these topics; however, special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB) are in place.

12.1.2 Procedures for reporting and recording adverse events

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

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

In addition, the Investigator should review any self-assessment procedures 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 and the corresponding medical terminology should be clarified in the source documentation.

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

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

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

12.1.2.2 Rule for repetition of an adverse event

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

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

12.1.2.3 Additional procedures for reporting serious adverse events

If an SAE is reported, UCB must be informed within 24 hours of receipt of this information by the site. The Investigator must enter the information regarding the SAE into the appropriate eCRFs and transmit to UCB via the clinical database, even if the data are incomplete, or if it is obvious that more data will be needed in order to draw any conclusions. This information will be received by UCB and entered into the global safety database. Any ancillary documentation (eg, autopsy or other documentation) that is valid for the SAE can be sent to UCB using the contact

information (fax/email) for SAE reporting listed in the Serious Adverse Event Reporting section at the front of the protocol.

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

Additional information received by the Investigator must be provided within 24 hours. All documents in the local language must be accompanied by a translation in English or the relevant information included in the same document must be summarized in the eCRF and transmitted to UCB via the clinical database.

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

Upon receipt of the electronic transmission of the SAE, UCB will perform as assessment of expectedness of the reported SAE. The assessment of 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 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; AESMs, further details regarding follow-up of PDILI events is provided in Section 12.2.1.4.

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.

12.1.4 Pregnancy

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

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

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

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

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

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

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

12.1.5 Suspected transmission of an infectious agent via a medicinal product

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

12.1.6 Overdose of investigational medicinal product

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

12.1.7 Safety signal detection

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

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

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

In addition, an independent Data Monitoring Committee (DMC) will periodically review and monitor 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 studies. 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 PA0010. The DMC may also be asked to provide a review of final study results, as deemed appropriate. The DMC procedures will ensure that data remain blind to the study team and Investigators at all times throughout the conduct of the study. The detailed role, scope, responsibilities, and complete procedures, as well as the identity of the DMC members, will be described in a separate charter document. A Cardiovascular Adjudication Committee and a Neuropsychiatric Adjudication Committee will be in place for this study. Specific procedures will be outlined in the charters, which will be developed by the committee members.

12.2 Laboratory measurements

Clinical laboratory assessments consist of serum biochemistry, hematology, urinalysis, and pregnancy tests (serum or urine) (Table 5-1). A centralized laboratory will be used to supply all laboratory test supplies and analyze all blood and urine samples for hematology and biochemistry. Any unscheduled laboratory testing should also be collected using the central

laboratory (with the exception of urgent safety laboratory measurements which should be performed locally and centrally simultaneously). Testing to rule out hepatitis B, hepatitis C, and HIV will be performed at Screening. Rheumatoid factor and anti-CCP testing will also be performed at Screening. Testing of HLA-B27 will be performed at Baseline.

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

Laboratory parameters to be measured are presented in Table 12-2.

Table 12-2: Laboratory measurements

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

Table 12-2: Laboratory measurements

Hematology	Biochemistry	Urinalysis

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ET=early termination; GGT=gamma-glutamyltransferase; HDL=high density lipoprotein; hs-CRP=high sensitivity C-reactive protein; IMP=investigational medicinal product; IMS=International Menopause Society; LDH=lactate dehydrogenase; LDL=low density lipoprotein; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; SFU=Safety Follow-up; WBC=white blood cell

[a] Biochemistry will include triglycerides, cholesterol, HDL cholesterol, and LDL cholesterol at Baseline, Weeks 12 and 24, and at the ET Visit.

[b] Pregnancy testing will consist of serum testing at the Screening Visit for all women of childbearing potential. The pregnancy test will be urine at all other visits.

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

12.2.1 Evaluation of potential drug-induced liver injury

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

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.2.1.1). 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 12.2.1.4).

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

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

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

When IMP is discontinued, all concomitant medications and herbal supplements that are not medically necessary should also be discontinued. In these cases, the Investigator should also consider dose reduction for medically necessary concomitant medication and consider changing

any medically required concomitant medication known to be hepatotoxic to a suitable alternative.

When IMP is stopped due to PDILI (as described in Section 6.3.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 12.2.1.2.1 are met, rechallenge with IMP may be appropriate.

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

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate IMP discontinuation.[d]	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[e]
≥3xULN	NA	Yes				
≥8xULN	NA	NA				

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase. • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 4 weeks of monitoring without evidence of resolution.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.2.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[e] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • ALT or AST remains ≥5xULN <8xULN, IMP should be temporarily withheld and subject should undergo repeat test in 2 weeks. • Continue IMP if ALT or AST values <5xULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values.

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
						• If ALT or AST remains ≥5xULN after second re-test, immediate IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[e]

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 12.2.1.1. 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 12.2.1.2.1.

[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.

12.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 12.2.1.3) and SAE report (if applicable).

12.2.1.2 Immediate action: determination of IMP discontinuation

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

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

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

12.2.1.2.1 IMP restart/rechallenge

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

- The results of additional testing and monitoring described in Section 12.2.1.3 and Section 12.2.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the subject.
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥3xULN.
- Subject's total bilirubin is <1.5xULN.
- Subject has no signs or symptoms of hypersensitivity.
- The rechallenge is approved by the UCB responsible physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the investigator-recommended monitoring plan and understands their individual benefit risk for restarting IMP and this is adequately documented.

12.2.1.3 Testing: identification/exclusion of alternative etiology

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

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

The following measurements are to be assessed:

Table 12-4: PDILI laboratory measurements

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

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

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

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

Additional information to be collected is presented in Table 12-5.

Table 12-5: PDILI information to be collected

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

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

12.2.1.4 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.

12.3 Other safety measurements

12.3.1 Vital signs

The Investigator or designee should measure all vital signs (BP, temperature [oral, axillary, or otic], and pulse rate) after the subject has been sitting for at least 5 minutes, and the subject should remain seated during the measurements. At Baseline and at Week 16, vital signs will be measured prior to IMP administration and then at approximately 30 minutes and 1 hour after dosing. At all other visits, vital signs will be measured only once prior to dosing.

12.3.2 Body weight and height

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.

12.3.3 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; gastrointestinal; 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.

12.3.4 12-lead electrocardiogram

The Investigator or designee will perform the ECGs which will be read centrally. Full details of ECG recording will be provided in the ECG Manual.

12.3.5 Assessment and management of TB and TB risk factors

All subjects will be assessed for TB at Screening and at the time points specified in the schedule of study assessments (Table 5-1) through physical examination for signs and symptoms of TB, chest x-ray (Section 12.3.5.2), laboratory testing (Section 12.3.5.1), and subject questionnaire (Section 12.3.5.3).

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

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

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

b. High risk of acquiring TB infection:
   - Known close exposure to another person with active TB infection within the 3 months prior to Screening.
   - Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high.

c. Latent TB infection (unless appropriate prophylaxis is initiated at least 4 weeks prior to IMP dosing and continued to completion of prophylaxis):

   – The absence of signs, symptoms, or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to IMP without further evaluation by a TB specialist and discussion with the Study Physician, if LTBI 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 (Center for Disease Control diagnosis of LTB infection; http://www.cdc.gov/TB/topic /testing/default.htm).

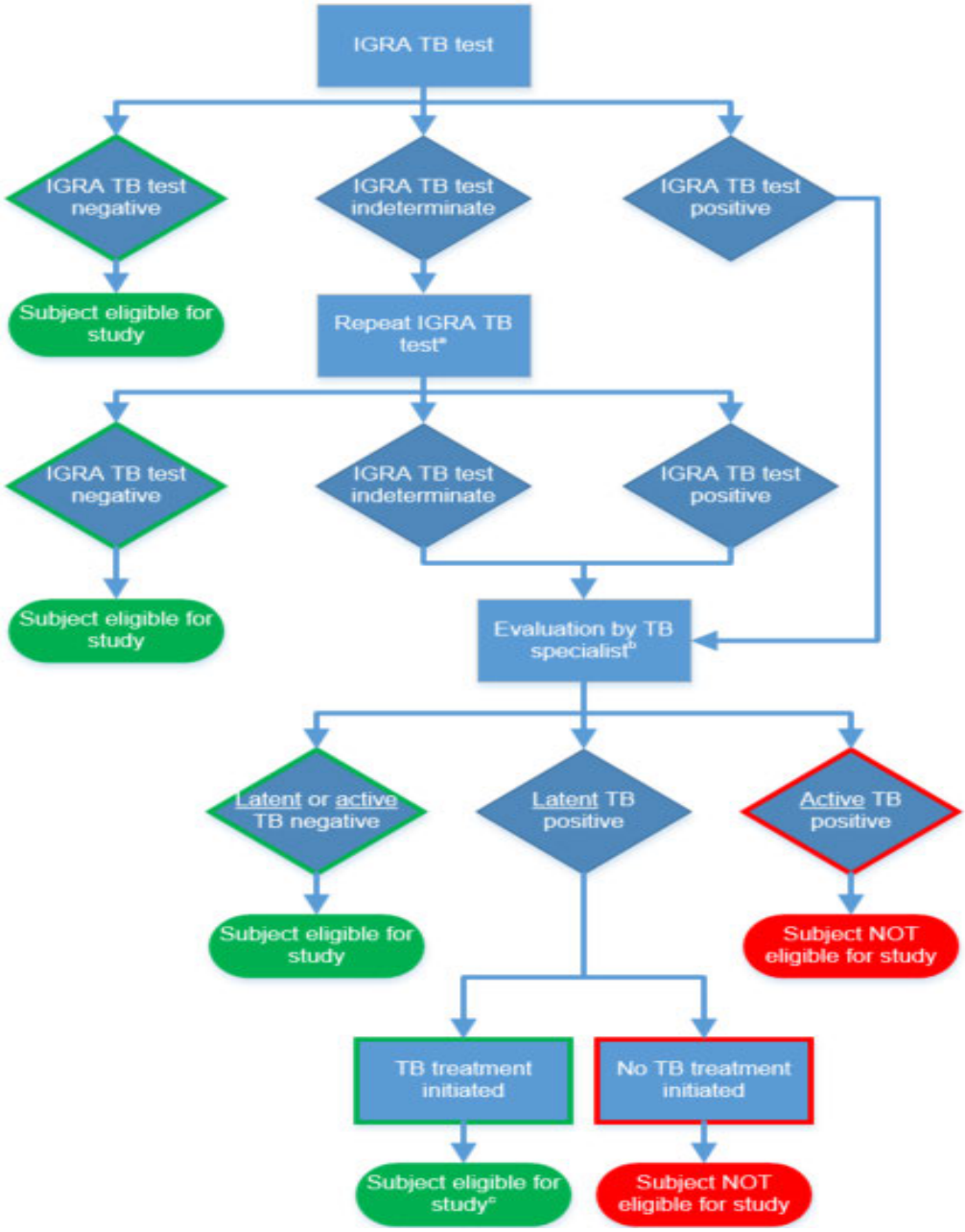
d. NTMB infection is defined as a clinical infection caused by mycobacterial species other than those belonging to the Mycobacterium tuberculosis complex.

e. Tuberculosis test conversion:

   – A positive IGRA result for the current test when previous IGRA test results were negative. All subjects with TB test conversion must immediately stop IMP administration and be referred to a TB specialist for further evaluation. Confirmed TB test conversions should be classified as due to LTBI, active TB infection, or NTMB, and reported to the UCB PS function.

Subject eligibility, retesting requirements, and treatment requirements are presented in Figure 12-1. A schematic diagram of TB test results during the study is presented in Figure 12–2.

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



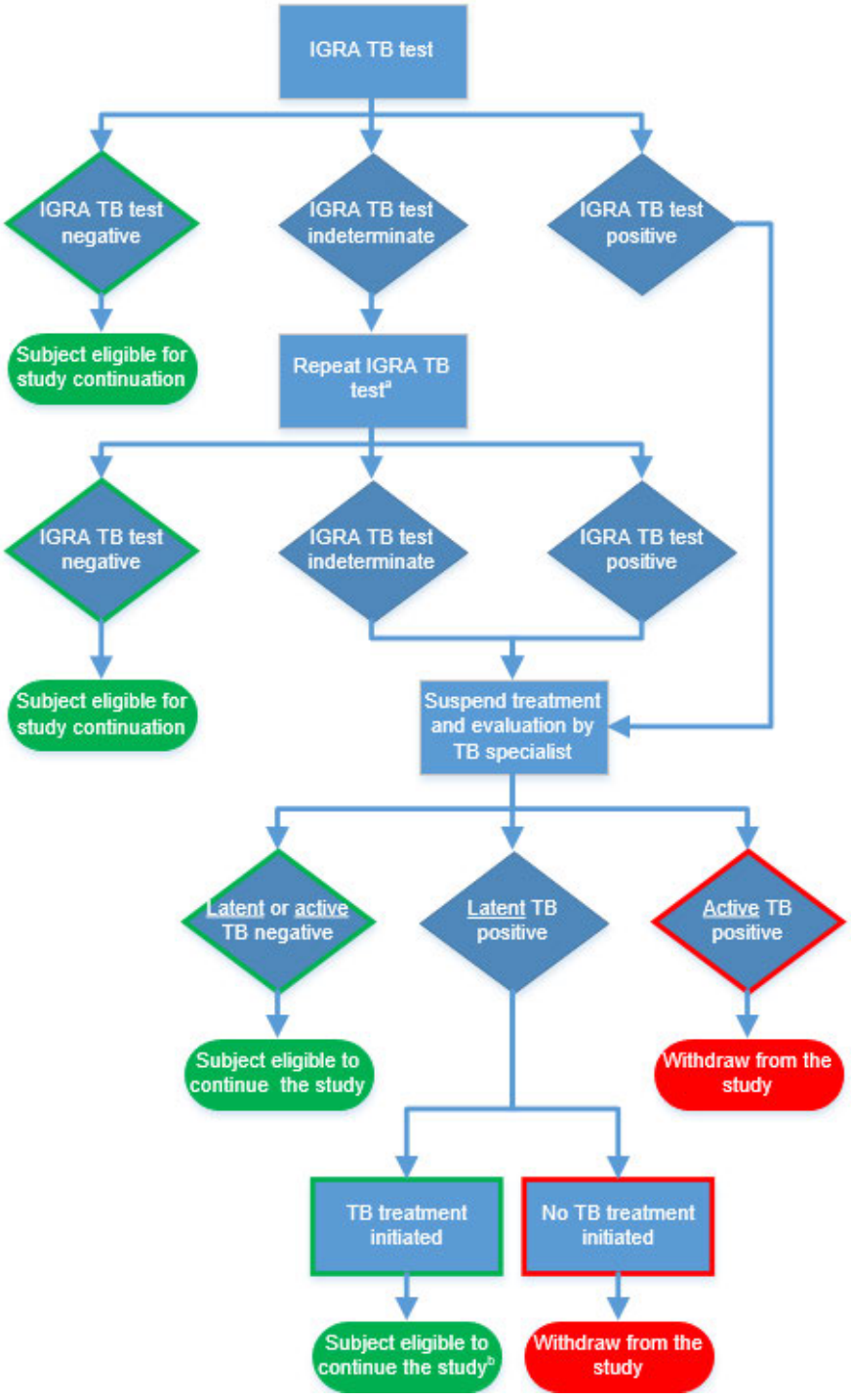
CDC=Center for Disease Control; IGRA=interferon-gamma release assay; LTBI= latent tuberculosis infection; TB=tuberculosis; WHO=World Health Organization

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

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

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

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



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

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

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

12.3.5.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB Test is recommended) will be performed as described in Table 5-1 for all subjects. The test results will be reported as positive, negative, or indeterminate. Positive and indeterminate TB test results that occur during the course of the study must be reported as an AE and appropriately updated once the final diagnosis is known (eg, active TB, latent TB, or false positive TB test). UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, subject must undergo appropriate study-specified withdrawal procedures. The retest during Screening must be done during the protocol-defined Screening window.

12.3.5.2 Chest x-ray for tuberculosis

A plain posteroanterior chest x-ray must be performed in the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The chest x-ray (or, if done, Computed Axial Tomography [CAT] of the chest) must be clear of signs of TB infection (previous or current) before first IMP administration. All chest imaging (particularly x-rays) should be available for review by the Investigator before randomization of the subject. The chest x-ray reading should be repeated if the TB test was confirmed positive. If the second read of the pretreatment chest x-ray is confirmed to be clear, the subject may be included in the study 4 weeks after the start of the TB prophylactic treatment. If the pretreatment chest x-ray is not available for a re-read, it should be repeated after notification to the radiologist that this subject is IGRA positive and confirmed to be clear for signs of TB.

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

12.3.5.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed as described in Table 5-1. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has LTB or active TB (see Exclusion Criterion #10 in Section 6.2). A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection.

12.3.5.4 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 should be withdrawn from the study and receive appropriate TB or prophylaxis therapy.

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

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

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

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

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

12.3.6 Pregnancy testing

Pregnancy testing will consist of serum testing at Screening for all women of childbearing potential. The pregnancy test will be urine at all other visits.

The Screening Visit serum pregnancy test results must be negative and received and reviewed prior to randomization. A negative urine pregnancy test result should be obtained immediately prior to each administration of IMP at the visits specified in Table 5-1. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

12.3.7 Assessment of suicidal ideation and behavior

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

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

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

12.3.8 Patient Health Questionnaire-9 (PHQ-9)

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

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

The PHQ-9 will be assessed at the visits specified in Table 5-1.

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

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

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

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

13.2 Monitoring

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

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

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each subject). 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.

13.2.1 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, or Quality of Life questionnaires, 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.

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by UCB (or designee).

Electronic Patient-Reported Outcome (ePRO) measures (eg, EQ-5D-3L, FACT-F, HAQ-DI, PGA-PsA and, PGA-arthritis) will be completed by each subject and will be collected electronically.

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

13.2.2 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 13.2.1.

13.3 Data handling

13.3.1 Case Report form completion

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

Any change or correction to the eCRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry.

Corrections made after the Investigator's review and signature of the completed eCRF will be resigned and dated by the Investigator.

The Investigator should maintain a list of personnel authorized to enter data into the eCRF. The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic eCRFs and in all required reports.

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

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.

13.3.2 Database entry and reconciliation

Case Report forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. Case Report form data are entered into the clinical database using independent, double-data entry, with the exception of comment fields, which are verified by a second person. The data are entered into the eCRFs once and are subsequently verified if the study is performed using electronic data capture.

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

13.3.3 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.

13.4 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.

13.5 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.

13.6 Audit and inspection

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

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

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

13.7 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.

14 STATISTICS

A description of statistical methods follows and will be described in more detail in the SAP.

14.1 Definition of analysis sets

The following analysis sets were defined:

- The Enrolled Set (ES) consists of all subjects who have given informed consent.
- The Randomized Set (RS) consists of all randomized subjects.
- The Safety Set (SS) consists of all randomized subjects who received at least 1 dose of the IMP.
- The Full Analysis Set (FAS) consists of all randomized subjects who received at least 1 dose of IMP and have valid measurement of all the components of the primary efficacy variable at Baseline.
- The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding of the data. Exclusions from the FAS will be considered important protocol deviations that also result in exclusion from the PPS.

- The Pharmacokinetic Per-Protocol Set (PK-PPS) consists of all randomized subjects who received at least one dose of the IMP and provided at least one quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration. Exclusions from the FAS will be considered important protocol deviations that also result in exclusion from the PK-PPS.
- The Radiographic Set will consist of all subjects in the RS who received at least 1 dose of the IMP and have a valid radiographic image of the hands and feet at Baseline.
- The COVID-19-free Set will consist of all subjects in the RS who had no COVID-19 impact up to the primary efficacy endpoint. This will be defined as subjects not having a COVID-19 related important protocol deviation, nor having an impact based on the COVID-19 eCRF nor having an AE related to COVID-19 nor discontinuing due to COVID-19 up to the time of the primary endpoint.

14.2 General statistical considerations

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

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

14.3 Planned efficacy analyses

14.3.1 Analysis of the primary and secondary efficacy variables

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

For each test, on each binary efficacy endpoint, the null hypothesis is that the conditional odds ratio is equal to one.

H_0: $OR_{T1T2} = 1$

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

H_A: $OR_{T1T2} \neq 1$

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

H_0: $T_1 - T_2 = 0$

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

H_A: $T_1 - T_2 \neq 0$

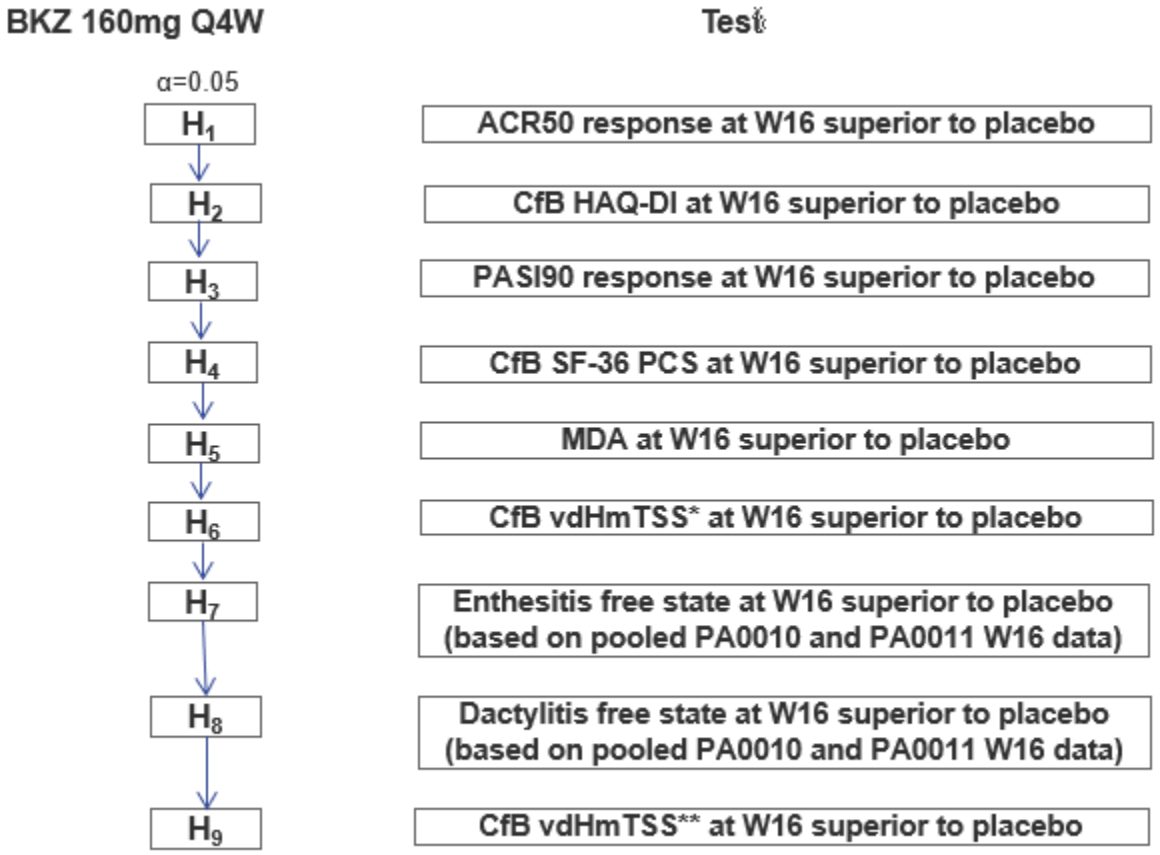
For the primary and secondary variables, the primary comparison is the bimekizumab 160mg sc Q4W vs placebo. Point estimates and 95% confidence intervals (CI) will be calculated.

No formal statistical comparisons will be made with the adalimumab 40mg sc Q2W treatment group.

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

The fixed sequence testing procedure of primary and secondary efficacy endpoints is shown in Figure 14-1.

Figure 14-1: Sequential testing procedure of primary/secondary efficacy endpoints (fixed sequence testing procedure)



ACR=American College of Rheumatology; BKZ=bimekizumab; CfB=change from Baseline; H=hypothesis; HAQ-DI=Health Assessment Questionnaire—Disability Index; hs-CRP=high sensitivity C-reactive protein; MDA=Minimal Disease Activity; PASI=Psoriasis Area and Severity Index; PCS=Physical Component Summary; Q4W=every 4 weeks; SF-36=Short-Form 36-item Health Survey; vdHmTSS=Van der Heijde modified Total Sharp Score; W=Week

* It is planned to enroll a minimum of 45% of subjects who are positive for elevated hs-CRP (hs-CRP ≥6mg/L) and/or who have at least 1 bone erosion at Screening.

** Based on the overall population

14.3.1.1 Analysis of the primary efficacy variable

The primary efficacy variable will be analyzed for all subjects in the RS.

The primary endpoint is the ACR50 response at Week 16. The primary efficacy analysis will evaluate the composite estimand in the RS. The composite estimand combines the clinically meaningful improvement from Baseline in ACR50 response and not discontinuing treatment early. This composite estimand is similar to nonresponder imputation (NRI).

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

1. Population = Subjects enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
2. Subject-level outcome = ACR50 at Week 16.
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving ACR50 at Week 16 and not discontinuing study treatment through Week 16.
4. Population-level summary measure = Conditional odds ratio comparing bimekizumab to placebo.

As the ACR response is based on 7 different component scores, it is necessary to consider various data scenarios that could impact the calculation of response. The rules described here are applicable in the context of the calculation of ACR response and may differ from the rules applied for calculating and summarizing the components individually (some values may need to be imputed for component analysis but are not required here to evaluate ACR response).
The following rules will be applied prior to invoking any imputation analysis at the variable level:

- If a subject has a component value that is equal to 0 at Baseline and the post-Baseline value is greater than or equal to 0, then the percent improvement for that component will be treated as 0 for purposes of ACR response calculations.
- If a subject has component values that are missing at Baseline, then the percent improvement for that component will be treated as missing for purposes of ACR response calculations.

Observed data will be used to calculate ACR response where possible. In case of partial missing data where an observed response may be calculated, imputed data will not change the result.

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

The statistical hypothesis for the ACR50 response at Week 16 is that the conditional odds ratio for ACR50 response in the bimekizumab treatment compared with placebo treatment is equal to 1.

A logistic regression model will be used to assess the treatment effect on ACR50 response at Week 16. The model will include a fixed effect for treatment. The suitability of including the randomization stratification variables, region and bone erosion at Baseline will be assessed and will be added to the model if appropriate. Comparisons will be made using the 2-sided Wald test at a significance level of α=0.05 (ie, H_1 in Figure 14-1). The odds ratio versus placebo, p-value, and the 95% CI will be calculated.

Any use of prohibited or rescue medications through Week 16 would constitute an important protocol deviation which would be accounted for when the sensitivity analysis based on the PPS is performed (see Section 14.3.1.1.1).

14.3.1.1.1 Supportive analyses

Supportive analyses for the primary efficacy variable will be conducted:

1. The analysis will be repeated based on the PPS to evaluate the effect of important protocol deviations on the analysis.
2. The analyses will be repeated for all subjects in the FAS to evaluate the consistency between the RS and the more restrictive FAS. This analysis will only be performed if the number of subjects in RS and FAS are different.
3. The primary comparison will also be repeated for all individual components of the ACR50 response to explore the effect of the signs and symptoms of the individual components on the composite endpoint. Since all ACR components are continuous variables (eg, change from Baseline in TJC), an analysis of covariance (ANCOVA) with treatment, region, and bone erosion at Baseline as fixed effects and the Baseline value as a covariate will be used for the analysis. Note as outlined above, some additional values may need to be imputed for component analysis which are not required to evaluate the overall ACR response.
4. The analysis will be repeated using a modified composite estimand where intercurrent events are defined only as discontinuation due to AE or lack of efficacy.
5. The analysis will be repeated using a treatment policy approach.
6. The analysis will be repeated using observed cases only.
7. The analysis will be repeated using the COVID-19-free Set.

Additional sensitivity and supportive analyses to evaluate varying assumptions related to the handling of missing data will also be performed and are described in Section 14.7.

14.3.1.2 Analysis of the secondary efficacy variables

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

All binary variables that are part of the testing hierarchy are given below:

- PASI90 responders at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines the clinically meaningful improvement from Baseline in PASI90 response and not discontinuing treatment early.
- The proportion of subjects achieving MDA status at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines (1) achieving the MDA status with (2) not discontinuing treatment early.
- The proportion of subjects with enthesitis at Baseline achieving enthesitis-free status at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines (1) achieving the enthesitis-free status with (2) not discontinuing treatment early. For this analysis, the PA0010 and PA0011 data will be pooled.

- The proportion of subjects with dactylitis at Baseline achieving dactylitis-free status at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines (1) achieving the dactylitis-free status with (2) not discontinuing treatment early. For this analysis, the PA0010 and PA0011 data will be pooled.

The statistical hypothesis for the binary variables at Week 16 is that the conditional odds ratio for binary variables in the bimekizumab treatment compared with placebo treatment groups is equal to 1.

The binary variables will be analyzed using the same analysis methods and estimand approach as used for the primary variable (Section 14.3.1.1).

If appropriate ie, where the outcome variable (eg, PASI90 response) is an assessment of skin/dermatological manifestations of PsA the fitted model will exclude the fixed term bone erosion at Baseline.

All continuous variables that are part of the testing hierarchy are given below:

- Change from Baseline in HAQ-DI at Week 16
- Change from Baseline in the SF-36 PCS score at Week 16
- Change from Baseline in vdHmTSS at Week 16

Continuous variables will be analyzed to evaluate the hypothetical estimand as defined below:

1. Population = Subjects enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
2. Subject level outcome = variable as stated in Section 4.2.1
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment prior to Week 16. A hypothetical strategy for addressing intercurrent events will be implemented. This estimand targets the treatment difference in a scenario where withdrawal from study treatment does not occur, such that outcomes for subjects without an intercurrent event are as observed, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16. A multiple imputation strategy will be used to impute data following an intercurrent event.
4. Population-level summary measure = the difference in the adjusted means between bimekizumab 160mg Q4W and placebo.

Any missing data at Week 16 that are not preceded by an intercurrent event (ie, discontinuation of study medication) will also be imputed based on a predefined MI model. In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by monotone regression for monotone missing data.

In the case of vdHmTSS missing data, as vdHmTSS is only collected at Baseline prior to Week 16; missing data at Week 16 will be imputed using monotone regression.

The statistical model for continuous endpoints for the comparison of bimekizumab and placebo will be an ANCOVA model with treatment, bone erosion, and region as fixed effects and the

Baseline value as covariate. The statistical hypothesis for the continuous variables at Week 16 is that the treatment difference between the bimekizumab treatment group and placebo is equal to 0.

All secondary efficacy variables will also be summarized based on observed case data as well as multiple imputation using the modified composite estimand for binary variables.

Variables that are included in the hierarchy will additionally be rerun using the COVID-19-free Set.

14.3.2 Analysis of the other efficacy variables

All other efficacy variables will be analyzed for all subjects in the RS.

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

1. Population = Subjects enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.
2. Subject-level outcome = The given variable and time point being summarized (eg, ACR50 at Week 24)
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment prior to the time point being summarized. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving the given variable at the specified time point and not discontinuing study treatment through that time point.
4. Population-level summary measure = Unadjusted proportion of responders

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

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

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

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

Other binary and continuous efficacy variables will also be summarized based on observed case data (ie, subjects with missing data or who have prematurely discontinued study treatment are treated as missing). Further, binary outcomes will be summarized using the modified composite estimand.

Time to ACR20/50/70 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in days from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects in the placebo group who are rerandomized at Week 16 without achieving response will be censored at the date of the Week 16 Visit. The median time to response, including the 2-sided 95% CI, will be calculated for each treatment. Between group differences will be analyzed with a log-rank statistic.

The time to ACR20/50/70 endpoints with missing data that are not preceded by an intercurrent event as described above will be imputed based on a predefined multiple imputation model as described for the primary efficacy variable.

The time to ACR20/50/70 endpoints will also be analyzed using observed case (OC) data.

14.3.3 Subgroup analyses

Subgroup analyses will be performed on the ACR50 response and the PASI90 response at Week 16. The following variables for subgroup analyses will be defined:

- Age (<45 years of age, ≥45 years of age)
- Gender (male, female)
- Disease duration (<1 year, ≥1 year)
- Region (eg, Asia, Eastern Europe, North America, Western Europe)
- Race
- Weight at Baseline (≤100kg, >100kg)
- Bone erosion (≥1) at Baseline (Yes, No)
- hs-CRP at Baseline (<6mg/L, ≥6mg/L)
- Bone erosion (≥1) and/or hs-CRP ≥6mg/L at Baseline (Yes, No)
- Prior cDMARDs (0, 1, ≥2)
- Concomitantly receiving cDMARDs versus no concomitant cDMARDs
- Concomitantly receiving MTX versus no concomitant MTX
- PSO affected BSA at Baseline (<3%, ≥3% to 10%, >10%)
- BASDAI at Baseline (≤4, >4)

- Anti-bimekizumab antibody status (positive, negative)
- HLA-B27 (positive, negative)

14.4 Planned safety analyses

14.4.1 Safety analyses

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

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

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

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

14.5 Other planned analyses

14.5.1 Pharmacokinetics analyses

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

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

The relationship between bimekizumab plasma concentrations and efficacy response (for example ACR20/50/70) and/or safety endpoints may be explored via a graphical and/or a model based (PK-PD) approach. The data may also be combined with that from other bimekizumab trials. The details of such analysis will be described separately in a data analysis plan, and the analysis itself will be reported separately from the CSR.

14.5.2 Immunological analyses

Anti-bimekizumab antibodies will be assessed using a tiered approach: screening, confirmatory, and titer assays will be used. Anti-bimekizumab antibodies (including positivity) will be summarized by treatment at each scheduled visit at which samples are collected.

14.6 Handling of protocol deviations

Important protocol deviations are deviations from the protocol, which potentially could have a meaningful impact on study conduct or on the primary efficacy, key safety, or PK outcomes for

an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

14.7 Handling of dropouts or missing data

The primary method for assessing the efficacy variables will be the composite estimand approach to handling missing data that is similar to NRI. The sensitivity of results to the approach for handling missing data will be evaluated via supportive analyses using different missing data mechanisms.

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

Missing data will be evaluated as sensitivity analyses using different missing data mechanisms. The following sensitivity analyses for the primary efficacy variable will be conducted:

1. Multiple imputation as described above will be performed using the modified composite estimand. The definition of an intercurrent event is changed from all treatment discontinuation, to discontinuation of treatment due to AE or lack of efficacy.
2. A tipping point analysis will be performed to evaluate missingness assumptions. The tipping point analysis will be performed on the monotone missing data and only if the primary analysis is significant at α=0.05. Various delta adjustments will be made to the assumed responses on the monotone missing data in each treatment group independently with various degrees of plausibility. It will include scenarios where subjects who have missing data and are randomized to bimekizumab have a lower probability of response compared to subjects who have missing data and were randomized to placebo. For binary variables, this includes the worst-case scenario where subjects who have missing data and are randomized to bimekizumab are considered nonresponders, while subjects who have missing data and were randomized to placebo are considered responders. The goal of the tipping point analysis is to systematically vary assumptions until there is no evidence of a treatment effect (if possible). The plausibility of such required delta adjustment will then be assessed. Details will be provided in the SAP.
3. The treatment policy strategy for addressing intercurrent events will be considered. This will be based on an analysis in which all available data at Week 16 regardless of the occurrence of intercurrent events will be considered. This analysis will use the same models specified for the primary and secondary analyses where subjects are analyzed according to their randomized treatment, even if they discontinued study treatment for any reason prior to Week 16 and were no longer on the randomized study treatment when the assessment was performed at Week 16. Even though efforts will be made to collect the primary outcome data for all subjects at Week 16, there may still be some subjects for whom Week 16 efficacy data cannot be obtained. In this case, missing data will be imputed using MI under the assumption of MAR. Results will be combined into a single inference using Rubin's rule. It should be noted that this measures something different from the primary analysis and could be

confounded by placebo subjects who withdraw and are subsequently on another active medication at the time of the Week 16 assessment. Therefore, the results of this analysis should be interpreted in the appropriate context.

4. An additional sensitivity analysis will be based on observed data only for subjects who are still on the initially randomized treatment at Week 16. Subjects with missing data or who have prematurely discontinued study treatment will be treated as missing. The same procedure described as in the main efficacy analysis will be used.

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

14.8 Planned interim analyses and data monitoring

14.8.1 Interim analyses

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

The purpose of the Week 24 interim analysis is to perform a comprehensive evaluation of all available double-blind data for the 3 treatment arms and to prepare a regulatory submission for a marketing authorization application based on this analysis.

For the Week 24 interim analysis, the database will be locked and the treatment codes will be made available to UCB personnel with exception of operational staff working on the study. An interim report will be written. The Investigators and subjects will remain blind to the assigned bimekizumab dosing regimen until the final analysis is completed.

The Week 24 interim analysis will evaluate the primary and secondary efficacy variables, as well as all other efficacy, safety, and PK variables up to Week 24 according to the statistical methods specified in the SAP. No formal alterations to the further study conduct (eg, stopping rules, sample size re-estimation, or changes to eligibility criteria) are planned for this interim analysis.

To ensure blinding of Investigators and subjects, a blinding plan will be written to evaluate the potential bias of the Active Treatment-Blind period, define blinded and unblinded teams, and describe the process of interim results generation and dissemination. The plan will be finalized prior to the lock of the database at the interim analysis.

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

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

Additional data cuts may be prepared following regulatory requests or for publication purposes.

14.8.2 Data monitoring

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

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

Other adjudication committees may be added as necessary.

Both Data Monitoring and Adjudication Committee members may not participate in the study as principal or co-Investigators, or as study subject care physicians and must not be members of the study team at UCB or the conducting CRO. The duration of membership for the committees will be inclusive of planned analyses for PA0010.

14.9 Determination of sample size

Approximately 840 subjects will be randomly assigned in a 3:2:1 ratio to the following treatment groups: bimekizumab 160mg sc Q4W (420 subjects), placebo (280 subjects), adalimumab 40mg sc Q2W (140 subjects).

The primary efficacy analysis is based on the bimekizumab dose versus placebo for ACR50 response at Week 16. It is planned that only descriptive summaries will be provided for the adalimumab reference arm. No statistical comparisons will be made between adalimumab and the other treatment groups.

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

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

14.9.1 Power calculation for primary endpoint

The sample size assumptions for bimekizumab versus placebo are based on the ACR50 response data from the Phase 2b bimekizumab study in subjects with moderate to severe PsA (PA0008). The median ACR50 responses of the top three dose groups (bimekizumab 160mg, 320mg, and 320mg [initial dose] plus 160mg) at Week 12 in the TNF-naïve population are conservatively assumed for the Week 16 endpoint. The observed median ACR50 response rate of the top three bimekizumab doses in the TNF-naïve population in study PA0008 was 43.8%.

The placebo ACR50 response at Week 16 is based on the TNFα-naïve population in PA0008 (6.1% at Week 12, n=33); Mease et al, 2015), FUTURE 2 study in the subgroup of TNFα-naïve subjects (15.9%, n=63; McInnes et al, 2015), FUTURE 3 study (11.8%, n=93; Nash and Mease, 2018), and FUTURE 5 study in a mixed TNFα exposure population (8.1% at Week 16, n=332; Mease et al, 2018). Therefore, the estimated ACR50 response at Week 16 in the placebo group is assumed to be 16%.

The sample size for showing statistical superiority of bimekizumab vs placebo was calculated using a 2-sided 2-sample Chi-square test with continuity correction (Fleiss et al, 1980). Assuming 420 subjects in the bimekizumab group and 280 subjects in the placebo group, the test for detecting statistical superiority of bimekizumab 160mg Q4W vs placebo based on ACR50 response at Week 16 has >99% power to detect a true treatment difference of 27.8% (odds ratio 4.09).

14.9.2 Power calculations for secondary endpoints

The assumptions for power calculations of the secondary endpoints included in the hierarchy, and for which supporting data exists, are based on the interim results of the Phase 2b

bimekizumab study PA0008 and the FUTURE 1, FUTURE 2, FUTURE 5, and SPIRIT P1 studies. All power calculations for binary endpoints were performed using a 2-sided 2-sample Chi-square test with continuity correction (Fleiss et al, 1980). All power calculations for continuous endpoints were performed using a 2-sided 2-group Satterthwaite t-test (Moser et al, 1989).

For the PASI90 response at Week 16, the bimekizumab 160mg Q4W treatment response at Week 12 is 45% (n=20) in the TNFα-naïve population of PA0008 at Week 12 and 46% (n=28) at Week 12 in the mixed TNFα exposure population. The placebo PASI90 response at Week 16 is based on the subgroup analyses of TNFα therapy-naïve subjects in PA0008 (9.1% at Week 12; n=22), FUTURE 2 study (9.7% at Week 24; n=63), and SPIRIT P1 study (1.5% at Week 12; n=67). Therefore, a placebo PASI90 response rate of 10% is assumed. With those assumptions, the study has >99% power to detect a true treatment difference at an assumed 60% of subjects with BSA ≥3% of the planned sample size.

For change from Baseline in HAQ-DI at Week 16, the between treatment differences of the change from Baseline in HAQ-DI of in the mixed TNFα exposure population of the PA0008 at Week 12 were used. The bimekizumab 160mg Q4W treatment group mean change from Baseline in HAQ-DI at Week 12 of -0.37, SD=0.47 (n=41) versus placebo mean change from Baseline in HAQ-DI at Week 12 of -0.13, SD=0.50 (n=42). With those assumptions, the study has >99% power to detect a true treatment difference of -0.24 at the planned sample size.

For change from Baseline in PCS of SF-36 at Week 16, the between treatment differences of the change from Baseline in PCS of SF-36 of the TNFα-naïve population of FUTURE 2 study (Kavanaugh et al, 2016) at Week 24 were used. The bimekizumab 160mg Q4W treatment group assumes the secukinumab 150mg treatment group mean change from Baseline in SF-36 PCS at Week 24 of 7.91, SD 7.38 (N=63) versus placebo mean change from Baseline in SF-36 PCS at Week 24 of 2.08, SD 9.51 (N=63). With those assumptions, the study has >99% power to detect a true treatment difference of 5.83 at the planned sample size.

For MDA at Week 16, the bimekizumab 160mg Q4W treatment response at Week 12 in PA0008 is 46.3% (N=41) in the mixed TNFα exposure population of PA0008. In the placebo group, 14.3% of subjects achieved MDA at Week 12 (n=42). With those assumptions, the study has >99% power to detect a true treatment difference of 32% (odds ratio 5.17) at the planned sample size.

For change from Baseline in vdHmTSS at Week 16, the between treatment differences of the change from Baseline in vdHmTSS at Week 16 of the SPIRIT P1 study in a TNFα-naive population (Mease et al, 2017) were used. The SPIRIT P1 study ixekizumab 80mg sc Q2W treatment group least square (LS) mean change from Baseline at Week 16 0.06 and SD 0.720; and LS mean change from Baseline 0.36 and SD 0.710 for placebo are assumed. With those assumptions, the study has a 95% power to detect a true treatment difference of -0.30, assuming 45% of subjects with elevated hs-CRP and/or bone erosion, in the planned sample size.

There is uncertainty in the final percentage of subjects with elevated hs-CRP and/or bone erosion at Baseline that will be recruited to the study and the variability in the subgroup. To demonstrate the sensitivity of the sample size calculation for this study, Table 14–1 shows the power function for a fixed total sample size of 840 subjects in the RS population for this secondary efficacy analysis, varying the percentage of subjects with elevated hs-CRP and/or bone erosion at

Baseline and the treatment difference and estimated standard deviation on the change from Baseline in vdHmTSS at Week 16.

Table 14–1: Treatment effect by elevated hs-CRP and/or bone erosion at Baseline for secondary efficacy analyses

Subjects with elevated hs-CRP and/or bone erosion at Baseline	Treatment difference/standard deviation	
	Treatment effect = -0.3 SD=0.72 vs 0.71	Treatment effect = -0.35 SD=0.81 vs 0.93
20%	67	62
25%	76	72
30%	84	79
35%	89	85
40%	92	89
45%	95	92
50%	96	95

hs-CRP=high sensitivity C-reactive protein; SD=standard deviation

For enthesis free-state at Week 16, enthesis resolution data from the FUTURE 5 study at Week 16 were used to estimate the bimekizumab 160mg Q4W treatment and placebo groups. In FUTURE 5 The treatment effect estimate from the secukinumab 150mg treatment group at Week 16 was 55% (n=141) and the placebo group estimate was 36% (n=192). Assuming a BKZ response of 55% and a placebo rate of 39% and having 25% of subjects with Baseline enthesis the pooled PA0010/PA0011 the studies have a 69% power to detect a true treatment difference of 16% (odds ratio 1.91).

For dactylitis-free state at Week 16, dactylitis resolution data of the FUTURE 5 study (Mease et al, 2018) at Week 16 were used to estimate the bimekizumab 160mg Q4W treatment and placebo groups. The treatment effect estimate from the secukinumab 150mg treatment group at Week 16 of 56% (n=103) is assumed versus a placebo group estimate of 32% (n=124). With those assumptions and having 11% of subjects with Baseline dactylitis, the pooled PA0010/PA0011 studies have a 66% power to detect a true treatment difference of 24% (odds ratio 2.71).

Treatment difference in change from Baseline in vdHmTSS at Week 16 in the overall population is estimated using the data from the FUTURE 5 study in a mixed TNFα exposure population. The bimekizumab 160mg Q4W group treatment difference compared to placebo is estimated to be the same as the difference in change from Baseline in vdHmTSS at Week 16 between the secukinumab 150mg group and placebo which is 0.42, assuming a SD of 1.13 for bimekizumab and SD=2.44 for placebo. With these assumptions the study has 76% power to detect a treatment difference of 0.42 in the planned sample size.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 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 US must include the use of a Health Insurance Portability and Accountability Act Authorization form.

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

15.2 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.

15.3 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.

15.4 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).

15.5 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.

16 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.

17 REFERENCES

Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, et al. Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). Arthritis Rheum. 2005a;52:1227-36.

Antoni C, Krueger GG, de Vlam K, Birbara C, Beutler A, Guzzo C, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005b;64:1150–57.

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

Cella D, Wilson H, Shalhoub H, Revicki DA, et al. Content validity and psychometric evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in patients with psoriatic arthritis. J Patient Rep Outcomes. 2019;3(1):5.

CHMP/EWP/438/04. Guideline of Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis. 14 December 2006.

Coates LC, FitzGerald O, Mease PJ, et al. Development of a disease activity and responder index for psoriatic arthritis – Report of the Psoriatic Arthrits Module at OMERACT 11. J Rheumatol 2014;41:782-91.

Coates LC, Fransen J, Helliwell PS. Defining minimal disease activity in psoriatic arthritis: a proposed objective target for treatment. Ann Rheum Dis. 2010;69:48–53.

Coates LC, Gladman DD, Nash P, et al. Secukinumab provides sustained PASDAS-defined remission in psoriatic arthritis and improves health-related quality of life in patients achieving remission: 2-year results from the Phase III FUTURE 2 study. Arthritis Res Ther. 2018;20(1):272. doi: 10.1186/s13075-018-1773-y.

Cochran WG. Some Methods for Strengthening the Common $\chi 2$ Tests. Biometrics. 1954;10(4):417–51.

Feldman SR, Krueger GG. Psoriasis assessment tools in clinical trials. Ann Rheum Dis 2005;64(Suppl II):ii65–ii68.

Felson DT, Anderson J, Boers M, Bombardier C, Chernoff M, Fried B. The American college of rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis & Rheum. 1993;36(6):729-740.

Fernández-Sueiro JL, Willisch A, Pertega-Díaz S, Tasende JA, Fernández-Lopez C, Galdo F, et al. Evaluation of ankylosing spondylitis spinal mobility measurements in the assessment of spinal involvement in psoriatic arthritis. Arthritis Rheum. 2009;61:386-92.

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

Fujishima S, Watanabe H, Kawaguchi M, Suzuki T, Matsukura S, Homma T, et al. Involvement of IL-17F via the induction of IL-6 in psoriasis. Arch Dermatol Res. 2010;302:499-505.

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(12):2286-91.

Genovese MC, Mease PJ, Thomson GT, Kivitz AJ, Perdok RJ, Weinberg MA, et al. Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. J Rheumatol. 2007;34:1040–50.

Genovese MC, Van den Bosch F, Roberson SA, Bojin S, Biagini IM, Ryan P, et al. LY2439821, a humanized anti-interleukin-17 monoclonal antibody, in the treatment of patients with rheumatoid arthritis: a phase I randomized, double-blind, placebo-controlled, proof-of-concept study. Arthritis Rheum. 2010;62:929-39.

Gladman DD. Clinical features and diagnostic considerations in psoriatic arthritis. Rheum Dis Clin North Am. 2015;41(4):569-79

Gladman DD, Mease PJ, Cifaldi MA, Perdok RJ, Sasso E, Medich J. Adalimumab improves joint-related and skin-related functional impairment in patients with psoriatic arthritis: patient reported outcomes of the Adalimumab Effectiveness in Psoriatic Arthritis Trial. Ann Rheum Dis. 2007;66:163–68.

Gossec L, de Wit M, Klitz U, Braun J, Kalyoncu U, Scrivo R, et al. A patient-derived and patient-reported outcome measure for assessing psoriatic arthritis: elaboration and preliminary validation of the Psoriatic Arthritis Impact of Disease (PsAID) questionnaire, a 13-country EULAR initiative. Ann Rheum Dis. 2014;73:1012-19.

Gottlieb A, Menter A, Mendelsohn A, Shen Y-K, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. Lancet. 2009;373:633-40.

Harper EG, Guo C, Rizzo H, Lillis JV, Kurtz SE, Skorcheva I, et al. Th17 cytokines stimulate CCL20 expression in keratinocytes in vitro and in vivo: implications for psoriasis pathogenesis. J Invest Dermatol. 2009;129:2175-83.

Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: Which is the best instrument to use? J Rheumatol. 2007;34:1302-6.

Helliwell PS, Firth J, Ibrahim GH, Melsom RD, Shah I, Turner DE. Development of an assessment tool for dactylitis in patients with psoriatic arthritis. J Rheumatol. 2005;32:1745-50.

Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A on psoriasis, rheumatoid arthritis, and uveitis. Sci Transl Med. 2010;2:52-72.

HUMIRA SPC. http://www.rxaabbvie.com/pdf/humira.pdf. Revised October 2016.

Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. Br J Dermatol. 2009;160:319-24.

Kavanaugh A, Antoni C, Krueger GG, Yan S, Bala M, Dooley LT, et al. Infliximab improves health related quality of life and physical function in patients with psoriatic arthritis. Ann Rheum Dis. 2006;65:471–77.

Kavanaugh A, McInnes I, Mease P, Krueger GG, Gladman D, Gomez-Reino J, et al. Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: twenty-four–week efficacy and safety results of a randomized, placebo-controlled study. Arthritis Rheum. 2009;60:976-86.

Kavanaugh A, Van der Heijde D, McInnes IB, Mease P, Krueger GG, Gladman DD, et al. Golimumab in psoriatic arthritis: one-year clinical efficacy, radiographic, and safety results from a phase III, randomized, placebo controlled trial. Arthritis Rheum. 2012;64:2504-17.

Kavanaugh A, McInnes I, Mease P, Hall S, Chinoy H, Kivitz AJ, et al. Efficacy of subcutaneous secukinumab in patients with active psoriatic arthritis stratified by prior tumor necrosis factor inhibitor use: results from the randomized placebo-controlled FUTURE 2 study. J Rheum. 2016;43:9.

Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. P T 2010;35:680-9.

Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. N Engl J Med. 2012;366:1190-9.

Maksymowych WP, Mallon C, Morrow S, Shojania K, Olszynski WP, Wong RL, et al. Development and validation of the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index. Ann Rheum Dis. 2009;68(6):948-953

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

McHugh NJ, Balachrishnan C, Jones SM. Progression of peripheral joint disease in psoriatic arthritis: a 5-year prospective study. Rheumatology. 2003;42:778–83.

McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386:1137-46.

McInnes IB, Sieper J, Braun J, Emery P, Van der Heijde D, Isaacs JD, et al. Efficacy and safety of secukinumab, a fully human anti interleukin-IL17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. Ann Rheum Dis. 2014;73:349-56.

Mease PJ. Measures of psoriatic arthritis. Arthritis Care & Research 2011;63(S11):S64-85.

Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, et al. Adalimumab for the treatment of subjects with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo controlled trial. Arthritis Rheum. 2005;52:3279-89.

Mease PJ, Kivitz AJ, Burch FX, Siegel EL, Cohen SB, Ory P, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum. 2004;50:2264–72.

Mease PJ, McInnes IB, Kirkham B, Kavanaugh, A, Rahman, P, Van der Heijde D, et al. Secukinumab inhibition of Interleukin-17A in patients with psoriatic arthritis. N Engl J Med. 2015;373:1329-39.

Mease P, van der Heijde D, Landewé R, Mpofu S, Rahman P, Tahir H, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis. 2018;77(6):890-7.

Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al and SPIRIT-P1 Study Group. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis. 2017;76(1):79-87.

Moser BK, Stevens GR, Watts CL. The Two-Sample T Test Versus Satterthwaite's Approximate F Test Article. Communication in Statistics-Theory and Methods 1989(11):3963-3975.

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.

Nash P, Mease PJ, McInnes IB, Rahman P, Ritchlin CT, Blanco R, et al and FUTURE 3 study group. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). Arthritis Res Ther. 2018;15;20(1):47.

Ogdie A, Weiss P. The epidemiology of psoriatic arthritis. Rheum Dis Clin North Am. 2015;41(4):545-68.

Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, et al. Brodalumab, an anti–interleukin-17–receptor antibody for psoriasis. N Engl J Med. 2012;366:1181-9.

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.

Raychaudhuri SP, Raychaudhuri SK, Genovese MC. IL-17 receptor and its functional significance in psoriatic arthritis. Mol Cell Biochem. 2012;359:419–29.

Reilly MC, Zbronzek AS, Dukes EM. The Validity and Reproducibility of a Work Productivity and Activitiy Impairment Instrument. PharmacoEconomics. 1993:4(5):353-365.

Salaffi F, Carotti M, Gasparini S, INtorcia M, Grassi W. The health-related quality of life in rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis: a comparison with a selected sample of healthy people. Health Qual Life Outcomes. 2009;7:25.

Van der Heijde D, Sharp J, Wassenberg S, Gladman DD. Psoriatic arthritis imaging: a review of scoring methods. Ann Rheum Dis. 2005;64;ii61-ii64.

Van der Heijde D, Landewé RB, Mease PJ, McInnes IB, Conaghan PG, Pricop L, et al. Brief Report: Secukinumab Provides Significant and Sustained Inhibition of Joint Structural Damage in a Phase III Study of Active Psoriatic Arthritis. Arthritis Rheumatol. 2016;68(8);1914-21.

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.

Watanabe H, Kawaguchi M, Fujishima S, Ogura M, Matsukura S, Takeuchi H, et al. Functional characterization of IL-17F as a selective neutrophil attractant in psoriasis. J Invest Dermatol. 2009;129:650-6.

18 APPENDICES

18.1 Classification Criteria for Psoriatic Arthritis

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

Table 18-1: CASPAR Criteria

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

CASPAR=Classification Criteria for Psoriatic Arthritis

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

18.2 Protocol Amendment 1

Rationale for the amendment

This protocol has been amended to update the completed and ongoing studies information, clarify study procedures, update the description of the IMP, and to apply a minimum percentage for enrollment of subjects who are positive for elevated hs-CRP and/or have at least 1 bone erosion at Screening.

Modifications and changes

Global changes:

The following changes were made throughout the protocol and are not included in specific changes section:

- The company name was changed from UCB Biopharma SPRL to UCB Biopharma SRL
- The term “legal representative” was deleted from protocol, as it is not applicable to PA0010
- “joint erosion” was changed to “bone erosion”
- Minor spelling, editorial, and formatting changes were made throughout the document

Specific changes:

Change #1

Study Contact Information

Sponsor

UCB Biopharma SPRL

Allée de la Recherche 60

1070 Brussels

BELGIUM

Sponsor Study Physician

Name:	[redacted]
Address:	208 Bath Road Slough SL1 3WE
Phone:	[redacted]

Clinical Project Manager

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

Clinical Trial Biostatistician

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

Has been changed to:

Sponsor

UCB Biopharma ~~SPRL~~ **SRL**

Allée de la Recherche 60

1070 Brussels

BELGIUM

Sponsor Study Physician

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

Clinical Project Manager

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

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB ~~BIOSCIENCES GmbH~~ ~~Alfred Nobel Strasse 10~~ **208 Bath Road** ~~40789 Monheim am Rhein~~ **Slough SL1 3WE** ~~GERMANY~~ **UNITED KINGDOM**
Phone:	[redacted]

Change #2

List of Abbreviations

The following abbreviations were added:

HS	**hidradenitis suppurativa**
OS	**observed case**
TNF	**tumor necrosis factor**
TNFα	**tumor necrosis factor alpha**
UC	**ulcerative colitis**

Change #3

Section 1 Summary, paragraphs 7 through 10 (last paragraph)

It is planned to enroll a minimum of 35% of subjects with elevated high sensitivity C-reactive protein (hs-CRP) and/or with at least one bone erosion (hs-CRP ≥6mg/L and/or erosion-positive).

During the Double-Blind Treatment and Active Treatment-Blind Periods, permitted rescue therapy after Week 16 is described in Section 5.4. Subjects' permitted background medications may be changed if the subject is not responding as per Investigator assessment.

Subjects completing Week 52 are eligible for enrollment in an extension study where all subjects will receive bimekizumab.

Approximately 840 subjects will be randomly assigned in a 3:2:1 ratio (stratified by region and joint erosion [≥1]) to the following treatment groups: bimekizumab 160mg sc Q4W (420 subjects), placebo (280 subjects), and adalimumab sc 40mg every 2 weeks (Q2W) (140 subjects). The planned number of study sites is approximately 150.

Has been changed to:

It is planned to enroll a minimum of ~~35~~**45**% of subjects **who are positive for** ~~with~~ elevated high sensitivity C-reactive protein (hs-CRP **≥6mg/L**) and/or ~~with~~**who have** at least ~~one~~**1** bone erosion **at Screening**~~(hs-CRP ≥6mg/L and/or erosion-positive)~~.

During the Double-Blind Treatment and Active Treatment-Blind Periods, permitted rescue therapy after Week 16 is described in Section 5.4. Subjects' permitted background medications may be changed if the subject is not responding as per Investigator assessment.

Subjects completing Week 52 are eligible for enrollment in an extension study where all subjects will receive bimekizumab.

Approximately 840 subjects will be randomly assigned in a 3:2:1 ratio (stratified by region and ~~joint~~ **bone** erosion [**0,** ≥1]) to the following treatment groups: bimekizumab 160mg sc Q4W (420 subjects), placebo (280 subjects), and adalimumab sc 40mg every 2 weeks (Q2W) (140 subjects). The planned number of study sites is approximately 150.

Change #4

Section 2.2 Bimekizumab, paragraph 2

While anti-IL-17A antibodies have demonstrated efficacy in subjects with PSO, PsA, and AS, there is currently no therapeutic approach available that fully inhibits the activity of IL-17F. Bimekizumab selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro. Therefore, it permits an evaluation of the potential for additional efficacy, which may be conferred by dual inhibition of both cytokines in patients with diseases in which both cytokines are active. Furthermore, a proof-of-concept study with bimekizumab in subjects with moderate to severe PsA demonstrated a strong efficacy signal that warrants further exploration of bimekizumab in this indication. A Phase 2b, dose-ranging study (PA0008) is an ongoing study that was designed to investigate the efficacy and safety of various bimekizumab dose regimens in subjects with active PsA. The current Phase 3, randomized, double-blind, placebo-controlled, and active controlled confirmatory study (PA0010) is designed to investigate the efficacy and safety of bimekizumab in subjects with active PsA.

Has been changed to:

While anti-IL-17A antibodies have demonstrated efficacy in subjects with PSO, PsA, and AS, there is currently no therapeutic approach available that fully inhibits the activity of IL-17F. Bimekizumab selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro. Therefore, it permits an evaluation of the potential for additional efficacy, which may be conferred by dual inhibition of both cytokines in patients with diseases in which both cytokines are active. Furthermore, a proof-of-concept study **(PA0007)** with bimekizumab in subjects with moderate to severe PsA demonstrated a strong efficacy signal that warrants further exploration of bimekizumab in this indication. A Phase 2b, dose-ranging study (PA0008) ~~is an ongoing study~~

~~that~~ was designed to investigate the efficacy and safety of various bimekizumab dose regimens in subjects with active PsA. The current Phase 3, randomized, double-blind, placebo-controlled, and active controlled confirmatory study (PA0010) is designed to investigate the efficacy and safety of bimekizumab in subjects with active PsA.

Change #5

Section 2.2.1 Nonclinical, paragraph 4

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

Has been changed to:

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

Change #6

Section 2.2.2.1 Completed studies

This section was updated to reflect the studies that have completed since the original protocol was written. Study descriptions for non-PsA studies were deleted and cross-reference to the bimekizumab IB was added for detail of these studies. PA0007 summary remains, and a summary of the recently completed PA0008 study was added.

Change #7

Section 2.2.2.2 Ongoing studies

This section was updated to reflect studies that are ongoing as of 02 Dec 2019.

Change #8

Section 4.2.1 Secondary efficacy variables

The secondary efficacy variables for this study are as follows:

- PASI90 response at Week 4 and Week 16 in the subgroup of subjects with PSO involving at least 3% BSA at Baseline

- Change from Baseline in Health Assessment Questionnaire—Disability Index (HAQ-DI) at Week 16
- Change from Baseline in the Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Week 16
- Minimal Disease Activity (MDA) response at Week 16
- Change from Baseline in Van der Heijde modified Total Sharp Score (vdHmTSS) at Week 16
- Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of subjects with dactylitis at Baseline
- Enthesitis-free state based on the Leeds Enthesitis Index (LEI) at Week 16 in the subgroup of subjects with enthesitis at Baseline
- ACR20 response at Week 16
- ACR70 response at Week 16
- Proportion of subjects with an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) AND at least a 2-grade reduction from Baseline at Week 4 and Week 16 in the subset of subjects with psoriatic skin lesions at Baseline
- Change from Baseline in the Patient's Assessment of Arthritis Pain (PtAAP) at Week 16
- Enthesitis-free state based on the Spondyloarthritis Research Consortium of Canada (SPARCC) index at Week 16 in the subgroup of subjects with enthesitis at Baseline
- Change from Baseline in Psoriatic Arthritis Impact of Disease-12 (PsAID-12) at Week 16

Has been changed to:

The secondary efficacy variables for this study are as follows:

- Change from Baseline in Health Assessment Questionnaire—Disability Index (HAQ-DI) at Week 16
- PASI90 response at Week 4 and Week 16 in the subgroup of subjects with PSO involving at least 3% BSA at Baseline
- Change from Baseline in the Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Week 16
- Minimal Disease Activity (MDA) response at Week 16
- Change from Baseline in Van der Heijde modified Total Sharp Score (vdHmTSS) **in subjects with elevated hs-CRP and/or at least 1 bone erosion at Baseline** at Week 16
- Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of subjects with dactylitis at Baseline
- **Change from Baseline in** ~~Enthesitis-free state based on~~ the Leeds Enthesitis Index (LEI) at Week 16 in the subgroup of subjects with enthesitis at Baseline
- **Change from Baseline in vdHmTSS in the overall population at Week 16**

- ACR20 response at Week 16
- ACR70 response at Week 16
- Proportion of subjects with an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) AND at least a 2-grade reduction from Baseline at Week 4 and Week 16 in the subset of subjects with psoriatic skin lesions at Baseline
- Change from Baseline in the Patient's Assessment of Arthritis Pain (PtAAP) at Week 16
- Enthesitis-free state based on the Spondyloarthritis Research Consortium of Canada (SPARCC) index at Week 16 in the subgroup of subjects with enthesitis at Baseline
- Change from Baseline in Psoriatic Arthritis Impact of Disease-12 (PsAID-12) at Week 16

Change #9

Section 4.2.2 Secondary safety variables

Secondary safety variables to be assessed are as follows:

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

Has been changed to:

Secondary safety variables to be assessed are as follows:

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

Change #10

Section 4.3.1 Other efficacy variables, the following variables had changes and/or clarifications

- The percentage of ACR50 responders at Week 16 and maintaining response at Week 52
- Change from Baseline in vdHmTSS total score and in erosion and joint space narrowing (subscores)
- Percentage of subjects with no radiographic joint damage progression (Change from Baseline vdHmTSS of ≤0.5)
- Change from Baseline in PsAID-12
- Change from Baseline in the Patient Health Questionnaire-9 (PHQ-9)
- Change from Baseline in the EQ-5D-3L utility score

Has been changed to:

- The ~~percentage~~**proportion** of ACR50 responders at Week 16 and maintaining response at Week 52
- Change from Baseline in vdHmTSS total score and in erosion and joint space narrowing (subscores) **in subjects with elevated hs-CRP and/or with at least 1 bone erosion at Baseline**
- ~~Percentage~~**Proportion** of subjects with no radiographic joint damage progression (change from Baseline vdHmTSS of ≤0.5)
- Change from Baseline in PsAID-12**, in the individual domains of PsAID-12**
- ~~Change from Baseline in the Patient Health Questionnaire-9 (PHQ-9)~~
- ~~Change from Baseline in the EQ-5D-3L utility score~~

Change #11

Section 4.3.1 Other efficacy variables, the following new variables were added:

- **Change from Baseline in vdHmTSS total score and in erosion and joint space narrowing (subscores) in the overall population**
- **Subjects achieving PsAID-Score ≤4**
- **Change from Baseline in Physician's Global Assessment of Arthritis (PhGA-Arthritis)**
- **Change from Baseline in Patient's Global Assessment of Arthritis (PGA-Arthritis)**

Change #12

Section 4.3.2 Other safety variables, PHQ-9 variable added (was removed from Section 4.3.1 Other efficacy variables)

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

Change #13

Section 5.1 Study description, paragraphs 1 through 5

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-reference study to evaluate the efficacy and safety of bimekizumab in subjects with active PsA. To be eligible to participate in this study, subjects must be adults with a diagnosis of active PsA based on the CASPAR criteria and have active disease with TJC ≥3 and SJC ≥3. It is planned to enroll a minimum of 35% of subjects with elevated hs-CRP and/or with at least one bone erosion (hs-CRP ≥6mg/L and/or erosion-positive).

Subjects should not have previously been treated with any biologic drugs for PsA or PSO. Detailed inclusion and exclusion criteria are presented in Section 6.1 and Section 6.2, respectively.

The study will include 3 periods: a Screening Period (≥14 days to ≤35 days), a Treatment Period (52 weeks), and a Safety Follow-up Period (20 weeks after the final dose of IMP). The Treatment Period will consist of a 16-week Double-Blind Treatment Period followed by a 36-week Active Treatment-Blind Period. Permitted rescue therapy changes after Week 16 are described in Section 5.4. The maximum study duration per subject will be up to 73 weeks.

Eligible subjects will be randomized 3:2:1 (stratified by region and joint erosion [≥1]) to receive 1 of 3 blinded treatments (bimekizumab 160mg sc Q4W, placebo, or active-reference [adalimumab 40mg sc Q2W]), and will remain on their allowable background medication. Details of the Treatment Period are provided in Section 5.3.

Subjects completing Week 52 are eligible for enrollment in an extension study to continue to receive bimekizumab.

Has been changed to:

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-reference study to evaluate the efficacy and safety of bimekizumab in subjects with active PsA. To be eligible to participate in this study, subjects must be adults with a diagnosis of active PsA based on the CASPAR criteria and have active disease with TJC ≥3 and SJC ≥3. It is planned to enroll a minimum of ~~35~~**45**% of subjects ~~with~~**who are positive for** elevated hs-CRP **(hs-CRP ≥6mg/L)** and/or ~~with~~**who have** at least ~~one~~**1** bone erosion **at Screening** ~~(hs-CRP ≥6mg/L and/or erosion positive)~~.

Subjects should not have previously been treated with any biologic drugs for PsA or PSO. Detailed inclusion and exclusion criteria are presented in Section 6.1 and Section 6.2, respectively.

The study will include 3 periods: a Screening Period (≥14 days to ≤35 days), a Treatment Period (52 weeks), and a Safety Follow-up Period (20 weeks after the final dose of IMP). The Treatment Period will consist of a 16-week Double-Blind Treatment Period followed by a 36-week Active Treatment-Blind Period. Permitted rescue therapy changes after Week 16 are described in Section 5.4. The maximum study duration per subject will be up to 73 weeks.

Eligible subjects will be randomized 3:2:1 (stratified by region and ~~joint~~**bone** erosion [**0,** ≥1]) to receive 1 of 3 blinded treatments (bimekizumab 160mg sc Q4W, placebo, or active-reference [adalimumab 40mg sc Q2W])~~,~~ and will remain on their allowable background medication. Details of the Treatment Period are provided in Section 5.3.

Subjects completing Week 52 **and meeting eligibility criteria** are eligible for enrollment in an extension study to continue to receive bimekizumab.

Change #14

New Section 5.2.1 Within-study rescreening/retesting requirements

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

- **Subjects who fail to meet the eligibility criteria for PHQ-9, electronic Columbia-Suicide Severity Rating Scale (eC-SSRS), or the tuberculosis (TB) questionnaire are not allowed to be rescreened.**

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

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

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

Change #15

Section 5.3.1 Double-Blind Treatment Period, paragraph 1

During the Double-Blind Treatment Period, subjects will be randomized 3:2:1 (stratified by region and joint erosion [≥1]) to 1 of 3 blinded treatments.

Has been changed to:

During the Double-Blind Treatment Period, subjects will be randomized 3:2:1 (stratified by region and ~~joint~~**bone** erosion [**0,** ≥1]) to 1 of 3 blinded treatments.

Change #16

Section 5.7 Planned number of subjects and sites

Approximately 840 subjects will be randomly assigned in a 3:2:1 ratio (stratified by region and joint erosion) to the following treatment groups: bimekizumab 160mg sc Q4W (420 subjects), placebo (280 subjects), and adalimumab 40mg sc Q2W (140 subjects). The planned number of study sites is approximately 150.

Has been changed to:

Approximately 840 subjects will be randomly assigned in a 3:2:1 ratio (stratified by region and ~~joint~~**bone** erosion **[0, ≥1]**) to the following treatment groups: bimekizumab 160mg sc Q4W (420 subjects), placebo (280 subjects), and adalimumab 40mg sc Q2W (140 subjects). The planned number of study sites is approximately 150.

Change #17

Section 5.7.1 Enrollment of hs-CRP/bone erosion positive subjects

It is planned to enroll a minimum of 35% of subjects with elevated hs-CRP and/or with at least one bone erosion (hs-CRP ≥6mg/L and/or erosion-positive).

Has been changed to:

It is planned to enroll a minimum of ~~35~~**45**% of subjects ~~with~~**who are positive for** elevated hs-CRP **(hs-CRP ≥6mg/L)** and/or ~~with~~**who have** at least ~~one~~**1** bone erosion **at Screening** ~~(hs-CRP ≥6mg/L and/or erosion-positive)~~.

Change #18

Table 5-1: Schedule of study assessments footnote a

[a] Visit windows of ±2 days are allowed for all visits up to Week 16 and ±3 days are allowed for all visits after Week 16. The time between study treatment doses should be ≥12 days and ≤16 days or ≥11 days and ≤17 days, respectively. The Safety Follow-Up Visit window is scheduled -3 and +7 days from the final dose.

Has been changed to:

[a] Visit windows of ±2 days are allowed for all visits up to Week 16 and ±3 days are allowed for all visits after Week 16. The time between study treatment doses should be ≥12 days and ≤16 days or ≥11 days and ≤17 days, respectively. ~~The Safety Follow-Up~~**For the SFU** Visit ~~window is~~**, the visit should occur no more than 3 days prior to the** scheduled ~~-3~~**visit date** and ~~+~~**within** 7 days ~~from the final dose~~.**after the scheduled visit date (-3 days/+7 days)**.

Change #19

Table 5-1: Schedule of study assessments footnote o

[o] Circumference measured in millimeters.

Has been changed to:

[o] Circumference measured in millimeters. **The LDI assessment of dactylitis will be obtained for all subjects at the Baseline visit. Subsequent to the Baseline visit, the LDI assessment will be obtained only for those subjects who had dactylitis at Baseline (as per the LDI assessment performed at Baseline).**

Change #20

Section 6.1 Inclusion criteria, #1 and #2

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

Has been changed to:

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

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

Change #21

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

The PDILI criterion below requires immediate discontinuation of IMP for:

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

Has been changed to:

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

- Subjects with either of the following:
  - ALT or AST ≥8xULN
  - ALT or AST ≥3xULN and coexisting total bilirubin ≥2xULN

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

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

Change #22

Section 7.1 Description of investigational medicinal products, first bullet

- [redacted]

Has been changed to:

- [redacted].

Change #23

Table 7-2: Prohibited or restricted medications and required wash-out periods, third row

Oral corticosteroids	Any dose regimen	Any change in dose/dose regimen in the 28 days prior to the Baseline Visit.

Has been changed to:

Oral corticosteroids	Any dose regimen	Any change in dose/dose regimen in the ~~28~~**14** days prior to the Baseline Visit.

Change #24

Table 7-2: Prohibited or restricted medications and required wash-out periods, 10th row

-methotrexate [a]	Any dose regimen	Initiation within 12 weeks prior to the Baseline Visit unless Inclusion Criterion #11 is met. Administration of LEF and MTX together is not permitted at any time during the study.

Has been changed to:

-methotrexate [a]	Any dose regimen	Initiation ~~within~~**less than** 12 weeks prior to the Baseline Visit unless Inclusion Criterion #11 is met. Administration of LEF and MTX together is not permitted at any time during the study.

Change #25

Section 8 Study Procedures By Visit, paragraph 1

The schedule of study assessments (Table 5-1) provides an overview of study assessments. A list of procedures to be completed at each visit is described below. Visit windows of ±2 days are allowed from the first dose at all visits through to Week 16. During the 16-week Double-Blind Period, the time between doses should be ≥12 days and ≤16 days. Visit windows of ±3 days are allowed for all visits after Week 16. The time between doses during the Active Treatment-Blind Period should be ≥11 days and ≤17 days. For the SFU Visit (20 weeks after the final dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

Has been changed to:

The schedule of study assessments (Table 5-1) provides an overview of study assessments. A list of procedures to be completed at each visit is described below. Visit windows of ±2 days are allowed from the first dose at all visits through to Week 16. During the 16-week Double-Blind Period, the time between doses should be ≥12 days and ≤16 days. Visit windows of ±3 days are allowed for all visits after Week 16. The time between doses during the Active Treatment-Blind Period should be ≥11 days and ≤17 days. 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/+7 days).

Change #26

Section 9.8.1 Body surface area-psoriasis (BSA-PSO), paragraph 2

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

- Subject's palm=1%
- Head and neck=10% (10 palms)
- Upper extremities=20% (20 palms)
- Trunk=30% (30 palms)
- Lower extremities=40% (40 palms)
- Total BSA=100%

Has been changed to:

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

- ~~Subject's palm=1%~~
- Head and neck=10% (10 palms)
- Upper extremities=20% (20 palms)
- Trunk=30% (30 palms)
- Lower extremities=40% (40 palms)
- Total BSA=100%

Change #27

Section 9.8.3 Investigator's Global Assessment (IGA) – new paragraphs added after Table 9-3

The IGA response is defined as a clear [0] or almost clear [1] assessment with at least a 2-category improvement from Baseline, meaning that this parameter will be evaluable only for subjects with psoriatic skin lesions (IGA score ≥2) at Baseline.

In this study, only subjects with BSA ≥ 3% at Baseline will have IGA assessed at post-Baseline Visits.

Change #28

Section 9.10 Disease Activity Index for Psoriatic Arthritis (DAPSA), formula

SJC (range 0-66) + TJC (range 0-68) + PGA-Arthritis and patient's pain assessment (VAS range 0-10; 0=best, 10=worst) + hs-CRP.

Has been changed to:

DAPSA=*SJC (range 0-66) + TJC (range 0-68) + PGA-Arthritis ~~and patient's pain assessment~~ (VAS range 0-10**cm**; 0=best, 10=worst) +* ***PtAAP (VAS range 0-10cm) +*** *hs-CRP.*

Change #29

Section 12.1.4 Pregnancy, paragraph 1

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

- The subject should return for the ET Visit.
- The subject should immediately stop the intake of the IMP.
- A Safety Follow-Up Visit should be scheduled 20 weeks after the final dose of IMP.

Has been changed to:

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

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

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

Change #30

Section 12.1.4 Pregnancy, last paragraph of section was deleted

~~Should a subject become pregnant while participating in the study, the subject may be offered the option to enroll in a separate observational pregnancy follow-up study sponsored by UCB and conducted independently from study PA0010. If the study is available locally, the PA0010 Investigator will be provided with locally approved information about the observational pregnancy follow-up study to inform the subject at the time the pregnancy is reported. Participation in this separate study will be voluntary and will not impact the therapeutic management of the subject nor interfere with termination and follow-up procedures as described in protocol PA0010.~~

Change #31

Table 12-2: Laboratory measurements, footnote c

[c] Urine drug screen will be performed at Screening Visit and ET Visit

Has been changed to:

[c] Urine drug screen will be performed at Screening Visit ~~and ET Visit~~**.**

Change #32

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥3xULN	NA	Yes				
≥8xULN	NA	NA	Need for hepatology consult to be discussed (required if ALT or AST ≥8xULN). Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.		

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase. • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 4 weeks of monitoring without evidence of resolution.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.2.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • ALT or AST remains ≥5xULN <8xULN, IMP should be temporarily withheld and subject should undergo repeat test in 2 weeks. • Continue IMP if ALT or AST values <5xULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values. • If ALT or AST remains ≥5xULN after second re-test, immediate,

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
						permanent IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[d]

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

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

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

[c] Details provided in Section 12.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

Has been changed to:

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate~~,~~ ~~permanent~~ IMP discontinuation.[d]	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.2.1.3); recommended to	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.~~d~~[e]
≥3xULN	NA	Yes				

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥8xULN	NA	NA	~~Need for hepatology consult to be discussed (required if ALT or AST ≥8xULN).~~ ~~Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.~~	~~Immediate, permanent IMP discontinuation.~~	occur at the site with HCP.	

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase. • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 4 weeks of monitoring without evidence of resolution.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.2.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d~~e~~] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • ALT or AST remains ≥5xULN <8xULN, IMP should be temporarily withheld and subject should undergo repeat test in 2 weeks. • Continue IMP if ALT or AST values <5xULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values. • If ALT or AST remains ≥5xULN after second re-test, immediate~~,~~

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
						~~permanent~~ IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[d~~e~~]

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

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

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

[c] Details provided in Section 12.2.1.1. 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 12.2.1.2.1.**

[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 #33

Section 12.2.1.2 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 ~~and permanent~~ discontinuation (see Section 6.3.1 and Table 12-3 for details).

Change #34

Section 12.2.1.2.1 IMP restart/rechallenge, paragraph 1

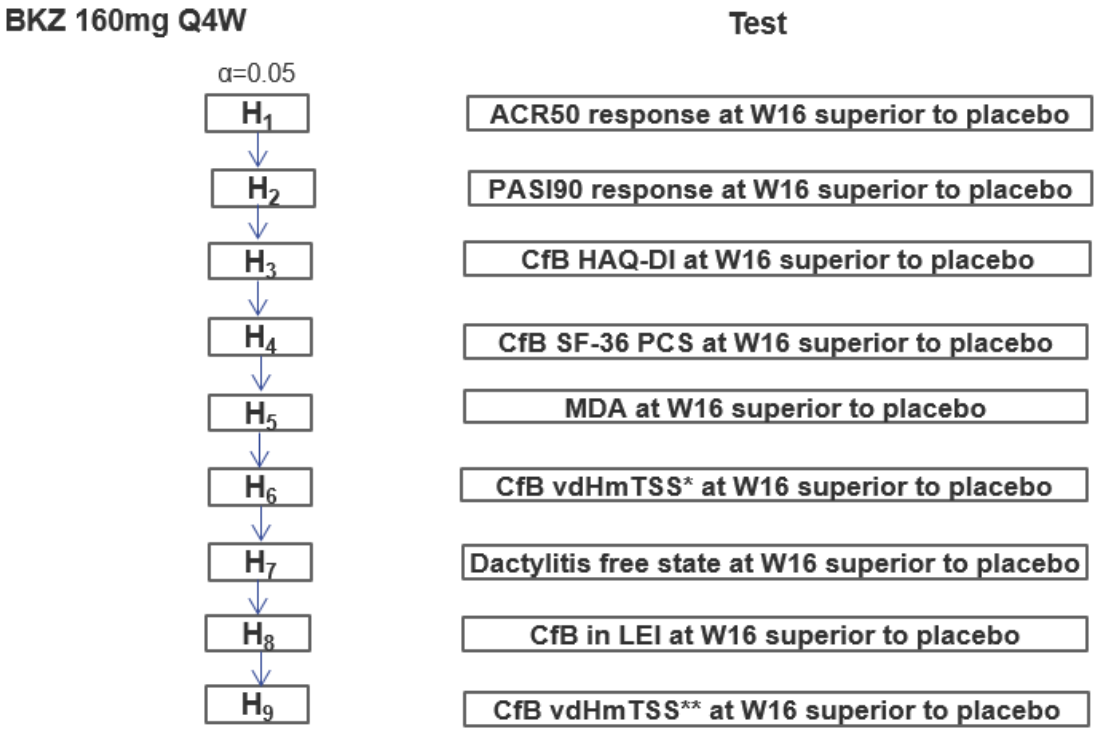
Subjects who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 6.3.1 and Table 12-3), but for whom an alternative diagnosis is confirmed, ie, drug-induced liver injury is excluded, can rarely restart IMP. Rechallenge with IMP can occur only if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

Has been changed to:

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

Change #35

Figure 14-1: Sequential testing procedure of primary/secondary efficacy endpoints (fixed sequence testing procedure)



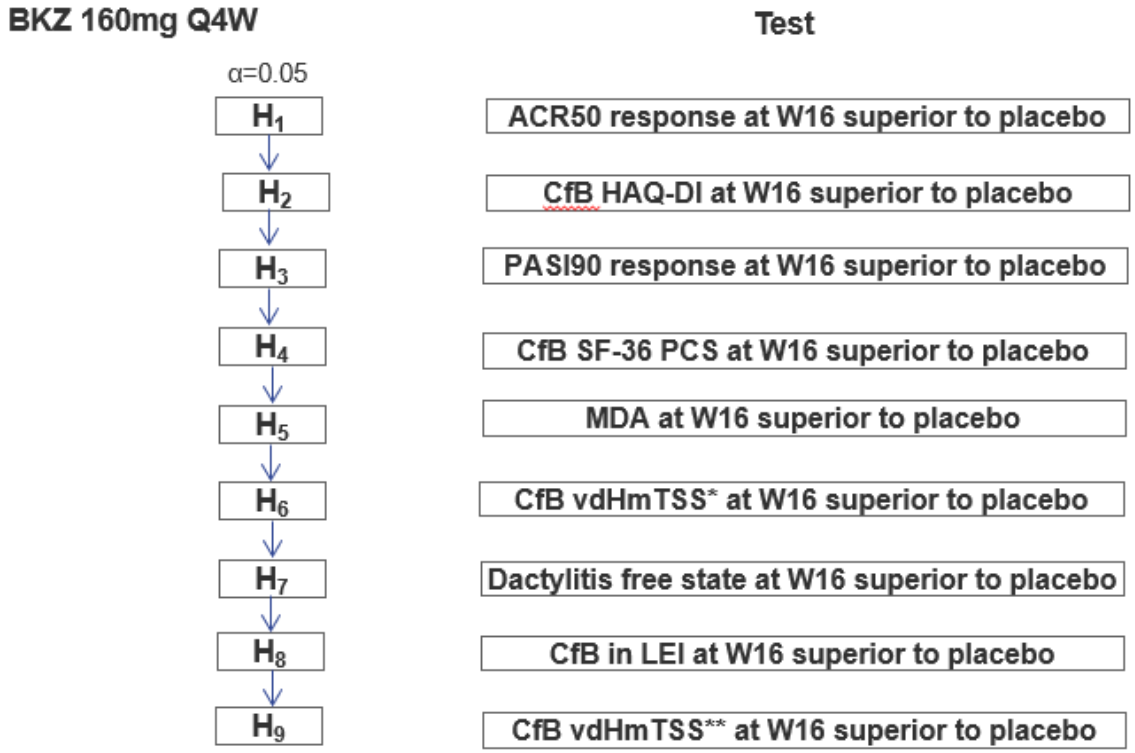
ACR=American College of Rheumatology; BKZ=bimekizumab; CfB=change from Baseline; H=hypothesis; HAQ-DI=Health Assessment Questionnaire—Disability Index; hs-CRP=high sensitivity C-reactive protein; LEI=Leeds Enthesitis Index; MDA=Minimal Disease Activity; PASI=Psoriasis Area and Severity Index; PCS=Physical Component Summary; Q4W=every 4 weeks; SF-36=Short-Form 36-item Health Survey; vdHmTSS=Van der Heijde modified Total Sharp Score; W=Week

* It is planned to enroll a minimum of 35% of subjects with elevated hs-CRP and/or with at least one bone erosion (hs-CRP ≥6mg/L and/or erosion-positive).

** Based on the overall population

Has been changed to:

(in the revised figure [below], the "CfB HAQ-DI at W16 superior to placebo" has moved to the H_2 position from the H_3 position and the "PASI90 response at W16 superior to placebo" has moved to the H_3 position from the H_2 position.)



ACR=American College of Rheumatology; BKZ=bimekizumab; CfB=change from Baseline; H=hypothesis; HAQ-DI=Health Assessment Questionnaire—Disability Index; hs-CRP=high sensitivity C-reactive protein; LEI=Leeds Enthesitis Index; MDA=Minimal Disease Activity; PASI=Psoriasis Area and Severity Index; PCS=Physical Component Summary; Q4W=every 4 weeks; SF-36=Short-Form 36-item Health Survey; vdHmTSS=Van der Heijde modified Total Sharp Score; W=Week

* It is planned to enroll a minimum of ~~35~~**45**% of subjects ~~with~~**who are positive for** elevated hs-CRP **(hs-CRP ≥6mg/L)** and/or ~~with~~**who have** at least ~~one~~**1** bone erosion **at Screening**~~(hs-CRP ≥6mg/L and/or erosion positive)~~.

** Based on the overall population

Change #36

Section 14.3.1.1 Analysis of the primary efficacy variable

The primary efficacy variable will be analyzed for all subjects in the RS.

The primary endpoint is the ACR50 response at Week 16. The primary efficacy analysis will evaluate the composite estimand in the RS. The composite estimand combines the clinically meaningful improvement from Baseline in ACR50 response and not discontinuing treatment early due to an AE or lack of efficacy.

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

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria.
2. Subject-level outcome = ACR50 at Week 16.
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving ACR50 at Week 16 and not discontinuing study treatment due to an AE or lack of efficacy through Week 16.
4. Population-level summary measure = Conditional odds ratio comparing bimekizumab to placebo.

Any missing data at Week 16 that is not preceded by an intercurrent event (ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined multiple imputation model (MI). In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the Markov-Chain Monte Carlo (MCMC) method followed by logistic regression for monotone missing data.

Any use of prohibited or rescue medications through Week 16 would constitute an important protocol deviation which would be accounted for when the sensitivity analysis based on the PPS is performed (see Section 14.3.1.1.1).

The statistical hypothesis for the ACR50 response at Week 16 is that the conditional odds ratio for ACR50 response in the bimekizumab treatment compared with placebo treatment is equal to 1.

A logistic regression model will be used to assess the treatment effect on ACR50 response at Week 16. The model will include a fixed effect for treatment. The suitability of including the randomization stratification variables, region and joint erosion at Baseline will be assessed, and will be added to the model if appropriate. Comparisons will be made using the 2-sided Wald test at a significance level of α=0.05 (ie, H_1 in Figure 14-1). The odds ratio versus placebo, p-value, and the 95% CI will be calculated.

Has been changed to:

The primary efficacy variable will be analyzed for all subjects in the RS.

The primary endpoint is the ACR50 response at Week 16. The primary efficacy analysis will evaluate the composite estimand in the RS. The composite estimand combines the clinically meaningful improvement from Baseline in ACR50 response and not discontinuing treatment early due to an AE or lack of efficacy.

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

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria.
2. Subject-level outcome = ACR50 at Week 16.

3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving ACR50 at Week 16 and not discontinuing study treatment due to an AE or lack of efficacy through Week 16.
4. Population-level summary measure = Conditional odds ratio comparing bimekizumab to placebo.

~~Any missing data at Week 16 that is not preceded by an intercurrent event (ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined multiple imputation model (MI).~~

As the ACR response is based on 7 different component scores, it is necessary to consider various data scenarios that could impact the calculation of response. The rules described here are applicable in the context of the calculation of ACR response and may differ from the rules applied for calculating and summarizing the components individually (some values may need to be imputed for component analysis but are not required here to evaluate ACR response).
The following rules will be applied prior to invoking any imputation analysis at the variable level:

- **If a subject has a component value that is equal to 0 at Baseline and the post-Baseline value is greater than or equal to 0, then the absolute and percent improvement for that component will be treated as 0 for purposes of ACR response calculations.**
- **If a subject has a single component value that is missing at Baseline, then the absolute and percent improvement for that component will be treated as 0 across all visits for purposes of ACR response calculations.**

After these rules have been implemented, the following rules will be applied to complete the derivation of ACR response based on the composite estimand definition:

- **If a given visit has been preceded by an intercurrent event:**
  - **The endpoint at all subsequent visits (whether the data were observed or not) will be set to "non-response" as the subject has not met the criteria for response.**
- **If a given visit has not been preceded by an intercurrent event:**
  - **If both the TJC and SJC are available and at least 3 of the other 5 components have observed data collected, the ACR response will be calculated based on observed data.**
  - **If either the TJC and SJC are missing or there are fewer than 3 of the other 5 components with observed data at Week 16, then imputation methods will be applied, consistent with the predefined approach for handling intercurrent events. Multiple imputation will be applied, where each of the components will be imputed separately before deriving the response based on imputed components. Note: In the case where there is partial missing data at a visit (missing data for some components), the available observed values and the imputed values will be used to derive the response.**

In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the Markov-Chain Monte Carlo (MCMC) method followed by logistic regression for monotone missing data.

~~Any use of prohibited or rescue medications through Week 16 would constitute an important protocol deviation which would be accounted for when the sensitivity analysis based on the PPS is performed (see Section 14.3.1.1.1).~~

The statistical hypothesis for the ACR50 response at Week 16 is that the conditional odds ratio for ACR50 response in the bimekizumab treatment compared with placebo treatment is equal to 1.

A logistic regression model will be used to assess the treatment effect on ACR50 response at Week 16. The model will include a fixed effect for treatment. The suitability of including the randomization stratification variables, region and ~~joint~~**bone** erosion at Baseline will be assessed~~,~~ and will be added to the model if appropriate. Comparisons will be made using the 2-sided Wald test at a significance level of α=0.05 (ie, H_1 in Figure 14-1). The odds ratio versus placebo, p-value, and the 95% CI will be calculated.

Any use of prohibited or rescue medications through Week 16 would constitute an important protocol deviation which would be accounted for when the sensitivity analysis based on the PPS is performed (see Section 14.3.1.1.1).

Change #37

Section 14.3.1.1.1 Sensitivity analyses, #3

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

Has been changed to:

3. The primary comparison will also be repeated for all individual components of the ACR50 response to explore the effect of the signs and symptoms of the individual components on the composite endpoint. Since all ACR components are continuous variables (eg, change from Baseline in TJC), an analysis of covariance (ANCOVA) with treatment, region, and ~~joint~~**bone** erosion at Baseline as fixed effects and the Baseline ~~values~~**value** as **a** covariate will be used for the analysis. **Note as outlined above, some additional values may need to be imputed for component analysis which are not required to evaluate the overall ACR response.**

Change #38

Section 14.3.1.2 Analysis of the secondary efficacy variables

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

All binary variables that are part of the testing hierarchy are given below:

PASI90 responders at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines the clinically meaningful improvement from Baseline in PASI90 response and not discontinuing treatment early due to an AE or lack of efficacy.

The proportion of subjects achieving MDA status at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines (1) achieving the MDA status with (2) not discontinuing treatment early due to an AE or lack of efficacy.

The proportion of subjects with dactylitis at Baseline achieving dactylitis-free status at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines (1) achieving the dactylitis-free status with (2) not discontinuing treatment early due to an AE or lack of efficacy.

The statistical hypothesis for the binary variables at Week 16 is that the conditional odds ratio for binary variables in the bimekizumab treatment compared with placebo treatment groups is equal to 1.

The binary variables will be analyzed using the same analysis methods and estimand approach as used for the primary variable (Section 14.3.1.1).

If appropriate ie, where the outcome variable (eg, PASI90 response) is an assessment of skin/dermatological manifestations of PsA the fitted model will exclude the fixed term joint erosion at Baseline.

All continuous variables that are part of the testing hierarchy are given below:

- Change from Baseline in HAQ-DI at Week 16
- Change from Baseline in the SF-36 PCS score at Week 16
- Change from Baseline in vdHmTSS at Week 16
- Change from Baseline in LEI at Week 16 in the subgroup of subjects with enthesitis at Baseline

Continuous variables will be analyzed to evaluate the hypothetical estimand as defined below:

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria
2. Subject level outcome = variable as stated in Section 4.2.1
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A hypothetical strategy for addressing intercurrent events will be implemented. This estimand targets the treatment difference in a scenario where withdrawal from study treatment due to an AE or lack of efficacy does not occur, such that outcomes for subjects without an intercurrent event are as observed, and outcomes for subjects with an intercurrent event are treated as though they had

completed the randomized study treatment through Week 16. A multiple imputation strategy will be used to impute data following an intercurrent event.

4. Population-level summary measure = the difference in the adjusted means between bimekizumab 160mg Q4W and placebo.

Any missing data at Week 16 that are not preceded by an intercurrent event (ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined MI model. In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by monotone regression for monotone missing data. In the case of vdHmTSS missing data, where there are only 2 timepoints; missing data at Week 16 will be imputed using the MCMC method.

The statistical model for the comparison of bimekizumab and placebo will be an ANCOVA model with treatment, joint erosion, and region as fixed effects and the Baseline value as covariate. The statistical hypothesis for the continuous variables at Week 16 is that the treatment difference between the bimekizumab treatment group and placebo is equal to 0.

All secondary efficacy variables will also be summarized based on observed case data.

Has been changed to:

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

All binary variables that are part of the testing hierarchy are given below:

- PASI90 responders at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines the clinically meaningful improvement from Baseline in PASI90 response and not discontinuing treatment early due to an AE or lack of efficacy.
- The proportion of subjects achieving MDA status at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines (1) achieving the MDA status with (2) not discontinuing treatment early due to an AE or lack of efficacy.
- The proportion of subjects with dactylitis at Baseline achieving dactylitis-free status at Week 16 will be analyzed to evaluate the composite estimand. The composite estimand combines (1) achieving the dactylitis-free status with (2) not discontinuing treatment early due to an AE or lack of efficacy.

The statistical hypothesis for the binary variables at Week 16 is that the conditional odds ratio for binary variables in the bimekizumab treatment compared with placebo treatment groups is equal to 1.

Any missing data at Week 16 which are not preceded by an intercurrent event (ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined MI model. In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method followed by logistic regression for monotone missing data.

In the case of MDA as the response is based on 7 different component scores, it is necessary to consider various data scenarios that could impact the calculation of response. The rules

described here are applicable in the context of the calculation of MDA response and may differ from the rules applied for calculating and summarizing the components individually (some values may need to be imputed for component analysis but are not required here to evaluate MDA response).

The following rules will be applied to complete the derivation of MDA response based on the composite estimand definition:

- **If a given visit has been preceded by an intercurrent event:**
  - **The endpoint at all subsequent visits (whether the data were observed or not) will be set to "non-response" as the subject has not met the criteria for response.**
- **If a given visit has not been preceded by an intercurrent event:**
  - **If at least 5 of the 7 components have observed data collected, the MDA response will be calculated based on observed data.**
  - **If there are fewer than 5 of the 7 components with observed data at Week 16, then imputation methods will be applied, consistent with the predefined approach for handling intercurrent events. Multiple imputation will be applied, where each of the components will be imputed separately before deriving the response based on imputed components. Note: In the case where there is partial missing data at a visit (missing data for some components), the available observed values and the imputed values will be used to derive the response.**

The binary variables will be analyzed using the same analysis methods and estimand approach as used for the primary variable (Section 14.3.1.1).

If appropriate ie, where the outcome variable (eg, PASI90 response) is an assessment of skin/dermatological manifestations of PsA the fitted model will exclude the fixed term ~~joint~~**bone** erosion at Baseline.

All continuous variables that are part of the testing hierarchy are given below:

- Change from Baseline in HAQ-DI at Week 16
- Change from Baseline in the SF-36 PCS score at Week 16
- Change from Baseline in vdHmTSS at Week 16
- Change from Baseline in LEI at Week 16 in the subgroup of subjects with enthesitis at Baseline

Continuous variables will be analyzed to evaluate the hypothetical estimand as defined below:

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria
2. Subject level outcome = variable as stated in Section 4.2.1
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A hypothetical strategy for addressing intercurrent events will be implemented. This estimand targets the treatment difference in a scenario where withdrawal from study treatment due to an AE or lack of

efficacy does not occur, such that outcomes for subjects without an intercurrent event are as observed, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment through Week 16. A multiple imputation strategy will be used to impute data following an intercurrent event.

4. Population-level summary measure = the difference in the adjusted means between bimekizumab 160mg Q4W and placebo.

Any missing data at Week 16 that are not preceded by an intercurrent event (ie, discontinuation of study medication due to an AE or lack of efficacy) will be imputed based on a predefined MI model. In MI, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data. Intermittent missing data will be imputed using the MCMC method, followed by monotone regression for monotone missing data. In the case of vdHmTSS missing data, where there are only 2 timepoints; missing data at Week 16 will be imputed using the MCMC method.

In the case of vdHmTSS missing data, where there are only 2 timepoints; missing data at Week 16 will be imputed using the MCMC method.

The statistical model for **continuous endpoints for** the comparison of bimekizumab and placebo will be an ANCOVA model with treatment, ~~joint~~**bone** erosion, and region as fixed effects and the Baseline value as covariate. The statistical hypothesis for the continuous variables at Week 16 is that the treatment difference between the bimekizumab treatment group and placebo is equal to 0.

All secondary efficacy variables will also be summarized based on observed case **data as well as nonresponder imputation (NRI) for binary variables**.

Change #39

Section 14.3.2 Analysis of the other efficacy variables, paragraph 3 through end

Any missing data that is not preceded by an intercurrent event as described above will be imputed based on a predefined multiple imputation model as described for the primary efficacy variable.

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

1. Population = Subjects meeting the protocol-specified inclusion/exclusion criteria
2. Subject-level outcome = The given variable and time point being summarized (eg, change from Baseline in HAQ-DI at Week 36)
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of study treatment due to an AE or lack of efficacy prior to the time point being summarized. A hypothetical strategy will be implemented in which outcomes for subjects without an intercurrent event are as observed at the given time point, and outcomes for subjects with an intercurrent event are treated as though they had completed the randomized study treatment

through the time point being summarized. A multiple imputation strategy will be used to impute data following an intercurrent event.

4. Population-level summary measure = Unadjusted mean

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

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

Time to ACR20/50/70 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in days from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects in the placebo group who are rerandomized at Week 16 without achieving response will be censored at the date of the Week 16 Visit. The median time to response, including the 2-sided 95% CI, will be calculated for each treatment. Between group differences will be analyzed with a log-rank statistic.

Has been changed to:

Any missing data that is not preceded by an intercurrent event as described above will be imputed based on a predefined multiple imputation model as described for the primary **and secondary** efficacy variable**s**.

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

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

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

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

Time to ACR20/50/70 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in days from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects in the placebo group who are rerandomized at Week 16 without achieving response will be censored at the date of the Week 16 Visit. The median time to response, including the 2-sided 95% CI, will be calculated for each treatment. Between group differences will be analyzed with a log-rank statistic.

The time to ACR20/50/70 endpoints with missing data that are not preceded by an intercurrent event as described above will be imputed based on a predefined multiple imputation model as described for the primary efficacy variable.

The time to ACR20/50/70 endpoints will also be analyzed using observed case (OC) data.

Change #40

Section 14.3.3 Subgroup analyses—the following subgroup analysis added:

- **Concomitantly receiving MTX versus no concomitant MTX**

Change #41

Section 14.7 Handling of dropouts or missing data, paragraph 2

Missing data will be evaluated as sensitivity analyses using different missing data mechanisms. The following sensitivity analyses for the primary efficacy variable and for those secondary efficacy variables that are part of the hierarchical testing will be conducted:

Has been changed to:

Missing data will be evaluated as sensitivity analyses using different missing data mechanisms. The following sensitivity analyses for the primary efficacy variable ~~and for those secondary efficacy variables that are part of the hierarchical testing~~ will be conducted:

Change #42

Section 14.7 Handling of dropouts or missing data, last paragraph (new text added before paragraph)

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

Has been changed to:

5. Nonresponder imputation analysis will also be performed where subjects will be considered "nonresponders" at the timepoint of interest if:

- **Subjects are missing data at the time point of interest.**
- **Subjects remained in the study but have discontinued study treatment due to an AE or lack of efficacy before the time point of interest.**

For the secondary efficacy variables, the binary endpoints will be analyzed using both NRI and OC and for continuous endpoints OC will be performed.

For the other efficacy endpoints, OC analysis will be conducted for both binary and continuous variables.

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

Change #43

Section 14.8.1 Interim analyses—new sentence added to end of section

Additional data cuts may be prepared following regulatory requests or for publication purposes.

Change #44

Section 14.8.2 Data monitoring—new sentence added after paragraph 2

Other adjudication committees may be added as necessary.

Change #45

Section 14.9.2 Power calculations for secondary endpoints, paragraph 6, paragraph 7, and Table 14-1

For change from Baseline in vdHmTSS at Week 16, the between treatment differences of the change from Baseline in vdHmTSS at Week 16 of the SPIRIT P1 study in a TNFα-naive population (Mease et al, 2017) were used. The SPIRIT P1 study ixekizumab 80mg sc Q2W treatment group least square (LS) mean change from Baseline at Week 16 0.06 and SD 0.720; and LS mean change from Baseline 0.36 and SD 0.710 for placebo are assumed. With those assumptions, the study has a 84% power to detect a true treatment difference of -0.30, assuming 30% of subjects with joint erosion, in the planned sample size.

There is uncertainty in the final percentage of subjects with joint erosion at Baseline that will be recruited to the study and the variability in the subgroup. To demonstrate the sensitivity of the sample size calculation for this study, Table 14-1 shows the power function for a fixed total sample size of 840 subjects in the RS population for this secondary efficacy analysis, varying the percentage of subjects with joint erosion at Baseline and the treatment difference and estimated standard deviation on the change from Baseline in vdHmTSS at Week 16.

Table 14-1: Treatment effect by joint erosion at Baseline for secondary efficacy analyses

Subjects with joint erosion at Baseline	Treatment difference/standard deviation	
	Treatment effect = -0.3 SD=0.72 vs 0.71	**Treatment effect = -0.35 SD=0.81 vs 0.93**
20%	67	62
25%	76	72
30%	84	79
35%	89	85
40%	92	89
45%	95	92
50%	96	95

SD=standard deviation

Has been changed to:

For change from Baseline in vdHmTSS at Week 16, the between treatment differences of the change from Baseline in vdHmTSS at Week 16 of the SPIRIT P1 study in a TNFα-naive population (Mease et al, 2017) were used. The SPIRIT P1 study ixekizumab 80mg sc Q2W treatment group least square (LS) mean change from Baseline at Week 16 0.06 and SD 0.720; and LS mean change from Baseline 0.36 and SD 0.710 for placebo are assumed. With those assumptions, the study has a ~~84~~**95**% power to detect a true treatment difference of -0.30, assuming ~~30~~**45**% of subjects with ~~joint~~**elevated hs-CRP and/or bone** erosion, in the planned sample size.

There is uncertainty in the final percentage of subjects with ~~joint~~**elevated hs-CRP and/or bone** erosion at Baseline that will be recruited to the study and the variability in the subgroup. To demonstrate the sensitivity of the sample size calculation for this study, Table 14-1 shows the power function for a fixed total sample size of 840 subjects in the RS population for this secondary efficacy analysis, varying the percentage of subjects with ~~joint~~**elevated hs-CRP and/or bone** erosion at Baseline and the treatment difference and estimated standard deviation on the change from Baseline in vdHmTSS at Week 16.

Table 14-1: Treatment effect by ~~joint~~**elevated hs-CRP and/or bone** erosion at Baseline for secondary efficacy analyses

Subjects with ~~joint~~**elevated hs-CRP and/or bone** erosion at Baseline	Treatment difference/standard deviation	
	Treatment effect = -0.3 SD=0.72 vs 0.71	Treatment effect = -0.35 SD=0.81 vs 0.93
20%	67	62
25%	76	72
30%	84	79
35%	89	85
40%	92	89
45%	95	92
50%	96	95

hs-CRP=high sensitivity C-reactive protein; SD=standard deviation

18.3 Protocol Amendment 2

The main purpose of this protocol amendment was to modify the secondary variables and fixed sequence testing procedure, update the statistical section, and make other procedural clarifications.

Modifications and changes

Global changes:

Throughout the protocol, FACIT-F has been corrected to FACIT-Fatigue subscale, as it is the fatigue subscale that is being assessed in this study. In addition, minor spelling, editorial, and formatting changes were made throughout the protocol. These global changes are not included in specific changes table that follows.

Specific changes:

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 1: Administrative section			
Study contact details	[redacted] UCB Celltech Ltd 208 Bath Road Slough SL1 3WE [redacted]	[redacted] [redacted] UCB Celltech Ltd 208 Bath Road Slough SL1 3WE [redacted]	The Sponsor Study Physician has changed.
	[redacted] UCB BIOSCIENCES Inc. 8010 Arco Corporate Drive Raleigh, NC 27617 UNITED STATES [redacted]	[redacted] UCB BIOSCIENCES **GmbH** **Alfred-Nobel-Str. 10** **40789 Monheim** **GERMANY** [redacted]	The Clinical Project Manager has changed.
Change 2: Abbreviation added			
List of abbreviations	Abbreviations and definitions added for the following: LN, PsARC, PASDAS		Abbreviations used in text.
Change 3: Updated text in clinical studies section			
Section 2.2.2.1	The list of completed studies was updated consistent with the current bimekizumab IB.		More studies have completed, and additional studies have started, since the last protocol amendment.
Section 2.2.2.2	The list of ongoing studies was updated consistent with the current bimekizumab IB.		

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 4: Updated 2 secondary efficacy variables			
Section 4.2.1	• Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of subjects with dactylitis at Baseline • Change from Baseline in the Leeds Enthesitis Index (LEI) at Week 16 in the subgroup of subjects with enthesitis at Baseline	• ~~Change from Baseline~~ **Enthesitis-free state** in the Leeds Enthesitis Index (LEI) at Week 16 in the subgroup of subjects with enthesitis at Baseline **in the pooled population of PA0010 and PA0011** • Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of subjects with dactylitis at Baseline **in the pooled population of PA0010 and PA0011**	In order to provide more clinically interpretable results for dactylitis and enthesitis endpoints across a more robust mixed population (TNF-inadequate responders and bDMARD-naïve), the endpoints of dactylitis free-state and enthesitis free-state will be analyzed using a pooled PA0010 and PA0011 population. Given similar power between dactylitis and enthesitis, the enthesitis endpoint was moved up in the statistical testing hierarchy as it is considered a more relevant clinical endpoint.
Section 14.3.1 Figure 14-1	In Figure 14-1 Sequential testing procedure of primary/secondary efficacy endpoints (fixed sequence testing procedure), the enthesitis and dactylitis variables were updated to be based on the pooled population of PA0010 and PA0011, and the enthesitis-free state variable was moved above the dactylitis-free state variable in the figure.		

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 5: Added 7 new Other efficacy variables			
Section 4.3.1	Added the following variables: • Composite endpoint composed of ACR50 and PASI100 response in subjects with PSO involving at least 3% BSA at Baseline • Proportion of Psoriatic Arthritis Response Criteria (PsARC) responders • Psoriatic Arthritis Disease Activity Score (PASDAS) categories • Change from Baseline in the PASDAS • Proportion of subjects with a decrease of HAQ-DI from Baseline of at least 0.35 in those subjects with HAQ-DI >0.35 at Baseline • Proportion of PSAID-12 responders (decrease from Baseline in PsAID-12 total score ≥3 in subjects with PsAID-12 total score >3 at Baseline • Proportion of FACIT-Fatigue subscale responders (minimum clinically important difference for FACIT-Fatigue subscale score, defined as an increase of ≥4		Updated to be consistent with variables added to the SAP
Change 6: Updated wording in other efficacy variables			
Section 4.3.1	• Dactylitis-free state based on the LDI in the subgroup of subjects with dactylitis at Baseline	• Dactylitis-free state based on the LDI in the subgroup of subjects with dactylitis at Baseline **in the pooled population of PA0010 and PA0011, as well as PA0010 alone**	Updated to be consistent with changes made to the dactylitis and enthesitis secondary efficacy variables and to specify that the PA0010-only population will also be analyzed.
	• Enthesitis-free state based on the LEI in the subgroup of subjects with enthesitis at Baseline	• Enthesitis-free state based on the LEI in the subgroup of subjects with enthesitis at Baseline **in the pooled population of PA0010 and PA0011, as well as PA0010 alone**	

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 4.3.1	• Enthesitis-free state based on the SPARCC index in the subgroup of subjects with enthesitis at Baseline	• Enthesitis-free state based on the SPARCC index in the subgroup of subjects with enthesitis at Baseline **in the pooled population of PA0010 and PA0011, as well as PA0010 alone**	Updated to be consistent with changes made to the dactylitis and enthesitis secondary efficacy variables and to specify that the PA0010-only population will also be analyzed.
	• Change from Baseline in the LEI in the subgroup of subjects with enthesitis at Baseline	• Change from Baseline in the LEI in the subgroup of subjects with enthesitis at Baseline **in the pooled population of PA0010 and PA0011, as well as for PA0010 alone**	
	• Change from Baseline in the SPARCC index in the subgroup of subjects with enthesitis at Baseline	• Change from Baseline in the SPARCC index in the subgroup of subjects with enthesitis at Baseline **in the pooled population of PA0010 and PA0011, as well as for PA0010 alone**	
	• Change from Baseline in the LDI in the subgroup of subjects with dactylitis at Baseline	• Change from Baseline in the LDI in the subgroup of subjects with dactylitis at Baseline **in the pooled population of PA0010 and PA0011, as well as for PA0010 alone**	

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Section 4.3.1	• Disease Activity Index for Psoriatic Arthritis (DAPSA)	• Disease Activity Index for Psoriatic Arthritis (DAPSA) **score categories**	Corrected wording
	• Change from Baseline in PsAID-12, in the individual domains of PsAID-12	• Change from Baseline in PsAID-12 **total score**, **as well as** ~~in~~ the individual domain scores	
	• Change from Baseline in the Psoriatic Arthritis Quality of Life (PsAQoL)	• Change from Baseline in the Psoriatic Arthritis Quality of Life (PsAQoL) **total score**	
	• Change from Baseline in Functional Assessment of Chronic Illness Therapy—Fatigue (FACIT-F)	• Change from Baseline in Functional Assessment of Chronic Illness Therapy—Fatigue ~~(FACIT-F)~~ **subscale score**	
Change 7: Made minor updates to Double-Blind Treatment Period section and Active Treatment Period section text			
Section 5.3.1	2nd paragraph: Investigational medicinal product treatment details are provided in Section 7.2. Visit windows of ±2 days are allowed for all visits up to Week 16. The visit window is relative to the Day 1 (Baseline) Visit. 5th paragraph: Subjects withdrawing early from the study will undergo the Early Termination (ET) Visit assessments and will enter the SFU Period. Subjects who withdraw from IMP during the Double-Blind Period will return for all scheduled visits up to Week 52 and for the SFU Visit (20 weeks after their final dose of IMP).	2nd paragraph: Investigational medicinal product treatment details are provided in Section 7.2. Visit windows of ±2 days are allowed for all visits ~~up to~~**through** Week 16. The visit window is relative to the Day 1 (Baseline) Visit. 5th paragraph: Subjects withdrawing early from the study will undergo the Early Termination (ET) Visit assessments and will enter the SFU Period. Subjects who withdraw from IMP during the Double-Blind Period will **be encouraged to** return for all scheduled visits up to Week 52 and for	Clarification of text.

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
		the SFU Visit (20 weeks after their final dose of IMP)**, as applicable**.	
Section 5.3.2	5th paragraph: Subjects who withdraw early from the study will undergo the ET Visit assessments and will enter the SFU Period. Subjects who withdraw from IMP during the Active-Treatment-Blind Period will return for all remaining scheduled visits up to Week 52 and the SFU Visit (20 weeks after their final dose of IMP).	5th paragraph: Subjects who withdraw early from the study will undergo the ET Visit assessments and will enter the SFU Period. Subjects who withdraw from IMP during the Active-Treatment-Blind Period will **be encouraged to** return for all remaining scheduled visits up to Week 52 and the SFU Visit (20 weeks after their final dose of IMP)**, as applicable**.	Clarification of text.
Change 8: Made minor updates to Schedule of study assessments footnote o			
Table 5-1	º Circumference measured in millimeters. The LDI assessment of dactylitis will be obtained for all subjects at the Baseline visit. Subsequent to the Baseline visit, the LDI assessment will be obtained only for those subjects who had dactylitis at Baseline (as per the LDI assessment performed at Baseline).	º Circumference measured in millimeters. ~~The LDI assessment of dactylitis will be obtained for all subjects at the Baseline visit. Subsequent to the Baseline visit, the LDI assessment will be obtained only for those subjects who had dactylitis at Baseline (as per the LDI assessment performed at Baseline)~~.	Correction of footnote 'o,' as the LDI assessment is being done at every visit.
Change 9: Added a withdrawal criterion			
Section 6.3	Added the following to the list of withdrawal criteria: 13. Any subject who develops a clinically important infection or recurrent infections not responsive to standard therapy during the study must discontinue IMP until resolution of the infection. The Investigator should use clinical judgement in deciding whether the subject should restart IMP		In line with the exclusion criterion 11 regarding infections, a specific infection-related withdrawal criterion was added to clarify that patients with serious or recurrent infections not responding

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
	and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.		to standard therapies are not exposed to immunomodulatory therapies until their infection is resolved. This is in line with most biologic therapies, including other anti-IL17s.
Change 10: Updated the permitted concomitant treatments section			
Section 7.8.1	Added the following paragraph to the section: Subjects are allowed to use any other medications, including biologics, after at least 28 days of last dose of the IMP. This is applicable for subjects who discontinue from IMP or the study early, including those permanently withdrawn from IMP, or subjects who have completed the study treatment without entering the extension study and are in the SFU period.		Clarification of permitted concomitant medications.
Change 11: Updated FACIT-F assessment section			
Section 9.19	The FACIT–F scale (Cella et al, 2005) will be used to assess fatigue in PsA patients. The FACIT-F has been validated in the general population, in patients with RA, and in patients with PsA. The minimum clinically important difference for FACIT-F in patients with RA was determined to be a 3 to 4-point change; this minimum clinically important difference will be used in evaluating clinically meaningful changes in fatigue for patients with PsA.	~~The FACIT–F scale (Cella et al, 2005) will be used to assess fatigue in PsA patients.~~ **The FACIT-Fatigue is a 40-item measure that assesses self-reported fatigue and its impact upon daily activities and function over the past 7 days (FACIT.org). The scale consists of 5 subscales (physical well-being, social/family well-being, emotional well-being, functional well-being, and fatigue). The fatigue subscale is the only one used in this study. It is composed of 13 items, all scored from 0 (Not at all) to 4 (Very much). The FACIT-Fatigue subscale score ranges from 0 to 52 with 0 being the**	Added a reference for FACIT-Fatigue subscale use in PsA. Wording changes implemented for consistency with the user manuals and to reflect precise description of the PRO tools and scoring (change in terminology but no change in the method).

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
		worst possible score and 52 being the best possible score. To obtain a score from 0 to 52, all negatively worded questions have to be recoded, so that responses range from worst (0) to the best (4) outcome. The FACIT-F**atigue subscale** has been validated in ~~the general population, in patients with RA, and in~~ patients with PsA. The minimum clinically important difference for FACIT-F**atigue subscale** in patients with ~~RA~~**PsA** was determined to be a ~~3 to~~ 4-point change **(Cella et al, 2019)**~~; this minimum clinically important difference will be used in evaluating clinically meaningful changes in fatigue for patients with PsA~~.	
Change 12: Updated SF-36 assessment section			
Section 9.20	In addition to domain scores, the PCS and MCS scores are calculated from the 8 domains (excluding the Health Transition item). Component scores appreciate the impact of each domain on physical and mental health status (Maruish, 2011). Each of the 8 domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status. The 2 component summary scores are standardized with a mean of	In addition to domain scores, the PCS and MCS scores are calculated from the 8 domains (excluding the Health Transition item). Component scores ~~appreciate~~ **reflect** the impact of each domain on physical and mental health status (Maruish, 2011). ~~Each of the 8 domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status.~~ The **norm-based T-scores for the** 2 **SF-36** component summary ~~scores~~ **(PCS and MCS) and**	Wording changes implemented for consistency with the user manuals and to reflect precise description of the PRO tools and scoring (change in terminology but no change in the method).

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
	50 and a standard deviation (SD) of 10 in the general US population.	**the 8 domains** are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general US population **(Maruish, 2011). .An individual respondent's score that falls outside the T-score range of 45 to 55 should be considered outside the average range for the US general population. When considering group-level data, a score below 47 should be considered indicative of impaired functioning within that health domain or dimension. Similar to individual respondent data, group mean scores of 47 or greater should be considered average or above average as compared to the general US population. Higher scores indicate a better health status**.	
Change 13: Added 2 new sections to describe the PsARC and PASDAS efficacy assessments added in new Other efficacy variables			
New Section 9.23	Section 9.23 Psoriatic Arthritis Response Criteria (PsARC) added to describe the PsARC efficacy assessment		The PsARC was added in a new Other efficacy variable
New Section 9.24	Section 9.24 Psoriatic Arthritis Disease Activity Score (PASDAS) added to describe the PASDAS efficacy assessment		The PASDAS was added in 2 new Other efficacy variables.

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 14: Moved PHQ-9 assessment section from efficacy assessments to safety assessments			
Old Section 9.23 moved to *New* Section 12.3.8	12.3.5 Assessment and management of TB and TB risk factors 12.3.6 Pregnancy testing 12.3.7 Assessment of suicidal ideation and behavior	12.3.5 Assessment and management of TB and TB risk factors 12.3.6 Pregnancy testing 12.3.7 Assessment of suicidal ideation and behavior **12.3.8 Patient Health Questionnaire-9 (PHQ-9)**	In PA0010 Protocol Amendment 1, the PHQ-9 was moved to Other safety variables from Other efficacy variables, but the assessment description section was not moved. In the current amendment (#2), the PHQ-9 assessment description section was moved to align with the variables.
Change 15: Updated Other safety topics of interest section			
Section 12.1.1.4	Prespecified safety topics of interest for the study are: infections (serious, opportunistic, fungal and TB), neutropenia, hypersensitivity, suicidal ideation and behavior, depression, major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel diseases (with gastroenterology referral, as appropriate).	Prespecified safety topics of interest for the study are: infections (serious, opportunistic, fungal and TB), neutropenia, hypersensitivity, suicidal ideation and behavior, ~~depression,~~ major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel diseases (with gastroenterology referral, as appropriate).	With progressive development of bimekizumab and based on the ongoing review of emerging safety data, depression has been removed as a safety topic of interest. Nevertheless, depression will continue to be monitored as a safety parameter by the PHQ-9 and will be captured via routine AE reporting during the study. This update is considered a procedural change.

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 16: Updated Evaluation of PDILI section			
Section 12.2.1	The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as AEs 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).	All PDILI events must be reported as an AE and ~~reported to the study site~~ **PDILI events meeting SAE criteria should be reported to** the Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported **within 24 hours of learning of their occurrence** as an AE of special interest (see Section 12.1.1.3), and, if applicable, also reported as an SAE (see Section 12.1.1.2).	Clarified PDILI event reporting procedure.
Section 12.2.1.2	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 discontinuation (see Section 6.3.1 and Table 12–3 for details).	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).	Clarify the range of potential actions.
Change 17: Updated the analysis set definition section			
Section 14.1	• The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will	• The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will	Clarified PPS and PK-PPS definitions. Added COVID-19-free analysis set to determine if COVID-19 has an impact on analyses.

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
	be evaluated during ongoing data cleaning meetings prior to unblinding of the data. • The Pharmacokinetic Per-Protocol Set (PK-PPS) consists of all randomized subjects who received at least one dose of the IMP and provided at least one quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration.	be evaluated during ongoing data cleaning meetings prior to unblinding of the data. **Exclusions from the FAS will be considered important protocol deviations that also result in exclusion from the PPS.** • The Pharmacokinetic Per-Protocol Set (PK-PPS) consists of all randomized subjects who received at least one dose of the IMP and provided at least one quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration. **Exclusions from the FAS will be considered important protocol deviations that also result in exclusion from the PK-PPS.** • **The COVID-19-free Set will consist of all subjects in the RS who had no COVID-19 impact up to the primary efficacy endpoint. This will be defined as subjects not having a COVID-19 related important protocol deviation, nor having an impact based on the COVID-19 eCRF, nor having an AE related to COVID-19, nor discontinuing due to COVID-19 up to the time of the primary endpoint.**	

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
Change 18: Updated text in analysis of the primary efficacy variables section			
Section 14.3.1.1	Updated text regarding the statistical approach to be used for analyzing primary efficacy variable.		Updated statistical methods based on feedback from the FDA.
Change 19: Updated title and text in former Sensitivity analyses section			
Section 14.3.1.1.1	Updated title of this section from Sensitivity analyses to ~~Sensitivity~~**Supportive** Analyses. Also, updated text regarding the statistical approach to be used for the supportive analyses.		Updated statistical methods based on feedback from the FDA.
Change 20: Updated text in analysis of the secondary efficacy variables section			
Section 14.3.1.2	Updated text regarding the statistical approach to be used for analyzing secondary efficacy variables.		Updated statistical methods based on feedback from the FDA.
Change 21: Updated text in analysis of the other efficacy variables section			
Section 14.3.2	Updated text regarding the statistical approach to be used for analyzing the other efficacy variables.		Updated statistical methods based on feedback from the FDA.
Change 22: Updated text in handling of dropouts or missing data section			
Section 14.7	Updated the statistical approach to be used for missing data.		Updated statistical methods based on feedback from the FDA.
Change 23: Updated the power calculation text for enthesitis-free state and dactylitis-free state			
Section 14.9.2	For dactylitis-free state at Week 16, it has been assumed that 25% of all subjects have dactylitis symptoms at Baseline. Dactylitis resolution data of the FUTURE 5 study (Mease et al, 2018) at Week 16 were used to estimate the bimekizumab 160mg Q4W treatment and placebo groups. The treatment effect estimate from the secukinumab 150mg treatment group at Week 16 of 56% (n=103) is assumed	For dactylitis-free state at Week 16, ~~it has been assumed that 25% of all subjects have~~ dactylitis ~~symptoms at Baseline. Dactylitis~~ resolution data of the FUTURE 5 study (Mease et al, 2018) at Week 16 were used to estimate the bimekizumab 160mg Q4W treatment and placebo groups. The treatment effect estimate from the secukinumab 150mg treatment group at Week 16 of 56% (n=103) is	Updated the power calculation based on pooled population of PA0010 and PA0011.

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
	versus a placebo group estimate of 32% (n=124). With those assumptions, the study has an 85% power to detect a true treatment difference of 24% (odds ratio 2.71), assuming 25% of subjects at Baseline with dactylitis of the planned sample size.	assumed versus a placebo group estimate of 32% (n=124). With those assumptions **and having 11% of subjects with Baseline dactylitis**, the ~~study has an 85~~ **pooled PA0010/PA0011 studies have a 66**% power to detect a true treatment difference of 24% (odds ratio 2.71)~~, assuming 25% of subjects at Baseline with dactylitis of the planned sample size~~.	
	For change from Baseline in LEI Week 16, it has been assumed that 50% of all subjects have enthesitis symptoms at Baseline. Enthesitis change from Baseline in LEI data at Week 16 of the FUTURE 2 study in the mixed TNFα exposure population (McInnes et al, 2015) were used to estimate the bimekizumab 160mg Q4W treatment and placebo groups. The FUTURE 2 treatment effect estimate from the secukinumab 150mg treatment group at Week 16 of -1.5 (SD=2.0) is assumed versus a placebo group estimate of -0.9 (SD=2.1). With those assumptions, the study has 76% power of detecting a true treatment difference of 0.6 assuming 50% of subjects with enthesitis at Baseline of the planned sample size.	~~For change from Baseline in LEI Week 16, it has been assumed that 50% of all subjects have enthesitis symptoms at Baseline. Enthesitis change from Baseline in LEI data at Week 16 of the FUTURE 2 study in the mixed TNFα exposure population (McInnes et al, 2015) were used to estimate the bimekizumab 160mg Q4W treatment and placebo groups. The FUTURE 2 treatment effect estimate from the secukinumab 150mg treatment group at Week 16 of -1.5 (SD=2.0) is assumed versus a placebo group estimate of -0.9 (SD=2.1). With those assumptions, the study has 76% power of detecting a true treatment difference of 0.6 assuming 50% of subjects with enthesitis at Baseline of the planned sample size.~~ **For enthesis free-state at Week 16, enthesis resolution data from the**	The secondary endpoint for enthesitis was updated to enthesitis-free state from change from Baseline in LEI, and the power calculation was updated based on pooled population of PA0010 and PA0011

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
		FUTURE 5 study at Week 16 were used to estimate the bimekizumab 160mg Q4W treatment and placebo groups. In FUTURE 5 The treatment effect estimate from the secukinumab 150mg treatment group at Week 16 was 55% (n=141) and the placebo group estimate was 36% (n=192). Assuming a BKZ response of 55% and a placebo rate of 39% and having 25% of subjects with Baseline enthesis the pooled PA0010/PA0011 the studies have a 69% power to detect a true treatment difference of 16% (odds ratio 1.91).	
Change 24: Updated reference list			
References	Deleted the following 2 references due to updates made in Section 14.7 Handling of dropouts or missing data: ~~Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharm Stat. 2012;11:456-61.~~ ~~Mallinckrodt CH. Preventing and Treating Missing Data in Longitudinal Clinical Trials: A Practical Guide. New York, NY: Cambridge University Press; 2013~~. Added the following 3 references, 1 for FACIT-Fatigue subscale and 2 for PASDAS: Cella D, Wilson H, Shalhoub H, Revicki DA, Cappelleri JC, Bushmakin AG, et al. Content validity and psychometric evaluation of Functional Assessment of Chronic Illness Therapy-Fatigue in patients with psoriatic arthritis. J Patient Rep Outcomes. 2019;3(1):5.		Deleted Mallinckrodt references, as they are no longer applicable due to statistical updates. Additional references were deleted/added to support the assessments of FACIT-Fatigue subscale and PASDAS.

Protocol section impacted	Key components of previous protocol text	Key components of revised protocol text	Rationale
	Coates LC, FitzGerald O, Mease PJ, Gladman DD, Strand V, Goel N, Campbell I, et al. Development of a disease activity and responder index for psoriatic arthritis – Report of the Psoriatic Arthrits Module at OMERACT 11. J Rheumatol 2014;41:782-91. Coates LC, Gladman DD, Nash P, FitzGerald O, Kavanaugh A, Kvien TK, et al. Secukinumab provides sustained PASDAS-defined remission in psoriatic arthritis and improves health-related quality of life in patients achieving remission: 2-year results from the Phase III FUTURE 2 study. Arthritis Res Ther. 2018;20(1):272. doi: 10.1186/s13075-018-1773-y. Deleted the following FACIT reference because it was superseded by the Cella et al, 2019 reference: ~~Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. J Rheumatol. 2005;32:811–19.~~		

19 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

20 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 GCP.

Approval Signatures

Name: pa0010-protocol-amend-2

Version: 1.0

Document Number: CLIN-000168964

Title: PA0010 Protocol-Phase 3 - Placebo and active-controlled - Double- blind - Amendment 2

Approved Date: 26 Feb 2021

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 26-Feb-2021 15:10:24 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Medical Date of Signature: 26-Feb-2021 15:54:01 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 26-Feb-2021 16:40:42 GMT+0000