PROTOCOL PS0016 AMENDMENT 3

A MULTICENTER, RANDOMIZED, SUBJECT-BLIND, INVESTIGATOR-BLIND STUDY TO EVALUATE THE TIME COURSE OF PHARMACODYNAMIC RESPONSE, SAFETY AND PHARMACOKINETICS OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

PHASE 2A

EudraCT Number: 2016-002368-15

IND Number: 128707

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Protocol/Amendment number	Date	Type of amendment
Final Protocol	06 Jun 2016	Not applicable
Protocol Amendment 1	04 Aug 2016	Not applicable
Protocol Amendment 2	06 Sep 2016	Nonsubstantial
Protocol Amendment 3	23 Sep 2016	Substantial

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** PPD **USA and Canada:** PPD or PPD
Email	**Global:** PPD

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AE	adverse event
AESI	adverse events of special interest
AESM	adverse events for special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area (affected by psoriasis)
cAMP	cyclic adenosine monophosphate
CDMS	clinical data management system
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRP	C-reactive protein
eCRF	electronic Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DAP	data analysis plan
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	Electronic Data Capture
EPM	Exploratory Project Manager
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FACS	Fluorescence-activated cell sorting
FAS	Full Analysis Set
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
HBV	hepatitis B virus
HBcAb	anti-hepatitis B core antibody
HBsAg	hepatitis B surface antigen

HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IgG1	immunoglobulin G1
IGRA	interferon-gamma release assay
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
iv	intravenous
IXRS	interactive voice or web response system (IVRS or IWRS)
kg	kilogram
LOCF	last observation carried forward
LTB	latent TB
mAb	monoclonal antibody
MCS	Mental Component Summary
MCID	minimal clinically important difference
MID	minimally important difference
MedDRA	Medical Dictionary for Regulatory Activities
mNAPSI	modified nail psoriasis severity index
NOAEL	no adverse effect level
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PBO	placebo
PD	pharmacodynamics
PDE4	phosphodiesterase 4
PDILI	potential drug-induced liver injury

PD-PPS	Pharmacodynamics Per-Protocol Set
PK	pharmacokinetics
PK-PPS	Pharmacokinetics Per-Protocol Set
PPS	Per-Protocol Set
PS	Patient Safety
PSO	psoriasis
PSSI	Psoriasis Scalp Severity Index
RS	Randomized Set
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SFU	Safety Follow-Up
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale
Q4W	every 4 weeks

1 SUMMARY

This is a Phase 2a, multicenter, randomized, subject-blind, investigator-blind, study to investigate the pharmacodynamics (PD), pharmacokinetics (PK), and safety of bimekizumab (also known as UCB4940) in adult subjects with moderate to severe chronic plaque psoriasis in order to guide the selection of doses and clinical indices in the Phase 3 development program.

The study population consists of adult subjects (≥18 years of age) with a diagnosis of moderate to severe chronic plaque psoriasis (Baseline Psoriasis Area and Severity Index [PASI] ≥12 and body surface area [BSA] affected by psoriasis ≥10% and Investigator's Global Assessment [IGA] score ≥3 [on a 5-point scale]) who are a candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy.

Approximately 90 subjects will be screened in order to have 45 subjects randomized in the study. There will be approximately 30 subjects in treatment arm A and 15 subjects in treatment arm B. For each subject, the study will last a maximum of 40 weeks and will consist of 3 periods, a Screening Period (up to 4 weeks), a Treatment Period (28 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the last dose of study medication). Between Week 20 and the end of the 28-week Treatment Period, eligible subjects will be allowed to enroll in an extension study.

During the Treatment Period eligible subjects will be randomized 2:1 to receive the following blinded study treatment:

- Treatment arm A: Bimekizumab 320mg administered subcutaneously (sc) at Baseline and Week 4, followed by placebo administration at Week 16
- Treatment arm B: Bimekizumab 320mg administered sc at Baseline and Weeks 4 and 16

Study medication will be administered in the clinic at Baseline, Week 4, and Week 16. Additional nondosing study visits will occur at Week 2, Week 8, Week 12, Week 20, Week 24, and Week 28. From Week 20 through Week 28, subjects who were previously PASI25 responders but subsequently relapse (defined as returning to less than PASI25 response) will undergo the study assessments for that visit (ie, Week 20, Week 24, or Week 28) before receiving their first dose of study treatment in the extension study at Week 20, Week 24, or Week 28. Subjects eligible for the extension study must have the assessments for SFU conducted prior to entering the extension study. Subjects who have not achieved a PASI25 response at any visit prior to Week 20 will not be eligible to enter the extension study. All subjects not enrolling in the extension study will continue in PS0016 until the SFU Visit at Week 36.

The primary objective of this study is to evaluate the time-course of PASI over a 28-week period following the administration of bimekizumab given at Baseline and Week 4 to subjects with moderate to severe chronic plaque psoriasis. The secondary objectives of the study are to evaluate the time-course of PASI over a 28-week period following the administration of bimekizumab given at Baseline and Weeks 4 and 16 in subjects with moderate to severe plaque psoriasis, to assess the PK and immunogenicity of bimekizumab and to assess the safety and tolerability of bimekizumab.

The other objectives of the study are 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.

The primary endpoint of this study is change from Baseline in PASI at Week 28. The secondary efficacy variables are PASI75, PASI90, and PASI100 response at Week 16, and IGA response (Clear or Almost Clear with at least a 2-category improvement from Baseline) at Week 16. The other efficacy variables are presented in Section 4.3.1.

Pharmacokinetic, PD, genomic, genetic, proteomic, and immunological variables will be evaluated to assess their relationship to treatment response.

Safety variables to be assessed are adverse events (AEs), vital signs, electrocardiograms (ECGs), physical examination, and measurements of laboratory parameters.

2 INTRODUCTION

2.1 Psoriasis

Psoriasis is a common, chronic inflammatory disease characterized by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils, and other types of leukocytes in affected skin. Though the pathophysiology of psoriasis is not fully understood, the importance of T-cells and inflammatory cytokines has been demonstrated by the clinical benefit provided by therapies directed at these targets (Krueger and Ellis, 2005).

There are a variety of forms including plaque, guttate, inverse, pustular, and erythrodermic. Plaque psoriasis is the most common, comprising approximately 80% to 90% of all cases. Approximately 17% of those with psoriasis have moderate to severe disease (Kurd et al, 2008).

In addition to the impact on skin, psoriasis has a multitude of psychosocial and emotional effects on patients, including increased self-consciousness, frustration, fatigue, depression, and suicidal ideation. As a result, patients frequently report sleeping problems, difficulties at work, problems interacting with family members, disrupted leisure activities, and sexual difficulties (Dowlatshahi et al, 2014; Gottlieb, 2005; Mukhtar et al, 2004; Ortonne, 2004; Krueger et al, 2001).

A number of comorbidities have been associated with psoriasis, especially with more severe psoriasis. Psoriatic arthritis, cardiovascular disease, metabolic syndrome, chronic pulmonary disease, peptic ulcer disease, renal disease, and diabetes have all been demonstrated to have an increased prevalence in psoriasis patients (Yeung et al, 2013; Christophers et al, 2010; Gisondi et al, 2007; Gelfand et al, 2006).

2.1.1 Global epidemiology of psoriasis

Psoriasis affects approximately 3% of the adult US population (Rachakonda et al, 2014; Kurd and Gelfand, 2009) and its onset can begin at any age (Augustin et al, 2010; Icen et al, 2009). The reported worldwide incidence and prevalence of psoriasis varies greatly depending on age, gender, ethnicity, and geography primarily due to genetic and environmental factors. Estimates of incidence and prevalence include all types of psoriasis. Plaques psoriasis is the most common form of psoriasis therefore reported estimates of the magnitude of this condition are likely weighted heavily by this subtype. Both the incidence and prevalence of psoriasis are higher among Caucasians and those living in higher latitudes. Psoriasis affects approximately 2% to 4% of the population of western countries. Geographical differences are also influenced by case

definition, study design, and the definition of prevalence (Parisi et al, 2013; Langley et al, 2005; Raychaudhuri and Gross, 2000).

2.1.2 Current treatments for psoriasis

Therapy for patients with psoriasis varies according to the severity of disease. Limited or mild disease is often treated with topical therapies such as corticosteroids and vitamin D analogs. Patients with more severe disease are often treated with chemophototherapy, methotrexate, the oral phosphodiesterase 4 (PDE4) inhibitor (apremilast), or biologic agents, such as tumor necrosis factor (TNF) antagonists, interleukin (IL) 12/23 inhibitors, and IL-17A inhibitors. The effectiveness of TNF inhibitors in the treatment of psoriasis has been demonstrated in many Phase 3 clinical studies and has led to the approval of multiple TNF inhibitors for use in patients with moderate to severe psoriasis. Interleukin inhibitors include secukinumab and ixekizumab, IL-17A inhibitors approved for treatment of moderate to severe psoriasis. Ustekinumab is an IL-12/23 antagonist approved for use in patients with moderate to severe psoriasis, and brodalumab, an IL-17 receptor antagonist, has completed pivotal Phase 3 studies in psoriasis. Standard therapies for psoriasis are listed below:

- Topical steroids (eg, triamcinolone, mometasone, clobetasol, betamethasone, hydrocortisone) are generally used as first-line treatment of psoriasis. High-strength steroids are typically reserved for use on the arms and legs. Areas such as the face and skin folds (axillary, inguinal regions, etc) are usually treated with a low potency steroid. Chronic use of topical steroids can lead to corticosteroid-related side effects and is generally discouraged.
- Vitamin D analogs (eg, calcipotriol and tacalcitol) are commonly used to treat mild to moderate psoriasis, and work best within the mild patients. They are safe but lack efficacy for many moderate to severe patients.
- Chemophototherapy is a frequent option for moderate to severe patients, but the inconvenience of multiple treatment visits and varying efficacy limits its use in the market.
- Methotrexate is a systemic immunosuppressant and is used in moderate to severe patients. Toxicity concerns, particularly in older patients, are a major drawback.
- Apremilast is an oral small-molecule inhibitor of PDE4 that is also approved for treatment of adults with moderate to severe plaque psoriasis. PDE4 inhibitors work intracellularly to modulate a network of pro-inflammatory and anti-inflammatory mediators. PDE4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. PDE4 inhibition elevates intracellular cAMP levels, which in turn down-regulates the inflammatory response by modulating the expression of TNFα, IL-23, IL-17, and other inflammatory cytokines.
- Biologics, including TNFα inhibitors (adalimumab, etanercept, and infliximab), IL-12/23 inhibitors (ustekinumab), and IL-17A inhibitors are the treatment options of choice for patients with moderate to severe plaques psoriasis who are candidates for systemic therapy or phototherapy. These products are injected sc or delivered via intravenous (iv) infusion and while effective, TNFα inhibitors come with boxed warnings including the risk of serious infections and reports of lymphoma and malignancy in children and adolescent patients. The efficacy of TNFα inhibitors in treating psoriasis has been attributed to their inhibition of Th17-T cells. Different from the traditional systemic drugs that impact the entire

immune system, biologics target specific parts of the immune system and offer reduced multi-organ toxicity and adverse effects associated with traditional treatments.

Secukinumab has been approved in the US and the EU for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab is a monoclonal antibody (mAb) that inhibits the activity of the IL-17A isoform and is the first approved drug in its class. Clinical study results have shown that secukinumab achieves higher efficacy response levels than other drugs historically, demonstrating that IL-17 is a very effective target for the development of drugs for the treatment of psoriasis.

Ixekizumab, an IgG4 mAb, has been approved in the US and the EU for the treatment of moderate to severe plaque psoriasis in adult patients. Clinical study results have shown that ixekizumab is effective for the treatment of psoriasis.

2.2 Bimekizumab

Bimekizumab is an engineered, humanized, full-length immunoglobulin G1 (IgG1) mAb, with high affinity for human IL-17A and IL-17F, important proinflammatory cytokines of the IL-17 family 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 psoriasis, ulcerative colitis, asthma, ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis. While anti-IL-17A antibodies have demonstrated efficacy in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis, as yet, no therapeutic approach is 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 that may be conferred by dual inhibition of both cytokines in patients suffering from diseases in which both cytokines are active.

2.2.1 Clinical

Three clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque psoriasis, RA0124 in 30 healthy volunteers, and PA0007 in 53 subjects with psoriatic arthritis. Two studies (RA0123 and UP0031) are ongoing in subjects with moderate to severe rheumatoid arthritis and in healthy subjects, respectively.

UP0008 was a Phase 1, single ascending dose study in adults with mild to moderate psoriasis affecting ≤5% BSA. In this blinded study, single doses of up to 640mg (approximately 8mg/kg in an 80kg adult) were evaluated without any safety concerns. A total of 26 subjects with psoriasis with less than 5% of body surface involvement were treated with a range of single iv doses from 8 to 640mg. There were no clinically relevant safety findings identified at any dose and all doses were well tolerated. The pre-specified exploratory assessment of disease activity showed clinically relevant and statistically significant improvements at the higher doses studied.

RA0124 was a Phase 1, open-label, parallel-group, single-dose study in healthy subjects. The primary objective of this study was to determine the absolute bioavailability of single sc doses of bimekizumab (80mg and 160mg). The secondary objectives were to evaluate the dose proportionality of bimekizumab 80mg and 160mg sc, and to evaluate the safety and tolerability of these sc doses and 160mg given by iv infusion. In RA0124, the absolute bioavailability was

similar for the 2 doses tested (0.656 and 0.631 for the bimekizumab 80mg and 160mg sc doses, respectively). The PK of bimekizumab was linear in the tested dose range and the median $t_{1/2}$ following sc administration was similar to that following iv administration (27.81 days and 28.25 days for bimekizumab 160mg sc and 160mg iv, respectively).

Bimekizumab has also 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 psoriatic arthritis. Four active doses and a placebo were tested. Drug was administered as a loading dose at Week 0, and 2 additional doses were administered at Week 3 and Week 6. 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 3 and 6
- 160mg loading dose followed by 80mg at Weeks 3 and 6
- 240mg loading dose followed by 160 mg at Weeks 3 and 6
- 560mg loading dose followed by 320mg at Weeks 3 and 6

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 1 local candida infection each (oropharhyngitis and vulvovaginitis, respectively) that were non-serious 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 convincing relationship to exposure to study medication. The exploratory analysis showed clinically relevant improvement in activity of psoriatic arthritis and in skin involvement in those subjects with concomitant active psoriatic lesions.

Two additional studies of bimekizumab are ongoing. RA0123 is a Phase 2a, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the safety, PK, PD, and efficacy of multiple doses of bimekizumab administered as add-on therapy to stable certolizumab pegol therapy in subjects with moderate to severe rheumatoid arthritis. UP0031 is a Phase 1 open-label, parallel-group, single-dose study to evaluate the relative bioavailability and tolerability of bimekizumab 160mg sc in healthy subjects.

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

2.2.2 Nonclinical

Parallel inhibition of IL-17A and IL-17F has been shown to be efficacious in a variety of animal models of inflammatory disease. Intravenously administered bimekizumab was well tolerated in repeat dose toxicology studies in Cynomolgus monkeys with a no adverse effect level (NOAEL) of 200mg/kg/week. The findings of note in toxicity studies were diarrhea related to infectious enteritis (observed in the single dose study) and asymptomatic mild colonic ulceration in a

proportion of animals (in the repeat dose study); this latter finding was not associated with hematology abnormalities. Data suggest that bimekizumab has induced primary lesions to the mucosa-associated lymphoid tissue via a pharmacologically-related mechanism. In a second repeat-dose study, none of the minor apoptosis/necrosis findings observed in gut associated lymph nodes were revealed. In animals given the highest dose of bimekizumab in the study (20mg/kg/week), a slightly higher number of protozoa (*Balantidium coli*) was observed in the cecum and colon as compared to the control animals and low dose animals. Therefore gut associated lymph node lesions observed in the first study are considered to be accidental and/or linked to exaggerated pharmacology and proliferation of *Balantidium coli* and is considered the consequence of a change in local mucosal immunity. To date, similar findings have not been seen in studies in humans.

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

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to evaluate the time-course of PASI over a 28-week period following the administration of bimekizumab given at Baseline and Week 4 to subjects with moderate to severe chronic plaque psoriasis.

3.2 Secondary objectives

The secondary objectives of the study are to:

- To evaluate the time-course of PASI over a 28-week period following the administration of bimekizumab given at Baseline and Weeks 4 and 16 in subjects with moderate to severe plaque psoriasis
- Assess the PK and immunogenicity of bimekizumab
- Assess the safety and tolerability of bimekizumab

3.3 Other objectives

The other objectives of the study are 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.

4 STUDY VARIABLES

4.1 Primary variables

4.1.1 Primary efficacy variable

The primary endpoint of this study is change from Baseline in PASI at Week 28.

4.1.2 Primary pharmacokinetic variable

The primary PK variable is plasma concentration of bimekizumab.

4.1.3 Primary immunogenicity variable

The primary immunological variable is anti-bimekizumab antibody detection prior to and following study treatment.

4.1.4 Primary safety variable

The primary safety variable is incidence of AEs.

4.2 Secondary variables

The secondary efficacy variables are:

- PASI75, PASI90, and PASI100 response at Week 16
- IGA response (Clear or Almost Clear with at least a 2-category improvement from Baseline) at Week 16

4.3 Other variables

4.3.1 Other efficacy variables

The other efficacy variables are listed below and will be evaluated at all scheduled visits in accordance with the Schedule of Assessments in Table 5–2. This excludes the primary and secondary variables as specified in Section 4.1 and Section 4.2.

- Absolute and % change from Baseline in PASI with time (Week 2 to Week 36)
- PASI75, PASI90, and PASI100 response at Weeks 2, 4, 8, 12, 20, 24, 28, and 36
- PASI25 and PASI50 response (Week 2 to 36)
- IGA response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Weeks 2, 4, 8, 12, 20, 24, 28, and 36
- Change from Baseline in IGA score
- Change from Baseline in the BSA affected by psoriasis
- Change from Baseline in Hospital Anxiety and Depression Scale (HADS) HADS-A and HADS-D scores
- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores)

4.3.2 Other pharmacodynamic variable

The PD variable is to determine the blood or blood derivative (eg, plasma) concentrations of cytokines of relevance to IL17-A/F signaling pathway and psoriasis biology, including but not limited to serum complement concentrations, mononuclear cell subtypes, and cytokines and other candidate biomarkers.

4.3.3 Other safety variables

Other safety variables to be assessed are:

- Change from Baseline in clinical laboratory values (chemistry, hematology, and urinalysis)
- Change from Baseline in vital signs

- Change from Baseline in physical examination
- ECG results

4.3.4 RNA, proteins, and metabolite variables

Blood and tissue biopsy samples will be collected at specific time points and stored for up to 20 years to allow for potential exploratory analyses of RNA, proteins, and metabolites biomarkers relevant to psoriasis and the inflammatory and immune response processes.

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

4.4 Immunological variable

The immunological variable is anti-bimekizumab antibody detection following study treatment.

5 STUDY DESIGN

5.1 Study description

This is a Phase 2a, multicenter, randomized, subject-blind and investigator-blind study to evaluate the PD, PK, and safety of bimekizumab administered sc to subjects with psoriasis. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe psoriasis (Baseline PASI ≥12 and BSA affected by psoriasis ≥10% and IGA score ≥3 [on a 5-point scale]) who are a candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy.

5.1.1 Study Periods

This study will include 3 periods: a Screening Period (up to 4 weeks), a Treatment Period (28 weeks), and a SFU Period (20 weeks after the last dose of study medication). Between Week 20 and the end of the 28-week Treatment Period, eligible subjects will be allowed to enroll in an extension study.

Screening Period

The Screening Period will last up to a total of 4 weeks in the event that applicable laboratory screening tests require retesting if the initial results are in error, borderline, or indeterminate. During this time, laboratory data (hematology, urine, and biochemistry tests) will be obtained, the doses of non-steroidal anti-inflammatory drug (NSAIDs) (if used to treat psoriatic arthritis), will be verified as stable.

Treatment Period

During the Treatment Period, subjects will be randomized 2:1 to receive the following blinded study treatment regimens:

- Treatment arm A: Bimekizumab 320mg administered sc at Baseline and Week 4, and placebo administered at Week 16
- Treatment arm B: Bimekizumab 320mg administered sc at Baseline and Weeks 4 and 16

There will be approximately 30 subjects in treatment arm A and 15 subjects in treatment arm B. Bimekizumab will be administered in the clinic at Baseline and Week 4, and at Baseline, Week 4, and Week 16 for those in treatment arm A and treatment arm B, respectively. Additional

nondosing study visits will occur at Week 2, Week 8, Week 12, Week 20, Week 24, and Week 28.

From Week 20 through Week 28, subjects who were previously PASI25 responders but subsequently relapse (defined as returning to a less than PASI25 response) will undergo the study assessments for that visit (ie, Week 20, Week 24, or Week 28) before receiving their first dose of study treatment in the extension study at Week 20, Week 24, or Week 28. Subjects eligible for the extension study must have the assessments for SFU conducted prior to entering the extension study. Subjects who have not achieved a PASI25 response at any visit prior to Week 20 will not be eligible to enter the extension study. All subjects not enrolling in the extension study will continue in PS0016 until the SFU Visit at Week 36.

Subjects withdrawing early from the study will undergo the Early Withdrawal Visit assessments (ie, Week 36) and will enter the SFU Period.

The assessments at each Treatment Period Visit are presented in Table 5–1.

Safety Follow-Up Period

All subjects not continuing in the extension study, including those withdrawn from study treatment, will have a SFU Visit 20 weeks after their last dose of study medication (ie, bimekizumab or placebo).

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

5.1.2 Study duration per subject

For each subject, the study will last a maximum of up to 40 weeks. This includes the following study period durations:

- Screening Period: up to 4 weeks
- Treatment Period: 28 weeks
- Safety Follow-Up Period: a SFU Visit is planned 20 weeks after the last dose of study medication

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

5.1.3 Planned number of subjects and sites

A sufficient number of subjects (anticipated to be approximately 90 subjects) will be screened in order to have approximately 45 subjects randomized in the study; 30 to Treatment arm A and 15 to Treatment arm B. The planned number of study sites is approximately 15.

5.1.4 Anticipated regions and countries

The regions planned for study conduct are Europe and North America, with possible extension to other regions and countries.

5.2 Schedule of study assessments

A schedule of study assessments is provided in Table 5–1.

Table 5–1: Schedule of assessments

Visit[a]/ Week / Protocol activity	Screening[b]	Baseline	Treatment Period (Time after the first dose)								Wk 36 EWD/ SFU[c]
			Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	
Informed consent[d]	X										
Inclusion/exclusion	X	X									
Demographic data	X										
Psoriasis history	X										
Significant past medical history and concomitant diseases[e]	X	X									
Physical examination	X										X
Height	X										
Body weight	X	X					X				X
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X
HADS	X	X		X	X	X	X	X	X	X	X
Hematology/biochemistry/ urinalysis	X	X[g]	X	X	X	X	X	X	X	X	X
12-lead ECG[h]	X	X		X			X				X
Pregnancy testing[i]	X	X		X	X	X	X	X	X	X	X
Hepatitis B and C testing[j]	X										
HIV testing	X										
Chest x-ray[k]	X										
IGRA tuberculosis test [l,m]	X										X
Tuberculosis questionnaire	X	X						X			X

Table 5–1: Schedule of assessments

Visit[a]/ Week / Protocol activity	Screening[b]	Baseline	Treatment Period (Time after the first dose)								Wk 36 EWD/ SFU[c]
			Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	
Blood sample for bimekizumab plasma concentrations[n]		X	X	X	X	X	X	X	X	X	X
Blood sample for anti-bimekizumab antibodies[n]		X		X	X	X	X	X	X	X	X
Blood sample for cytokines, complement, candidate biomarker analysis, and flow cytometry[n]		X			X	X	X				X
Blood sample for RNA, proteins, and metabolites biomarkers[n]	X	X			X	X	X			X	X
Skin biopsy[o]		X (2)			X (2)		X (1)			X (1)	
PASI	X	X	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X	X	X
BSA affected by psoriasis	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
IXRS	X	X		X			X				
Subject identification card	X										
Bimekizumab or placebo administration		X		X			X				

Table 5–1: Schedule of assessments

Visit[a]/ Week / Protocol activity	Screening[b]	Baseline	Treatment Period (Time after the first dose)							Wk 36 EWD/ SFU[c]
			Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	

BSA=body surface area; C-SSRS= Columbia Suicide Severity Rating Scale; ECG=electrocardiogram; EWD=Early Withdrawal; FSH=follicle stimulating hormone; HADS=Hospital Anxiety and Depression Scale; HIV=human immunodeficiency virus; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IXRS=interactive voice or web response system; PASI=Psoriasis Area and Severity Index; PK=pharmacokinetics; SFU=Safety Follow-Up; TB=tuberculosis; Wk=week

[a] Visit windows of ±3 days from the first dose at all visits except SFU. Safety Follow-Up Visit window is -3 and +7 days.

[b] The Screening Period will last up to a total of 4 weeks.

[c] The SFU Visit will occur 20 weeks after the last dose.

[d] A separate Informed Consent Form is required to be completed for the extension study.

[e] Ensure no significant changes in medical history.

[f] Vital signs (blood pressures, pulse rate, and temperature) are to be measured prior to blood sampling, and prior to dosing, where applicable.

[g] The FSH test should only be performed on postmenopausal females who have been postmenopausal for ≥1 year and last menstrual cycle occurred <2 years ago.

[h] At Baseline and Weeks 4 and 16, to be performed predose.

[i] Pregnancy testing will be serum testing at Screening and SFU. The pregnancy test will be urine at all other visits. If the subject is entering the extension study, a urine pregnancy test will be performed at SFU.

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

[k] A chest x-ray must be performed at Screening or must occur within 3 months prior to Screening and results must be available at Baseline. MMR is not acceptable.

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

[m] It is recommended that the QuantiFERON TB GOLD test be performed.

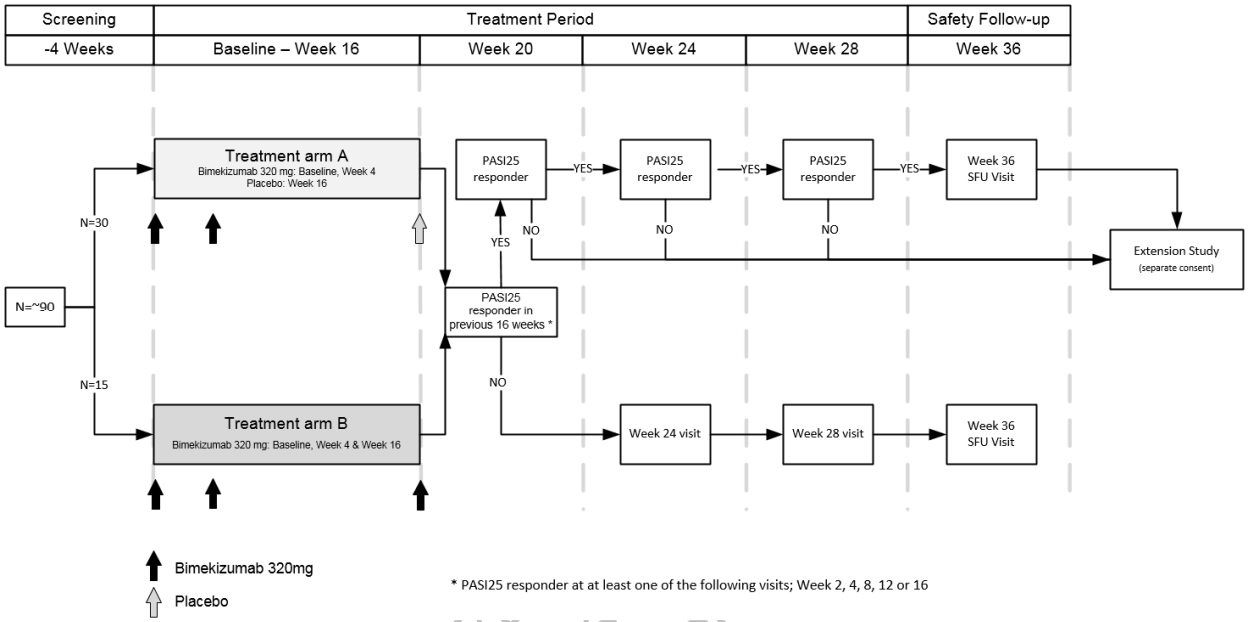
[n] All blood samples taken prior to dosing.

[o] Lesional and nonlesional biopsies to be obtained at Baseline and Week 8. Lesional biopsies to be obtained at Week 16 and Week 28.

5.3 Schematic diagram

The study schematic diagram for PS0016 is presented in Figure 5–1.

Figure 5–1: Schematic diagram of PS0016



PASI= Psoriasis Area and Severity Index; SFU=Safety Follow-Up

From Week 20 through Week 28, subjects who were previously PASI25 responders but subsequently relapse (defined as returning to less than PASI25 response) will undergo the study assessments for that visit (ie, Week 20, Week 24, or Week 28) before receiving their first dose of study treatment in the extension study at Week 20, Week 24, or Week 28. Subjects eligible for the extension study must have the assessments for SFU conducted prior to entering the extension study. Subjects who have not achieved a PASI25 response at any visit prior to Week 20 will not be eligible to enter the extension study. All subjects not enrolling in the extension study will continue in PS0016 until the SFU Visit at Week 36.

5.4 Rationale for study design and selection of dose

PS0016 is a Phase 2a, a multicenter, randomized, subject-blind, investigator-blind study to evaluate the PD, PK, and safety of bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis Treatment Period (28 weeks) and a SFU Period (20 weeks after the last dose of study medication).

The inclusion criteria are designed to ensure all subjects have moderate to severe disease activity. Some exclusion criteria are intended to eliminate subjects who may present an unacceptable safety risk were they to participate in this investigational study program. The full list of inclusion and exclusion criteria is provided in Section 6.

The study will evaluate 2 regimens of bimekizumab to understand the time course of PASI response following sc administration of bimekizuamb:

- Treatment arm A: Bimekizumab 320mg at Week 0 and 4 administered sc, placebo administered at Week 16
- Treatment arm B: Bimekizumab 320mg at Weeks 0, 4, and 16 administered sc

The dose level and regimens were chosen based on the efficacy and safety data from the 3 completed clinical studies of bimekizumab (UP0008, RA0124, and PA0007). The selected dosage regimens will in maximum likelihood provide information to evaluate the time-course of PASI response following administration of bimekizumab treatment in this patient population.

All the subjects in the study will receive 320mg of bimekizumab as a sc injection at Baseline and Week 4. Based on our current understanding of PKPD of bimekizumab this will enable maximum PASI response in the subjects. Subjects will then be administered either placebo (Treatment arm A) or 320mg of bimekizumab at Week 16 (Treatment arm B), in order to evaluate the change in time course of PASI response. The proposed doses are expected to be safe since doses greater than 320mg (ie, up to 640mg) have been previously tested, via intravenous administration, in the development of bimekizumab and were found to be safe and well tolerated.

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 re-confirmed at the Baseline Visit. (Note: the 1 exception relates to the laboratory tests performed at Baseline Visit, from which only the pregnancy test result needs to be known prior to administration of study medication.)

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 at least 18 years of age and less than or equal to 70.

4. Subject has had chronic plaque psoriasis for at least 6 months prior to Screening.

5. Subject has PASI ≥12 and BSA ≥10% and IGA score ≥3 on a 5-point scale.

6. Subject is a candidate for systemic psoriasis therapy and/or phototherapy and/or chemophototherapy.

7. **Female** subjects must be postmenopausal (at least 1 year; to be confirmed hormonally as part of the Screening process, if less than 2 years since last menstrual period), permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) or, if of childbearing potential, must be willing to use a highly effective method of contraception up until 20 weeks after last administration of study drug, and have a negative pregnancy test at Screening and immediately prior to first dose. The following methods are considered highly effective when used consistently and correctly.

- Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner (where postvasectomy testing had demonstrated sperm clearance).
- Sexual abstinence if it is in accordance with a subject's preferred and common lifestyle. Subjects who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse until 20 weeks after the last dose of study medication. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.

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

8. Subject agrees to not increase their usual sun exposure during the course of the study and to use ultraviolet A/ultraviolet B (UVA/UVB) sunscreens.

6.2 Exclusion criteria

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

1. Female subjects who are breastfeeding, pregnant, or plan to become pregnant during the study or within 20 weeks following last dose of study drug. Male subjects who are planning a partner pregnancy during the study or within 20 weeks following the last dose.
2. Subjects previously participating in a bimekizumab clinical trial.
3. Subjects participating in another study of a medication or a medical device under investigation within the last 3 months or at least 5 half-lives, whichever is greater, or is currently participating in another study of a medication or medical device under investigation.
4. Subjects with a known hypersensitivity to any excipients of bimekizumab.

5a. Subjects with erythrodermic, guttate, pustular form of psoriasis, or drug-induced psoriasis.

6. Subjects with a history of chronic or recurrent infections, or a serious or life-threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster). Subjects with a high risk of infection in the Investigator's opinion (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, prior prosthetic joint infection at any time, subjects who are permanently bedridden or wheelchair assisted).
7. Subject has any current sign or symptom that may indicate an active infection (except for common cold), or has had an infection requiring systemic antibiotics within 2 weeks of baseline.

8. Subjects with concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Subjects who have evidence of, or tested positive for hepatitis B or hepatitis C are excluded. A positive test for the hepatitis B virus (HBV) is defined as: 1) positive for hepatitis B surface antigen (HBsAg+); or, 2) positive for anti-hepatitis B core antibody (HBcAb+). A positive test for the hepatitis C virus (HCV) is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab), and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).
9. Subjects with known history of or current clinically active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria, Blastomyces, or Aspergillus or current active Candidiasis (local or systemic).
10. Subjects receiving any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted). Live vaccines are not allowed during the study or for 20 weeks after the last dose of study drug.
11. Subjects receiving Bacillus Calmette-Guerin (BCG) vaccinations within 1 year prior to study drug administration.
12. Subjects with a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
13. Subjects with primary immunosuppressive conditions, including subjects who are taking immunosuppressive therapy following an organ transplants.
14. Subjects with known TB infection, at high risk of acquiring TB infection, with latent TB infection (LTBI), or current or history of NTMB infection (refer to Section 12.6.1 for details on determining full TB exclusion criteria).
15. Subjects who have had a splenectomy.
16. Subjects with concurrent malignancy or history of malignancy (including surgically resected uterine/cervical carcinoma-in-situ) during the past 5 years, will be excluded, with the following exceptions, that may be included.
    a. ≤3 excised or ablated, basal cell carcinomas of the skin
    b. One squamous cell carcinoma of the skin (stage T1 maximum) successfully excised, or ablated only (other treatments, ie, chemotherapy, do not apply), with no signs of recurrence or metastases for more than 2 years prior to Screening
    c. Actinic keratosis(-es)
    d. Squamous cell carcinoma-in-situ of the skin successfully excised, or ablated, more than 6 months prior to Screening
17. Subjects having had major surgery (including joint surgery) within the 6 months prior to Screening, or planned surgery within 6 month after entering the study.
18. Subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac (eg, congestive heart failure, New York Heart Association [NYHA] Grade 3 and 4),

gastrointestinal (GI) (note: subjects with active peptic ulcer disease are excluded; subjects with a history of peptic ulcer disease are allowed), or neurological disease.

19. Subject has a history of uncompensated heart failure, fluid overload, or myocardial infarction, or evidence of new onset ischemic heart disease or in the opinion of the Investigator other serious cardiac disease, within 12 weeks prior to Baseline.

20a. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

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

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

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

21. Subjects with clinically significant laboratory abnormalities (eg, creatinine >1.5xULN, neutropenia <1.5x10^9/L, hemoglobin <8.5g/dL, lymphocytes <1.0 x10^9/L, platelets <100 x10^9/L). Individual screening tests for which the results are in error, borderline, or indeterminate for inclusion in the study, can be repeated once for confirmation during the screening period if they are within 25% of the exclusion limit. Upon retesting, subjects whose results remain outside this threshold should not be randomized.

22. Subjects with any other condition which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.

23. Subjects have been exposed to more than 1 biological response modifier (limited to anti-TNF or IL-12/-23) or have received any biologic response modifier during the three months prior to the Baseline Visit. The list of prohibited medications is presented in Section 7.8.2.

24. Subjects have received previous treatment with any anti-IL-17 therapy for the treatment of psoriasis or psoriatic arthritis.

25a. Subjects with a diagnosis of inflammatory conditions other than psoriasis or psoriatic arthritis, including but not limited to rheumatoid arthritis, sarcoidosis, or systemic lupus erythematosus. Subjects with a diagnosis of Crohn's disease or ulcerative colitis are allowed as long as they have no active symptomatic disease at Screening or Baseline.

26. Subjects taking psoriatic arthritis medications other than nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics. Subjects already receiving an established NSAID regimen (at least 8 weeks prior to Baseline) and who have been on a stable dose for at least 4 weeks prior to Baseline may continue their use during the study.

27. Subject has a history of chronic alcohol or drug abuse within the previous 6 months.

28. Subject has 12-lead ECG with changes considered to be clinically significant upon medical review (eg, QT corrected for heart rate [QTc] using Fridericia's correction [QTcF] >450ms, bundle branch block, evidence of myocardial ischemia).

29a. Presence of significant uncontrolled neuropsychiatric disorder, active suicidal ideation, or positive suicide behavior using the "Baseline" version of the C-SSRS and the HADS with either of the following criteria:

- Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening/Baseline" version of the C-SSRS at Screening.

– HADS Depression score >10 or Anxiety score ≥15

30. Subject is an Investigator site worker directly affiliated with this study and/or an immediate family member. Immediate family is defined as a spouse, parent, child or sibling, whether biological or legally adopted.

31. Subject is a UCB employee or employee of third-party organizations involved in the study.

32. Subjects who have been admitted to a mental hospital or other institution by an order of the court

6.3 Withdrawal criteria

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

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

1. Subject withdraws his/her consent.

2. The Sponsor or a regulatory agency requests withdrawal of the subject.

Subjects should be withdrawn from all study treatment and will be asked to return for the SFU Visit (20 weeks after the last received dose) if any of the following events occur:

1. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.

2a. Subject develops an illness that in the opinion of the Investigator would interfere with his/her continued participation if the risk of continuing participation outweighs the potential benefit.

3a. Subject develops erythrodermic, guttate, or pustular form of psoriasis.

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

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

Additional information on TB policies are provided in Section 12.6.1.

5. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
6. Subject uses prohibited concomitant medications, with the exception of topicals, as defined in this protocol (Section 7.8.2), that may present a risk to the safety of the subject in the opinion of the Investigator and/or the Medical Monitor.

8a. Subject has active suicidal ideation as indicated by a positive response ("Yes") to Questions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated Columbia Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

9a. Subjects with a HADS-D score ≥15 must be withdrawn. Any subject who develops a HADS-D score of >10 during the study should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.

10. Subject experiences an AE as described below:
    - Any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above AE that is assessed as related to study drug in the opinion of the Investigator
        - If the event is deemed to be not related to study drug by the Investigator, the subject may remain in the study after approval by the Medical Monitor.
    - Any CTCAE Grade 2 event that is evaluated as related to study drug in the opinion of the Investigator, is persistent, and falls into any of the following System Organ Classes (SOCs): "Blood and lymphatic disorders," "Cardiac disorders," or "Vascular disorders."
        - Persistent is defined as lasting 28 days or more, which spans at least 2 scheduled injections.
11. Subject has a clinical laboratory value meeting the following criteria:
    - CTCAE Grade 3 and above: subjects must be withdrawn regardless of relationship to study drug or duration of event.
    - CTCAE Grade 2
        - Subjects may remain in the study if the event is transient. If a subject has a Grade 2 laboratory abnormality, a retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat value is below Grade 2, the subject may receive the next scheduled study treatment. If the value on the repeat is still Grade 2 or above, a second repeat test must be performed and results made available prior to the next scheduled study treatment. If this second repeat value is still Grade 2 or above, the subject must be withdrawn.

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 Case Report Form (CRF) must document the primary reason for withdrawal or discontinuation.

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

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

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

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

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

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

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

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

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

6.4 Study Stopping Rules

During the study, planned dosing and procedures may be discontinued or suspended for all subjects in any part of the study and appropriate follow up procedures established. Where it is

possible to do so without threatening the safety of subjects, such discontinuation/suspension should be discussed with the UCB Study Physician prior to its implementation.

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

- A pattern of AEs occurs that contraindicates the further dosing of enrolled/additional subjects, including (but not limited to):
  - More than 1 subject meets any individual Withdrawal Criteria 4, 8a, 9a, 10 or 11 (as provided in Section 6.3), regardless of whether they met the same or different criteria.
  - Once a second subject meets any of those criteria, referral to the DMC may not be delayed while awaiting the outcome of either case.

  If the above criteria are reached, the DMC will meet as soon as possible to determine whether discontinuation or suspension of the study should occur, and to determine what investigations, analyses, procedural amendments, or other actions should occur, before making any recommendation regarding the possibility of recommencing the study. Further details on the role of the DMC are provided in Section 12.1.11 and Section 12.7.4.
- If the Sponsor or its designees judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations, and GCP.

6.5 Retesting/rescreening/replacement

In the event of an isolated exclusionary laboratory value outside the laboratory's normal range, the evaluation may be repeated on 1 occasion during the Screening Period. If the value from the repeated test is within the Screening-specified ranges, the subject maybe enrolled. Subjects whose Screening Period expires may be rescreened. Subjects who withdraw from the study may be replaced, up to a maximum of 10 subjects.

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

The investigational medicinal products (IMPs) used in this study are bimekizumab and placebo.

Bimekizumab will be supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative free solution in 2mL Type I, colorless glass vials (1.0mL extractable volume) closed with a rubber stopper and sealed with an aluminum cap overseal. Each single-use dose vial contains 160mg/mL bimekizumab in 55mM sodium acetate, 220mM glycine and 0.04% (w/v) polysorbate 80 at pH 5.0.

Placebo will be supplied as 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (USP/Ph.Eur) quality appropriate for injection.

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

7.2 Treatments to be administered

The study medication is to be administered in the clinic by study site staff as 2 sc injections. Suitable areas for sc injections are the lateral abdominal wall and upper outer thigh. During each dosing visit, each of the 2 sc injections should be administered at a separate injection site.

Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red or hard. The injection should last approximately 20 seconds.

In treatment arm A, bimekizumab will be administered at Baseline and Week 4, and placebo administered at Week 16. For treatment arm B, bimekizumab medication will be administered at Baseline, Week 4, and Week 16. The first dose of study treatment in the extension study will be at Week 20, Week 24, or Week 28. The minimum of time between doses should be no less than 24 days.

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

7.3 Packaging

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

7.4 Labeling

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

7.5 Handling and storage requirements

Study drug product (IMP) must be stored under refrigerated conditions (2ºC to 8ºC) and protected from light. The study drug must not be frozen.

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

Appropriate storage conditions must be ensured by controlled temperature and by completion of a temperature log in accordance with local requirements on a regular basis per study manuals, showing minimum and maximum temperatures reached over the time interval.

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

7.6 Drug accountability

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

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

Blinded study staff may be delegated the responsibility to receive, inventory, and destroy the used kits. The packaging identifies each kit by a unique number that does not correlate to the contents and therefore, does not unblind study site staff. Unblinded study staff will be responsible for preparation (breaking tamper proof sticker on kit, etc) of the clinical trial material.

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

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

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

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

7.7 Procedures for monitoring subject compliance

During the treatment period of this study, study medication will be administered in the clinic and compliance will be determined at the visit by study personnel. Drug accountability must be recorded on the Drug Accountability Form.

7.8 Concomitant medication(s)/treatment(s)

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

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

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

7.8.1 Permitted concomitant treatments (medications and therapies)

Topical medications

Subjects may continue to use topical moisturizers or emollients, bath oils, or oatmeal bath preparations for skin conditions during the study, as needed. Over-the-counter shampoos for the treatment of psoriasis of the scalp are also permitted.

Subjects who use prohibited topical medications will be allowed to stay in the study but will be counseled to not use them further. No other topical preparations are allowed in the 2 weeks before randomization or during the study unless medically required to treat an AE.

Other medications

Subjects who are already receiving an established NSAID regimen (at least 8 weeks prior to Baseline) and have been on a stable dose for at least 4 weeks prior to Baseline may continue their use during the study. However, initiation of, or increase in dosage of, NSAIDs during the study (especially in subjects with a history of GI intolerance to NSAIDs or a history of GI ulceration) should be done with caution. Intra-articular steroid injections for arthritis of the knee are allowed.

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

7.8.2 Prohibited concomitant treatments (medications and therapies)

The list of prohibited concomitant medications is provided Table 7–1.

As noted above, subjects who use prohibited topical medications will be allowed to stay in the study but will be counseled to not take them further.

Table 7–1: Prohibited psoriasis medications

Drug	Exclusion criteria prior to Baseline Visit
Systemic retinoids	12 weeks
Systemic treatment (non-biological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) systemic fumarate systemic corticosteroids phototherapy or chemophototherapy	8 weeks for methotrexate, azathioprine, and cyclosporine 4 weeks for everything other than methotrexate, azathioprine, and cyclosporine
Anti-TNFs: infliximab (including biosimilar), golimumab etanercept (including biosimilar) certolizumab pegol adalimumab (including biosimilar)	4 weeks for etanercept 12 weeks for everything other than etanercept
Other biologics and other systemic therapies: apremilast ustekinumab	12 weeks for apremilast 24 weeks for ustekinumab
Anti-IL-17 therapy	Any previous exposure excluded

Table 7–1: Prohibited psoriasis medications

Drug	Exclusion criteria prior to Baseline Visit
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)	24 weeks
Topical corticosteroids for dermatological use Vitamin D analogues and topical retinoids Keratolytic and coal tar	2 weeks
Any other antipsoriatic agent (topical) under investigation	4 weeks

IL-17=interleukin 17; TNF=tumor necrosis factor

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

Vaccines

Administration of live, attenuated vaccines is not allowed during the conduct of the study or for 20 weeks after the last dose of study drug (see Exclusion Criterion #10, 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 of the IMPs (bimekizumab and placebo), special precautions will be taken to ensure study blinding.

Bimekizumab and placebo injections will be prepared at the investigational sites by unblinded, dedicated study personnel. The unblinded personnel will not be involved in the study in any way other than assuring the medication is taken from the correct kit.

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

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

7.9.1 Procedures for maintaining and breaking the treatment blind

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

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

- Sponsor Clinical Study Supplies manager and qualified personnel
- Sponsor Patient Safety (PS) staff reporting SAEs to the regulatory authorities
- Site pharmacist involved in IMP preparation and dispensing
- Unblinded monitor who reviews the IMP related documentation and drug accountability
- Bioanalytical staff analyzing blood samples for bimekizumab and anti-bimekizumab antibody determination
- Any Sponsor staff and/or designee who are responsible for data analyses for the unblinded data cuts. This will be restricted to the UCB modeling and simulation team and UCB programming team.
- Unblinded programming team at Parexel for the purpose of sending unblinded data cuts

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

7.9.1.1 Maintenance of study treatment blind

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

7.9.1.2 Breaking the treatment blind in an emergency situation

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

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

7.10 Randomization and numbering of subjects

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by the Sponsor. The randomization schedule will be produced by an independent biostatistician with the Contract Research Organization (CRO) who is otherwise not involved in this study. The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

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

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

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

8 STUDY PROCEDURES BY VISIT

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

- Visit windows of ±3 days on either side of the scheduled dosing are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor.
- For the Safety Follow-Up Visit (20 weeks after the last dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

8.1 Screening Visit

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

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

- Obtain written informed consent
- Assessment of inclusion/exclusion criteria
- Demographic data
- Significant medical and procedure history and concomitant disease, including psoriasis disease history
- Concomitant medications
- Body height and weight
- Physical examination
- Vital signs (blood pressure, pulse rate, and temperature)
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Hospital Anxiety and Depression Scale (HADS)
- Record 12-lead ECG

- Chest x-ray (not necessary if performed within 3 months prior to Screening Visit and report is available)
- TB questionnaire
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - TB test (interferon gamma release assay; IGRA; it is recommended that the QuantiFERON TB GOLD test be performed)
  - Serum pregnancy test for women of childbearing potential
  - Standard safety laboratory tests (hematology and biochemistry)
  - Hepatitis B and C testing
  - HIV
  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for standard safety laboratory tests
- Record AEs
- Contact the IXRS
- Subject identification card

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

8.2 Baseline Visit

The following procedures or assessments will be performed/recorded prior to administration of study drug:

- Confirm inclusion/exclusion criteria
- Ensure no significant changes in medical procedure history and concomitant disease, including psoriasis disease history
- Vital signs (blood pressure, pulse rate, and temperature)
- Body weight
- Record 12-lead ECG
- TB questionnaire
- C-SSRS
- HADS
- PASI

- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential. (Note: A negative result must be received prior to administration of study medication.)
- Obtain skin biopsy (lesional and nonlesional)
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments completed)

8.3 Week 2 (+/-3 days)

The following procedures or assessments will be performed/recorded:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
- Obtain urine sample for:
  - standard safety laboratory tests
- Concomitant medications
- Record AEs

8.4 Week 4 (+/-3 days)

The following procedures or assessments will be performed/recorded prior to administration of study drug:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- HADS
- Record 12-lead ECG
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments completed)

8.5 Week 8 (+/-3 days)

The following procedures or assessments will be performed/recorded:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- HADS
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration

  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Obtain skin biopsy (lesional and nonlesional)
- Concomitant medications
- Record AEs

8.6 Week 12 (+/-3 days)

The following procedures or assessments will be performed/recorded:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- HADS
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs

8.7 Week 16 (+/-3 days)

The following procedures or assessments will be performed prior to administration of study drug:

- Body weight
- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- HADS
- Record 12-lead ECG
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Obtain skin biopsy (lesional)
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments completed)

8.8 Week 20 (+/-3 days)

The following procedures or assessments will be performed:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- HADS
- TB questionnaire
- PASI
- IGA
- BSA

- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs

8.9 Week 24 (+/-3 days)

The following procedures or assessments will be performed:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- HADS
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs

8.10 Week 28 (+/-3 days)

The following procedures or assessments will be performed:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS

- HADS
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Obtain skin biopsy (lesional)
- Concomitant medications
- Record AEs

8.11 Week 36/Safety Follow-Up Visit (20 weeks after the last dose)

All subjects not continuing in the extension study, including those withdrawn from study treatment, will have a SFU Visit at 20 weeks after their last dose of study medication.

The SFU Visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

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

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- HADS
- Body weight
- Physical examination
- Record 12-lead ECG
- TB questionnaire
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:

- TB test (interferon gamma release assay; IGRA; it is recommended that the QuantiFERON TB GOLD test be performed)
- Standard safety laboratory tests (hematology and biochemistry)
- Bimekizumab plasma concentration
- Anti-bimekizumab antibodies
- Cytokines, complement, candidate biomarker analysis, and flow cytometry
- RNA, proteins, and metabolites biomarkers
- Serum pregnancy test for women of childbearing potential. If the subject is entering the extension study, a urine pregnancy test will be performed.

- Obtain urine sample for standard safety laboratory tests
- Concomitant medications
- Record AEs

8.12 Early Withdrawal Visit

Subjects withdrawing early from the study (see Section 6.3) should undergo the same assessments scheduled for the Week 36 Visit (see Section 8.11) as soon as possible after withdrawal (as an Early Withdrawal Visit) and then enter the SFU Period, completing study participation with the SFU Visit (Week 36 Visit assessments again) 20 weeks after their last dose of study medication.

8.13 Unscheduled Visit

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

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

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

- Vital signs
- C-SSRS
- Physical examination
- Record 12-lead ECG
- If medically indicated, obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology, serum chemistry)
  - The blood sample may also be used for PK/PD assessments, if needed.
- Obtain urine sample for standard safety laboratory tests (including urine pregnancy test)

- Record concomitant medication
- Record AEs

9 ASSESSMENT OF EFFICACY

9.1 Psoriasis Area and Severity Index

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

The percent area of involvement (BSA%) is estimated across 4 body areas; head, upper limbs, trunk, and lower limbs and then transferred into a grade (Table 9–1).

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 9–1: 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 PASI25, PASI50, PASI75, PASI90, and PASI100 responses are based on at least 25%, 50%, 75%, 90%, and 100% improvement in the PASI score.

The PASI will be completed at the visits specified in Table 5–1.

9.2 BSA affected by psoriasis

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

Body surface area estimation uses the palm (subject's flat hand and thumb together, fingers included) as representing around 1% of the total BSA.

- 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%

Evaluation of BSA will be completed at the visits specified in Table 5–1.

9.3 Investigator's Global Assessment

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

The Investigator will assess the overall severity of psoriasis using the following 5-point scale presented in Table 9–2.

Table 9–2: Five-point Investigator's Global Assessment

Score	Short Descriptor	Detailed Descriptor
0	Clear	No signs of psoriasis; 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; predominately fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, clearly distinguishable to moderate thickening; moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

9.4 Hospital Anxiety and Depression Score

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

10 ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS/PHARMACOGENOMICS

10.1 Pharmacokinetic and pharmacodynamic variables

Blood samples for measurement of PK and PD variableswill be collected at the time points specified in the schedule of study assessments (Table 5–1).

Flow cytometry by fluorescence-activated cell sorting (FACS) analysis might include, but is not limited to: CD3, CD19, CD4, CD8, and CD69.

Candidate biomarkers might include, but are not limited to: IL-17A/IL17-F pathway signaling and psoriasis biology (eg, IL-17A, IL-17F, IL-23, IL-6, TNF, DC-STAMP, and circulating osteoclast precursors).

At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

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

10.2 Non-hereditary pharmacogenomic variables

10.2.1 RNA, proteins, and metabolites biomarkers

Where local regulations permit, blood samples will be drawn for exploratory RNA, proteins and metabolites biomarker analysis at the time points specified in the schedule of study assessments (Table 5–1).

Where local regulation permit, lesional and nonlesional skin biopsies for exploratory RNA, proteins, and metabolites biomarker analysis will be taken at the time points specified in the schedule of study assessments (Table 5–1).

Collection of these samples will enable evaluation of biomarkers relative to disease biology and progression, drug treatment and inflammatory and immune response processes.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. The nature and format of these tentative analyses will be determined at a later stage.

The samples will be stored at the secure long-term storage facility selected by UCB for up to 20 years.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLES

11.1 Assessment of immunogenicity

Blood samples for measurement of antibodies to bimekizumab will be collected at the visits specified in Table 5–1. The threshold for antibody positivity will be defined prior to analysis.

At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. 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.

11.2 Assessment of immunological variables

Blood samples for measurement of immunological variables will be collected 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.

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.

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definition of adverse event

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

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

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

12.1.2 Adverse events of special interest

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

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

12.1.3 Adverse events for special monitoring

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

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB, see Section 12.6.1), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the C-SSRS), depression-and anxiety (assessed using the

HADS, see Section 9.4), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.5.1), and malignancies and inflammatory bowel diseases.

12.1.4 Procedures for reporting and recording adverse events

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

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

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

12.1.5 Description of adverse events

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

When recording the severity of an AE in the CRF (ie, mild, moderate, or severe), the Investigator must refer to the CTCAE Version 4 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Details for completion of the Adverse Event CRF (including judgment of severity and relationship to IMP) are described in the CRF Completion Guidelines.

12.1.6 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

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

12.1.7 Rule for repetition of an adverse event

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

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

12.1.8 Pregnancy

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

as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The subject should return for an early Withdrawal Visit.
- The subject should immediately stop the intake of the IMP
- A SFU Visit should be scheduled 20 weeks after the subject has discontinued her IMP.

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

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

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

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

12.1.9 Suspected transmission of an infectious agent via a medicinal product

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

12.1.10 Overdose of investigational medicinal product

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

12.1.11 Safety signal detection

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

In addition, an independent Data Monitoring Committee (DMC) will periodically review and monitor the safety data from this study and advise UCB. Details are provided in the DMC Charter. A Cardiovascular (CV) Adjudication Committee will also periodically review and monitor the safety data from this study and advise UCB. Details are provided in the CV Adjudication Committee Charter.

12.2 Serious adverse events

12.2.1 Definition of serious adverse event

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

- Death
- Life-threatening

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

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

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

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

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

12.2.2 Procedures for reporting serious adverse events

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

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

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

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

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

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

12.2.3 Follow up of serious adverse events

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up.

Information on SAEs obtained after clinical database lock will be captured through the Drug Safety database without limitation of time.

12.3 Immediate reporting of adverse events

The following AEs must be reported immediately:

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

12.4 Anticipated serious adverse events

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

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

Table 12–1: Anticipated serious adverse events for the population of subjects with moderate to severe chronic plaque psoriasis

MedDRA® system order class	MedDRA preferred term
Skin and subcutaneous tissue disorders	Any psoriatic condition HLT
Musculoskeletal and connective tissue disorders	Psoriatic arthropathy

HLT=high level term; MedDRA=Medical Dictionary for Regulatory Activities
Note: Exception: Listed events will not be regarded as anticipated SAEs if they are life threatening or if they result in the death of the study subject.

12.5 Laboratory measurements

Clinical laboratory assessments consist of serum chemistry, hematology, and urinalysis. A centralized laboratory will be used to supply all laboratory test supplies and analyze all blood and urine samples for hematology, biochemistry and urinalysis measurements. Any unscheduled laboratory testing should also be collected using the central laboratory. Testing to rule out hepatitis B, hepatitis C, and HIV (see Exclusion Criterion #7, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12–2.

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

Table 12–2: Laboratory measurements

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

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

[a] Pregnancy testing will consist of serum testing at the Screening and SFU Visits. The pregnancy test will be urine at all other visits and will be performed locally. If the subject is entering the extension study, a urine pregnancy test will be performed at SFU.

[b] The FSH test should only be performed on postmenopausal females who have been postmenopausal for ≥1 year and last menstrual cycle occurred <2 years ago.

Assessments of immunological variables are described in Section 11. Assessments of PK and PD variables are described in Section 10.

12.5.1 Evaluation of PDILI

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

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

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

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

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

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

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

Table 12–3 summarizes the approach to investigate PDILI.

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

Laboratory value			Immediate		Follow up	
ALT or AST	**Total bilirubin**	**Symptoms[a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 12.5.1.4); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥3xULN	NA	Yes				
≥5xULN	NA	NA	Need for hepatology consult to be discussed.(required if ALT or AST ≥8xULN) Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation		

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 (and ≥2x baseline) and <5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 12.5.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥3xULN (and ≥2x baseline) after 2 weeks of monitoring without evidence of resolution	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 12.5.1.4).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • Discontinue IMP if levels remain ≥3xULN (and ≥2x baseline) without evidence of resolution[d] Continue to monitor until values normalize, stabilize, or return to within baseline values.[d]

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**

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

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

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

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

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

12.5.1.1 Consultation with Medical Monitor and local hepatologist

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

12.5.1.2 Immediate action: determination of IMP discontinuation

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

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

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

12.5.1.3 IMP restart/rechallenge

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

12.5.1.4 Testing: identification/exclusion of alternative etiology

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

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

The following measurements are to be assessed:

Table 12–4: 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/or quantitative)
Hematology	Eosinophil count
Urinalysis	Toxicology screen[a]
Chemistry	Amylase
	If total bilirubin ≥1.5xULN, obtain fractionated bilirubin to obtain % direct bilirubin
	Serum CPK and LDH to evaluate possible muscle injury causing transaminase elevation
Additional	Prothrombin time/INR[b]
	Serum pregnancy test
	PK sample

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

[a] For detecting substances such as amphetamines, benzodiazepines, opioids, marijuana, cocaine, phencyclidine, and tricyclic antidepressants. Additional tests may be performed based on the investigator's medical judgment and patient's history.

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

The following additional information is to be collected:

Table 12–5: PDILI information to be collected

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

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

12.5.1.5 Follow-up evaluation

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

12.6 Other safety measurements

12.6.1 Assessment and management of TB and TB risk factors

All subjects will be assessed for tuberculosis (TB) at Screening and at the timepoints specified in the Schedule of Assessments (Table 5–1) through physical examination for signs and symptoms of TB, chest x-ray (Section 12.6.1.2), laboratory testing (Section 12.6.1.1), and subject questionnaire (Section 12.6.1.3).

At Screening, all subjects will have an IGRA test (QuantiFERON TB GOLD is recommended), a chest x-ray (unless already performed within 3 months of Screening) and examination for signs

and symptoms of TB. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB.

Exclusion criteria at Screening

Subjects with known TB infection, at high risk of acquiring TB infection, or latent TB infection are excluded.

a. Known TB infection whether present or past is defined as:
   - Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)
   - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection, unless adequately treated and proven to be fully recovered upon consult with a TB specialist.
   - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history
b. High risk of acquiring TB infection is defined as:
   - Known exposure to another person with active TB infection within the 3 months prior to Screening
   - Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high
c. Latent TB infection is defined as:
   - The absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study medication. The retest must be done during the protocol-defined Screening window (up to 4 weeks).

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

Signs and Symptoms

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

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

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

LTBI is defined in the "Exclusion Criteria" above. If the result of the IGRA is indeterminate, the particular IGRA previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be randomized to study medication. If LTBI or active TB is identified, subject must undergo appropriate study specified withdrawal procedures. The retest must be done during the protocol-defined Screening window (up to 4 weeks). Laboratory diagnosis should be undertaken via mycobacteria culture media (or if available by preferred nucleic acid amplification test such as the Xpert MTB RIF test) and result must be negative for TB inducing pathogens.

Test Conversion

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

Latent TB

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

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

Once withdrawn from study treatment, subjects should return for the Week 36/EWD Visit, complete all Early Withdrawal Visit assessments, and complete a SFU Visit (20 weeks after the last dose of study medication).

Active TB or nontuberculosis mycobacterium infection

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

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

12.6.1.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD is recommended) will be performed at Screening and should be repeated at Week 36/Early

Withdrawal Visit for all subjects. The test results will be reported as positive, negative, or indeterminate. UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, subject must undergo appropriate study-specified withdrawal procedures. The retest during Screening must be done during the protocol-defined Screening window (up to 4 weeks).

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

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

12.6.1.3 Tuberculosis questionnaire

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

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

12.6.1.4 Tuberculosis management

LTB infection and active TB identified during study

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

Subjects diagnosed with active TB or LTB infection should be withdrawn from the study and receive appropriate TB or prophylaxis therapy.

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 Week 36/EWD Visit as soon as possible but no later than the next scheduled study visit and complete all Week 36/EWD Visit assessments.

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

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

12.6.2 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening and SFU Visits. The pregnancy test will be urine at all other visits. If the subject is entering the extension study, a urine pregnancy test will be performed at SFU.

The Screening Visit serum pregnancy testing 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 study drug and at all subsequent post-dosing visits. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

12.6.3 Vital signs

Vital signs will be collected at every visit and will include systolic and diastolic BP, pulse rate, and body temperature (oral or otic). Subjects should be sitting for 5 minutes before and during vital signs assessments.

Vital signs are to be measured prior to blood sampling, and prior to dosing, where applicable.

12.6.4 12-lead electrocardiograms

Standard 12-lead ECG will be recorded after 10 minutes of rest in the supine or semirecumbent position. The following ECG variables will be recorded: heart rate, PR interval, QRS duration, QT interval, Fridericia's QTc interval (QTcF), and the Investigator's interpretation of the ECG profile.

12.6.5 Physical examination

The physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; GI; musculoskeletal; hepatic; neurological (including limb reflexes); and mental status. Physical examination will be performed at the visits specified in Table 5–1. Findings considered clinically significant changes since the physical examination at the Screening Visit will be recorded as AEs.

12.6.6 Height and body weight

Height will be measured at Screening only.

Body weight will be measured at the visits specified in Table 5–1.

12.6.7 Assessment of suicidal ideation and behavior

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

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

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

12.7 Other study measurements

12.7.1 Demographic information

Demographic information will be collected in all subjects and include age, gender, race and ethnicity. Information on demographics will be collected according to local rules and regulations. Demographic information will be recorded in the eCRF.

12.7.2 Medical History

A complete medical history will be collected as part of the Screening assessment and include all clinically relevant past or coexisting medical conditions and surgeries. Findings will be recorded in the eCRF.

12.7.3 Psoriasis History

A detailed history of each subject's psoriasis history will be collected and include the date of onset and past treatments for psoriasis.

12.7.4 Data Monitoring Committee

The DMC membership includes experienced clinicians and a statistician, all of whom have 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 PS0016. The DMC may also be asked to provide a review of final study results, as deemed appropriate.

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.

The DMC procedures will ensure that data remain blind to the study team and Investigators at all times throughout the conduct of the study.

A cardiovascular (CV) Adjudication Committee will also periodically review the safety data from this study. Details will be described in a separate charter document.

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

The CRO will monitor the study using their own monitoring Standard Operating Procedures (SOPs), in line with ICH GCP guidelines and applicable regulatory requirements, and to ensure that study initiation, conduct, and closure are adequate.

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

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of 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. Source documentation should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of 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.

Sponsor or designee will review to ensure that computerized source documents produced by the site are compliant with FDA Part 11 requirements and document appropriately. Source documents that are computer generated and stored electronically that are not FDA Part 11 compliant, 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 PASI records, must be saved and stored as instructed by the Sponsor or designee.

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 eCRF and in all required reports.

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

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

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

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

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. This study is performed using EDC: the data are entered into the eCRFs once and are subsequently verified.

An electronic audit trail system will be maintained 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 study 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 is presented below and will be described in more detail in the statistical analysis plan (SAP).

14.1 Definition of analysis sets

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

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

The Safety Set (SS) will consist of all subjects who received at least 1 dose of the study medication.

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

The Per-Protocol Set (PPS) will consist of all randomized subjects who receive at least 1 dose of the study medication and have a valid measurement of the primary efficacy variable post-Baseline without important protocol deviations affecting the measurement.

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

The Pharmacodynamics Per-Protocol Set (PD-PPS) will consist of all randomized subjects who received at least 1 dose of the study medication and provided at least 1 PD measurement post-dose without important protocol deviations affecting the measurement.

14.2 General statistical considerations

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

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

14.3 Planned efficacy analyses

14.3.1 Analysis of the primary efficacy variable

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

The absolute and percentage (%) change from baseline in PASI will be listed and summarized by treatment group at each post-Baseline assessment.

Spaghetti plots of change from Baseline in PASI will be plotted for each subject over time by treatment group.

The analysis of the primary efficacy variable may be repeated on the PPS (if appropriate).

14.3.2 Other efficacy analyses

14.3.2.1 Analysis of the secondary efficacy variables

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

Subjects who achieve a PASI25, PASI50, PASI75, PASI90, and PASI100 response will be summarized and plotted by treatment group for each visit.

The 95% CIs for the PASI25/50/75/90/100 response rates will be included in the summaries and plots.

The IGA will be summarized using a frequency table by treatment group for each visit.

14.3.2.2 Analysis of the other efficacy variables

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

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

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

The change in IGA category from Baseline will be presented in shift tables at Week 8, Week 16, and Week 28.

14.3.2.3 PKPD analysis

A pooled PKPD analysis will be performed by combining data from this study and PS0010. The methodology for the PKPD analysis will be described in the data analysis plan (DAP). The results of the analysis will be reported in a PKPD report and added as an appendix to the CSR.

14.3.3 Planned safety and other analyses

14.3.3.1 Safety analyses

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

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

Treatment-emergent adverse events will be defined as events that have a start date on or following the first administration of study treatment up until the final administration of study treatment +140 days (covering the 20-week SFU Period). To allow for a fair comparison across all subjects, exposure at risk for defining treatment-emergence during the 28-week treatment period will be cut off at the Week 16 Visit (for subjects who complete through the Week 16 Visit) or at 20 weeks (140 days) after the last administration of study treatment (for subjects who discontinue prior to the Week 16 Visit).

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

14.4 Handling of protocol deviations

Important protocol deviations are deviations from the protocol which potentially could have a meaningful impact on study conduct, or on the primary efficacy, key safety, or PK/PD outcomes for an individual subject. The criteria for identifying important protocol deviations will be defined within the appropriate protocol-specific document. Important protocol deviations will be reviewed as part of the ongoing data cleaning process and all important deviations will be identified and documented prior to unblinding to confirm exclusion from analysis sets.

14.5 Handling of dropouts or missing data

For the primary efficacy analysis, missing data will be imputed using NRI. That is, subjects with missing data at Week 28 or who discontinue study treatment prior to Week 28 will be counted as non-responders for the analysis. Imputations (such as LOCF) will be considered for missing PASI scores for summary statistics and changes from baseline. More details will be included in the SAP. Sensitivity analyses may be performed and will be detailed in the SAP.

14.6 Planned interim analysis and data monitoring

No formal interim analysis will be performed; however, regular data cuts will be performed, and data may be evaluated. Data will also be made available, as requested, to the DMC overseeing the study.

14.7 Determination of sample size

No formal statistical sample size estimation has been performed due to the exploratory nature of this study. This clinical study is not powered for any conclusive statistical analysis of PK, safety or immunological variables. The sample size has been determined based on the number of subjects required in the current study to provide reliable PKPD model parameter estimates when the data was combined with PS0010. Reliable estimates of PKPD parameters are defined as number of subjects required to achieve a relative standard error of ≤30% for fixed effects parameters and ≤50% for all random effects parameters.

In order to determine the sample size required for the PKPD model, MCMC simulations were performed. Five hundred trials were simulated with the proposed design, and including 240 subjects from PS0010. The simulated data was re-estimated using the same model. The simulations re-estimations indicated that reliable estimates will be possible with a total N=45 (30 subjects in Treatment arm A vs. 15 subjects in Treatment arm B).

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

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

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

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the Informed Consent Form. 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, 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.

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18 APPENDICES

18.1 Protocol Amendment 1

Rationale for the amendment

The purpose of this amendment is the following:

- To revise the references to an "open-label extension study." Because of changes to the study design, the extension study is no longer planned to be an "open-label" study
- Clarify that subjects who have not achieved a PASI25 response prior to Week 20 will not be eligible to enter the extension study
- Clarify that subjects eligible for the extension study must have the assessments for SFU conducted prior to entering the extension study
- Clarify that Week 20 is the earliest a subject can enter the extension study.
- Extend the timing of the SFU Visit to 20 weeks after the last dose of study medication
- Remove references to legal representatives being able to provide consent on behalf of subjects. Subjects who lack the capacity to consent will not be included in the study
- Removed the blood sample for anti-bimekizumab antibodies at Baseline
- Clarify that the paper, not the electronic, version of the C-SSRS will be used
- Clarify that a urine pregnancy test will be performed at SFU for those subjects entering the extension study
- Clarify that lesional and nonlesional biopsies to be obtained at Baseline and Week 8, and lesional biopsies only at Week 16 and Week 28
- Clarify the exclusion criterion regarding laboratory values
- Added FSH test for postmenopausal females who have been postmenopausal for ≥1 year and last menstrual cycle occurred <2 years ago
- Clarify that subjects with any pustular PSO (ie, localized or generalized) are ineligible for study participation and that development of any form of pustular PSO (ie, localized or generalized) during the study will result in withdrawal from the study
- Clarify that subjects with a diagnosis of Crohn's disease or ulcerative colitis are allowed as long as they have no active symptomatic disease at Screening or Baseline
- Clarify the HADS thresholds for study eligibility in the Exclusion Criteria and for withdrawal of a subject in the Withdrawal Criteria
- Provide more detail in the Withdrawal Criterion regarding subjects that develop illnesses that would interfere with study participation
- Provide more detail in the Withdrawal Criteria regarding the withdrawal of subjects due to adverse events and clinical laboratory values
- Clarify the exclusion criterion prior to Baseline for etanercept

- Clarify the adverse events for special monitoring
- Provide additional detail and a reference for recording the severity of AEs
- Remove the requirement to test for alcohol in the PDILI urine toxicology screen
- Clarify the assessment of ECGs
- Added a DMC
- Clarify and correct text regarding the analyses sets, analyses of safety, and handling of dropouts and missing data

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- Section 2 Introduction was revised with updated information.
- The timing of the Safety Follow-Up Visit was changed from 17 weeks after the last dose of study medication to 20 weeks after the last dose of study medication, ie, from Week 33 to Week 36.
- The maximum study duration was changed from 37 weeks to 40 weeks.
- The List of Abbreviations was revised.
- The term "photochemotherapy" was changed to "chemophototherapy" throughout for consistency.
- The references to an "open-label extension study" were changed to "extension study."
- The eC-SSRS was changed to the C-SSRS.
- Minor editorial revisions were made.

Specific changes

Change #1

Section 1 Summary

Approximately 90 subjects will be screened in order to have 45 subjects randomized in the study. There will be approximately 30 subjects in treatment arm A and 15 subjects in treatment arm B, respectively. For each subject, the study will last a maximum of 37 weeks and will consist of 3 periods, a Screening Period (up to 4 weeks), a Treatment Period (28 weeks), and a Safety Follow-Up (SFU) Period (17 weeks after the last dose of study medication). After the 28-week Treatment Period, eligible subjects will be allowed to enroll in an open-label extension study.

Has been changed to

Approximately 90 subjects will be screened in order to have 45 subjects randomized in the study. There will be approximately 30 subjects in treatment arm A and 15 subjects in treatment arm B~~,~~

~~**respectively**~~. For each subject, the study will last a maximum of ~~**37**~~**40** weeks and will consist of 3 periods, a Screening Period (up to 4 weeks), a Treatment Period (28 weeks), and a Safety Follow-Up (SFU) Period (**20**~~**17**~~ weeks after the last dose of study medication). **Between Week 20 and the end of**~~**After**~~ the 28-week Treatment Period, eligible subjects will be allowed to enroll in an ~~**open-label**~~ extension study.

Change #2

Section 1 Summary

Study medication will be administered in the clinic at Baseline, Week 4, and Week 16. Additional nondosing study visits will occur at Week 2, Week 8, Week 12, Week 20, Week 24, and Week 28. At Week 16 through Week 28, subjects who relapse, defined as within 25% of their Baseline PASI value, will undergo the study assessments for that visit (ie, Week 16, Week 20, Week 24, or Week 28) before receiving their first open-label dose of bimekizumab at Week 20, Week 24, or Week 28. All subjects not enrolling in the open-label extension study will continue in PS0016 until the SFU Visit at Week 33. Subjects who are PASI25 responders will continue in the study until Week 33 and will then have the option to enter the open-label extension study.

Subjects who are PASI25 responders will continue in the study until Week 33 and will then have the option to enter the open-label extension study.

Subjects withdrawing early from the study will undergo the Early Withdrawal Visit assessments and will enter the SFU Period. Subjects who withdraw early from study treatment will be asked to return for study assessments 28 weeks after the first dose (ie, the Week 28 Visit) and for the SFU Visit.

Has been changed to

Study medication will be administered in the clinic at Baseline, Week 4, and Week 16. Additional nondosing study visits will occur at Week 2, Week 8, Week 12, Week 20, Week 24, and Week 28. **From**~~**At**~~ Week **20**~~**16**~~ through Week 28, subjects who **were previously PASI25 responders but subsequently** relapse~~**,**~~ **(**defined as **returning to less than PASI25 response** ~~**25% of their Baseline PASI value,)**~~-will undergo the study assessments for that visit (ie, ~~**Week 16,**~~ Week 20, Week 24, or Week 28) before receiving their first ~~**open-label**~~ dose of **study treatment in the extension study**~~**bimekizumab**~~ at Week 20, Week 24, or Week 28. **Subjects eligible for the extension study must have the assessments for SFU conducted prior to entering the extension study. Subjects who have not achieved a PASI25 response at any visit prior to Week 20 will not be eligible to enter the extension study.** All subjects not enrolling in the ~~**open-label**~~ extension study will continue in PS0016 until the SFU Visit at Week ~~**33**~~**36**. ~~**Subjects who are PASI25 responders will continue in the study until Week 33 and will then have the option to enter the open-label extension study.**~~

~~**Subjects who are PASI25 responders will continue in the study until Week 33 and will then have the option to enter the open-label extension study.**~~

~~**Subjects withdrawing early from the study will undergo the Early Withdrawal Visit assessments and will enter the SFU Period. Subjects who withdraw early from study**~~

~~**treatment will be asked to return for study assessments 28 weeks after the first dose (ie, the Week 28 Visit) and for the SFU Visit.**~~

Change #3

Section 2.1.2 Current treatments for psoriasis

Therapy for patients with psoriasis varies according to the severity of disease. Limited or mild disease is often treated with topical therapies such as corticosteroids and vitamin D analogs. Patients with more severe disease are often treated with photochemotherapy, methotrexate, the oral phosphodiesterase 4 (PDE4) inhibitor (apremilast), or biologic agents, such as tumor necrosis factor (TNF) antagonists, interleukin (IL) 12/23 inhibitors, and IL-17A inhibitors. The effectiveness of TNF inhibitors in the treatment of psoriasis has been demonstrated in many Phase 3 clinical studies and has led to the approval of multiple TNF inhibitors for use in patients with moderate to severe psoriasis. Interleukin inhibitors include secukinumab, an IL-17A inhibitor approved for treatment of moderate to severe psoriasis; and ixekizumab, an IL-17A inhibitor. Ustekinumab is an IL-12/23 antagonist approved for use in patients with moderate to severe psoriasis, and brodalumab, an IL-17 receptor antagonist, has completed pivotal Phase 3 studies in psoriasis. Standard therapies for psoriasis are listed below:

Has been changed to

Therapy for patients with psoriasis varies according to the severity of disease. Limited or mild disease is often treated with topical therapies such as corticosteroids and vitamin D analogs. Patients with more severe disease are often treated with ~~**photo**~~chemo**photo**therapy, methotrexate, the oral phosphodiesterase 4 (PDE4) inhibitor (apremilast), or biologic agents, such as tumor necrosis factor (TNF) antagonists, interleukin (IL) 12/23 inhibitors, and IL-17A inhibitors. The effectiveness of TNF inhibitors in the treatment of psoriasis has been demonstrated in many Phase 3 clinical studies and has led to the approval of multiple TNF inhibitors for use in patients with moderate to severe psoriasis. Interleukin inhibitors include secukinumab **and ixekizumab**, ~~**an**~~ IL-17A inhibitor**s** approved for treatment of moderate to severe psoriasis~~**; and ixekizumab, an IL-17A inhibitor**~~. Ustekinumab is an IL-12/23 antagonist approved for use in patients with moderate to severe psoriasis, and brodalumab, an IL-17 receptor antagonist, has completed pivotal Phase 3 studies in psoriasis. Standard therapies for psoriasis are listed below:

Change #4

Section 2.2.1 Clinical

Three clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque psoriasis, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with psoriatic arthritis. A fourth study in subjects with moderate to severe rheumatoid arthritis is ongoing (RA0123).

Has been changed to

Three clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque psoriasis, RA0124 in 30 healthy volunteers, **and** PA0007 in 53 subjects with psoriatic arthritis. **Two studies (RA0123 and UP0031) are ongoing in subjects with moderate**

to severe rheumatoid arthritis and in healthy subjects, respectively. ~~A fourth study in subjects with moderate to severe rheumatoid arthritis is ongoing (RA0123).~~

Change #5

Section 2.2.1 Clinical

A fourth study of bimekizumab is ongoing. RA0123 is a Phase 2a, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the safety, PK, PD, and efficacy of multiple doses of bimekizumab administered as add-on therapy to stable certolizumab pegol therapy in subjects with moderate to severe rheumatoid arthritis.

Has been changed to

Two additional studies of bimekizumab are ongoing ~~A fourth study of bimekizumab is ongoing~~. RA0123 is a Phase 2a, double-blind, randomized, placebo-controlled, multiple dose study to evaluate the safety, PK, PD, and efficacy of multiple doses of bimekizumab administered as add-on therapy to stable certolizumab pegol therapy in subjects with moderate to severe rheumatoid arthritis. **UP0031 is a Phase 1 open-label, parallel-group, single-dose study to evaluate the relative bioavailability and tolerability of bimekizumab 160mg sc in healthy subjects.**

Change #6

Section 4.1.3 Primary immunogenicity variable

The primary immunological variable is anti-bimekizumab antibody detection prior to and following study treatment.

Has been changed to

The primary immunological variable is anti-bimekizumab antibody detection **~~prior to and~~** following study treatment.

Change #7

Section 4.4 Immunological variable

The immunological variable is anti-bimekizumab antibody detection prior to and following study treatment.

Has been changed to

The immunological variable is anti-bimekizumab antibody detection **~~prior to and~~** following study treatment.

Change #8

Section 5.1.1 Study periods

This study will include 3 periods: a Screening Period (up to 4 weeks), a Treatment Period (28 weeks), and a SFU Period (17 weeks after the last dose of study medication). After the 28-week Treatment Period, eligible subjects will be allowed to enroll in an open-label extension study.

Has been changed to

This study will include 3 periods: a Screening Period (up to 4 weeks), a Treatment Period (28 weeks), and a SFU Period (**2017** weeks after the last dose of study medication). **~~After~~Between Week 20 and the end of** the 28-week Treatment Period, eligible subjects will be allowed to enroll in an **~~open-label~~** extension study

Change #9

Section 5.1.1, Study periods

There will be approximately 30 subjects in treatment arm A and 15 subjects in treatment arm B, respectively, and bimekizumab will be administered in the clinic at Baseline and Week 4, and at Baseline, Week 4, and Week 16, respectively. Additional nondosing study visits will occur at Week 2, Week 8, Week 12, Week 20, Week 24, and Week 28.

At Week 16 through Week 28, subjects who are not PASI25 responders may enroll in an OLE study after undergoing the assessments for that visit (ie, Week 16, Week 20, Week 24, or Week 28) before receiving their first open-label dose of bimekizumab at Week 20, Week 24, or Week 28. Subjects not electing to enroll in the OLE will continue in the study through Week 33. Subjects who are PASI25 responders will continue in the study until Week 33 and will then have the option to enter the open-label extension study.

Has been changed to

There will be approximately 30 subjects in treatment arm A and 15 subjects in treatment arm B**~~., respectively, and.~~ bB**imekizumab will be administered in the clinic at Baseline and Week 4, and at Baseline, Week 4, and Week 16 **for those in treatment arm A and treatment arm B**, respectively. Additional nondosing study visits will occur at Week 2, Week 8, Week 12, Week 20, Week 24, and Week 28.

From~~At~~ Week **2016** through Week 28, subjects who **were previously~~are not~~** PASI25 responders **but subsequently relapse~~,~~ (defined as returning to a less than PASI25 response) will~~may enroll in an OLE extension study after~~** undergo**~~ing~~** the **study** assessments for that visit (ie, **~~Week 16,~~** Week 20, Week 24, or Week 28) **before receiving their first ~~open-label~~ dose of study treatment~~bimekizumab~~ in the extension study at Week 20, Week 24, or Week 28. Subjects eligible for the extension study must have the assessments for SFU conducted prior to entering the extension study. Subjects who have not achieved a PASI25 response at any visit prior to Week 20 will not be eligible to enter the extension study. All** subjects not **~~electing to~~** enroll**ing in the extension study~~OLE~~** will continue in **~~the study~~ PS0016 until the**

SFU Visit ~~the study through~~ at Week 36~~33~~. ~~Subjects who are PASI25 responders will continue in the study until Week 33 and will then have the option to enter the open-label extension study.~~

Change #10

Table 5-1: Schedule of assessments

Visit[a]/ Week / Protocol activity	Screening[b]	Baseline	Treatment Period (Time after the first dose)								Wk 36 EWD/ SFU[c]
			Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	
Hematology/biochemistry/ urinalysis	X	X	X	X	X	X	X	X	X	X	X
Blood sample for bimekizumab plasma concentrations[m]		X	X	X	X	X	X	X	X	X	X
Blood sample for anti-bimekizumab antibodies [m]		X		X	X	X	X	X	X	X	X
Blood sample for cytokines, complement, candidate biomarker analysis, and flow cytometry [m]		X			X	X	X				X
Skin biopsy[n]		X (2)			X (2)		X (2)			X (2)	

Has been changed to

Table 5-1: Schedule of assessments

Visit[a]/ Week / Protocol activity	Screening[b]	Baseline	Treatment Period (Time after the first dose)								Wk 36 EWD/ SFU[c]
			Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	
Hematology/biochemistry/ urinalysis	X	X[g]	X	X	X	X	X	X	X	X	X
Blood sample for bimekizumab plasma concentrations[m]		X	X	X	X	X	X	X	X	X	X
Blood sample for anti-		~~X~~		X	X	X	X	X	X	X	X

Table 5-1: Schedule of assessments

Visit[a]/ Week / Protocol activity	Screening[b]	Baseline	Treatment Period (Time after the first dose)								Wk 36 EWD/ SFU[c]
			Wk 2	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	
bimekizumab antibodies [m]											
Blood sample for cytokines, complement, candidate biomarker analysis, and flow cytometry [m]		X			X	X	X				X
Skin biopsy[n]		X (2)			X (2)		X (~~21~~)			X (~~21~~)	

Change #11

Table 5-1 Schedule of assessments

The following footnote was added and subsequent footnotes letters were revised accordingly.

[g] The FSH test should only be performed on postmenopausal females who have been postmenopausal for ≥1 year and last menstrual cycle occurred <2 years ago.

Change #12

Table 5-1 Schedule of assessments

[h] Pregnancy testing will be serum testing at Screening and SFU. The pregnancy test will be urine at all other visits.

Has been changed to

[i] Pregnancy testing will be serum testing at Screening and SFU. The pregnancy test will be urine at all other visits. **If the subject is entering the extension study, a urine pregnancy test will be performed at SFU.**

Change #13

Table 5-1 Schedule of assessments

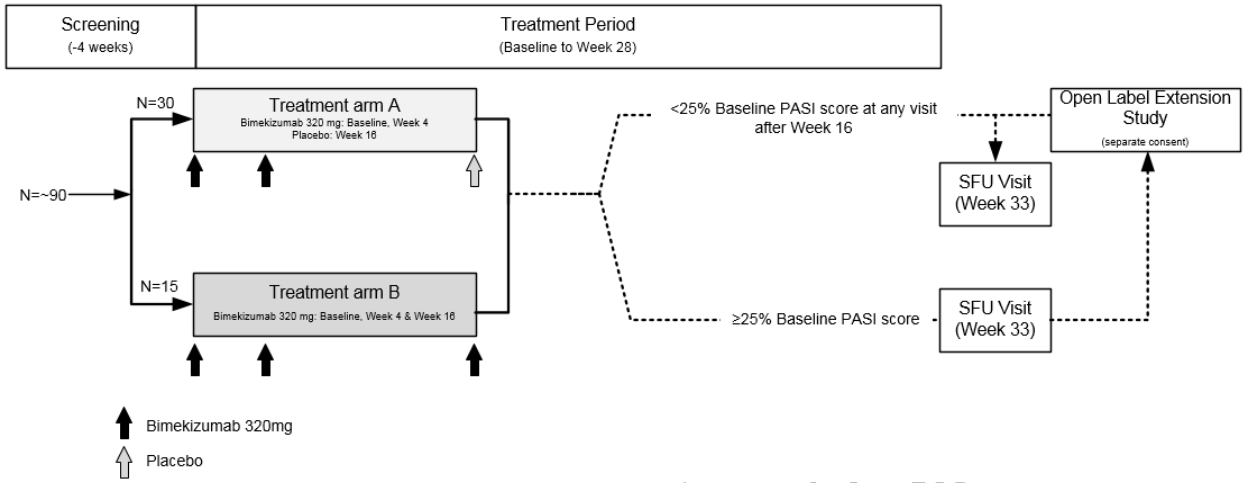
[n] Lesional and nonlesional biopsies to be obtained.

Has been changed to

[o] Lesional and nonlesional biopsies to be obtained **at Baseline and Week 8. Lesional biopsies to be obtained at Week 16 and Week 28.**

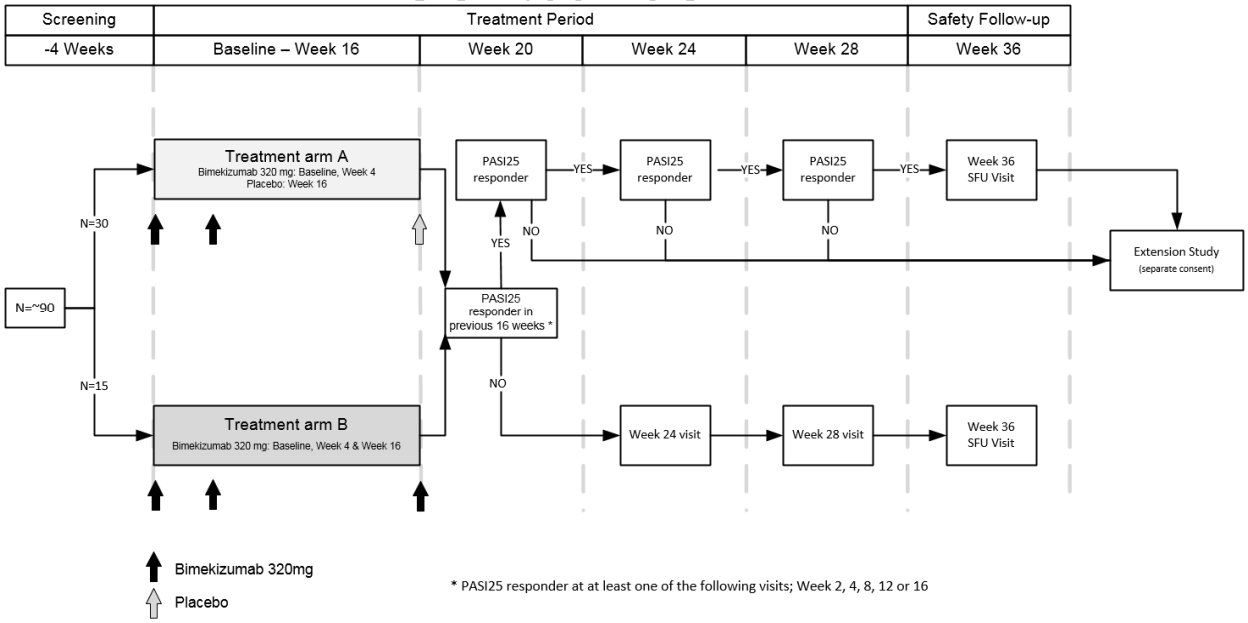
Change #14

Figure 5-1 Schematic diagram of PS0016



OLE=open-label extension; PASI= Psoriasis Area and Severity Index; SFU=Safety Follow-Up
Subjects who are not PASI25 responders may enroll into the OLE after their Week 16 assessments, but will not receive a dose in the OLE until at least Week 20. Subjects who do not enroll into the OLE will continue in PS0016 through Week 33.
Subjects who are PASI25 responders will continue in PS0016 until Week 33 and then have the opportunity to enroll into the OLE.

Has been changed to



~~**OLE=open-label extension;**~~ PASI= Psoriasis Area and Severity Index; SFU=Safety Follow-Up
~~**Subjects who are not PASI25 responders may enroll into the OLE after their Week 16 assessments, but will not receive a dose in the OLE until at least Week 20. Subjects who do not enroll into the OLE will continue in PS0016 through Week 33.**~~
~~**Subjects who are PASI25 responders will continue in PS0016 until Week 33 and then have the opportunity to enroll into the OLE.**~~ **From Week 20 through Week 28, subjects who were previously PASI25 responders but**

subsequently relapse (defined as returning to less than PASI25 response) will undergo the study assessments for that visit (ie, Week 20, Week 24, or Week 28) before receiving their first dose of study treatment in the extension study at Week 20, Week 24, or Week 28. Subjects eligible for the extension study must have the assessments for SFU conducted prior to entering the extension study. Subjects who have not achieved a PASI25 response at any visit prior to Week 20 will not be eligible to enter the extension study. All subjects not enrolling in the extension study will continue in PS0016 until the SFU Visit at Week 36.

Change #15

Section 6.1 Inclusion criteria

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.

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**~~.

Change #16

Section 6.1 Inclusion criteria

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

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 #17

Section 6.2 Exclusion criteria

5. Subjects with erythrodermic, guttate, generalized pustular form of psoriasis, or drug-induced psoriasis.

Has been changed to

5**a**. Subjects with erythrodermic, guttate, ~~**generalized**~~ pustular form of psoriasis, or drug-induced psoriasis.

Change #18

Section 6.2 Exclusion criteria

20. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), *alkaline phosphatase (ALP), or

>ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

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

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

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

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

Has been changed to

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

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

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

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

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

Change #19

Section 6.2 Exclusion criteria

25. Subjects with a diagnosis of inflammatory conditions other than psoriasis or psoriatic arthritis, including but not limited to rheumatoid arthritis, sarcoidosis, or systemic lupus erythematosus.

Has been changed to

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

Change #20

Section 6.2 Exclusion criteria

29. Presence of significant uncontrolled neuropsychiatric disorder, active suicidal ideation, or positive suicide behavior using the "Baseline" version of the eC-SSRS and the HADS with either of the following criteria:

- Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either question 4 or question 5 of the "Screening/Baseline" version of the eC-SSRS at Screening.
- HADS Depression score ≥10 and Anxiety score ≥15

Has been changed to

29**a**.Presence of significant uncontrolled neuropsychiatric disorder, active suicidal ideation, or positive suicide behavior using the "Baseline" version of the **e**C-SSRS and the HADS with either of the following criteria:

- Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either **Qq**uestion 4 or **Qq**uestion 5 of the "Screening/Baseline" version of the **e**C-SSRS at Screening.
- HADS Depression score **>**10 **or~~and~~** Anxiety score ≥15

Change #21

Section 6.3 Withdrawal criteria

2. Subject develops an illness that would interfere with his/her continued participation.

Has been changed to

2**a**. Subject develops an illness that **in the opinion of the Investigator** would interfere with his/her continued participation **if the risk of continuing participation outweighs the potential benefit**.

Change #22

Section 6.3 Withdrawal criteria

3. Subject develops erythrodermic, guttate, or generalized pustular form of psoriasis.

Has been changed to

3**a**. Subject develops erythrodermic, guttate, or ~~**generalized**~~ pustular form of psoriasis.

Change #23

Section 6.3 Withdrawal criteria

The following withdrawal criterion has been deleted

7. Subject develops total bilirubin >2xULN (except Gilbert's); neutropenia <$1.0x10^9$/L; lymphopenia <$0.5x10^9$/L or other laboratory abnormalities consistent with rheumatology Common Terminology Criteria (CTC) Grade 3 or higher if clinically relevant.

Change #24

Section 6.3 Withdrawal criteria

8. Subject has active suicidal ideation as indicated by a positive response ("Yes") to questions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated electronic Columbia Suicide Severity Rating Scale (eC-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
9. Subjects with a HADS-D score ≥15 must be withdrawn. Any subject who has a HADS-D score of ≥10 should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.

Has been changed to

8**a**. Subject has active suicidal ideation as indicated by a positive response ("Yes") to **Qq**uestions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated ~~**electronic**~~ Columbia Suicide Severity Rating Scale (~~e~~C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.

9**a**. Subjects with a HADS-D score ≥15 must be withdrawn. Any subject who ~~**has**~~**develops** a HADS-D score of >10 **during the study** should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.

Change #25

Section 6.3 Withdrawal criteria

The following withdrawal criteria have been added

10. Subject experiences an AE as described below:

- Any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above AE that is assessed as related to study drug in the opinion of the Investigator
  - If the event is deemed to be not related to study drug by the Investigator, the subject may remain in the study after approval by the medical monitor.
- Any CTCAE Grade 2 event that is evaluated as related to study drug in the opinion of the Investigator, is persistent, and falls into any of the following System Organ Classes (SOCs): "Blood and lymphatic disorders," "Cardiac disorders," or "Vascular disorders."
  - Persistent is defined as lasting 28 days or more, which spans at least 2 scheduled injections.

11. Subject has a clinical laboratory value meeting the following criteria:

- CTCAE Grade 3 and above: subjects must be withdrawn regardless of relationship to study drug or duration of event.
- CTCAE Grade 2
  - Subjects may remain in the study if the event is transient. If a subject has a Grade 2 laboratory abnormality, a retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat value is below Grade 2, the subject may receive the next scheduled study treatment. If the value on the repeat is still Grade 2 or above, a second repeat test must be performed and results made available prior to the next scheduled study treatment. If this second repeat value is still Grade 2 or above, the subject must be withdrawn.

Change #26

Section 7.2 Treatments to be administered

In treatment arm A, bimekizumab will be administered at Baseline and Week 4, and placebo administered at Week 16. For treatment arm B, bimekizumab medication will be administered at Baseline, Week 4, and Week 16. The minimum of time between doses should be no less than 24 days.

Has been changed to

In treatment arm A, bimekizumab will be administered at Baseline and Week 4, and placebo administered at Week 16. For treatment arm B, bimekizumab medication will be administered at Baseline, Week 4, and Week 16. **The first dose of study treatment in the extension study will be at Week 20, Week 24, or Week 28.** The minimum of time between doses should be no less than 24 days.

Change #27

Section 7.8.2 Prohibited concomitant treatments (medications and therapies)

The following paragraph was removed

~~**Subjects who use prohibited medications, with the exception of topicals, will be withdrawn from study treatment but followed until the SFU.**~~

Change #28

Table 7-1: Prohibited psoriasis medications

Drug	**Exclusion criteria prior to Baseline Visit**
Systemic retinoids	12 weeks
Systemic treatment (non-biological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) systemic fumarate systemic corticosteroids phototherapy or photochemotherapy	8 weeks for methotrexate, azathioprine, and cyclosporine 4 weeks for everything other than methotrexate, azathioprine, and cyclosporine
Anti-TNFs: infliximab (including biosimilar), golimumab etanercept (including biosimilar) certolizumab pegol adalimumab (including biosimilar)	12 weeks for everything

Has been changed to

Drug	Exclusion criteria prior to Baseline Visit
Systemic retinoids	12 weeks
Systemic treatment (non-biological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) systemic fumarate systemic corticosteroids phototherapy or **~~photo~~**chemo**photo**therapy	8 weeks for methotrexate, azathioprine, and cyclosporine 4 weeks for everything other than methotrexate, azathioprine, and cyclosporine
Anti-TNFs: infliximab (including biosimilar), golimumab etanercept (including biosimilar) certolizumab pegol adalimumab (including biosimilar)	**4 weeks for etanercept** 12 weeks for everything **other than etanercept**

Change #29

Section 7.9 Blinding

Bimekizumab and placebo injections will be prepared and administered at the investigational sites by unblinded, dedicated study personnel. The unblinded personnel will not be involved in the study in any way other than assuring the medication is taken from the correct kit and administering the drug to the subjects.

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

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

Has been changed to

Bimekizumab and placebo injections will be prepared **~~and administered~~** at the investigational sites by unblinded, dedicated study personnel. The unblinded personnel will not be involved in the study in any way other than assuring the medication is taken from the correct kit **~~and administering the drug to the subjects~~**.

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

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

Change #30

Section 8.2 Baseline Visit

- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers

Has been changed to

- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - ~~**Anti-bimekizumab antibodies**~~
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers

Change #31

Section 8.6 Week 12 (+/-3 days)

The following procedures or assessments will be performed/recorded prior to administration of study drug:

Has been changed to

The following procedures or assessments will be performed/recorded ~~**prior to administration of study drug**~~:

Change #32

Section 8.7 Week 16 (+/-3 days)

The following procedures or assessments will be performed/recorded:

- Obtain skin biopsy (lesional and nonlesional)

Has been changed to

The following procedures or assessments will be performed/recorded **prior to administration of study drug**:

- Obtain skin biopsy (lesional ~~**and nonlesional**~~)

Change #33

Section 8.10 Week 28 (+/-3 days)

- Obtain skin biopsy (lesional and nonlesional)

Has been changed to

- Obtain skin biopsy (lesional ~~**and nonlesional**~~)

Change #34

Section 8.11 Week 33/Safety Follow-Up Visit (17 weeks after last dose)

- Obtain blood sample(s) for:
  - TB test (interferon gamma release assay; IGRA; it is recommended that the QuantiFERON TB GOLD test be performed)
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers
  - Serum pregnancy test for women of childbearing potential

Has been changed to

Section 8.11 Week ~~33~~36/Safety Follow-Up Visit (~~17~~20 weeks after last dose)

- Obtain blood sample(s) for:
  - TB test (interferon gamma release assay; IGRA; it is recommended that the QuantiFERON TB GOLD test be performed)
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers

– Serum pregnancy test for women of childbearing potential**. If the subject is entering the extension study, a urine pregnancy test will be performed.**

Change #35

Section 12.1.3 Adverse events for special monitoring

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB, see Section 12.6.1), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the eC-SSRS), depression-and anxiety (assessed using the HADS, see Section 9.4), major cardiac events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.5.1), malignancies, and inflammatory bowel diseases.

Has been changed to

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB, see Section 12.6.1), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the ~~e~~C-SSRS), depression-and anxiety (assessed using the HADS, see Section 9.4), major ~~**cardiac**~~ **cardiovascular** events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.5.1), malignancies, and inflammatory bowel diseases.

Change #36

Section 12.1.5 Description of adverse events

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

Has been changed to

When recording the severity of an AE in the CRF (ie, mild, moderate, or severe), the Investigator must refer to the CTCAE Version 4 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Details for completion of the Adverse Event CRF (including judgment of **severity and** relationship to IMP) are described in the CRF Completion Guidelines.

Change #37

Section 12.1.11 Safety signal detection

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

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

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

Has been changed to

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. Details are provided in the DMC Charter. A Cardiovascular (CV) Adjudication Committee will also periodically review and monitor the safety data from this study and advise UCB. Details are provided in the CV Adjudication Committee Charter.

Change #38

Table 12-2 Laboratory measurements

Hematology	Chemistry	Urinalysis
	Total cholesterol	
	Serum pregnancy testing[a]	

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

[a] Pregnancy testing will consist of serum testing at the Screening and SFU Visits. The pregnancy test will be urine at all other visits and will be performed locally.

Has been changed to

Hematology	Chemistry	Urinalysis
	Total cholesterol	
	Serum pregnancy testing[a]	
	Serum FSH[b] (Screening)	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CRP=C-reactive protein; GGT=gamma glutamyltransferase; **FSH=follicle stimulating hormone;**

LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

[a] Pregnancy testing will consist of serum testing at the Screening and SFU Visits. The pregnancy test will be urine at all other visits and will be performed locally. **If the subject is entering the extension study, a urine pregnancy test will be performed at SFU.**

[b] **The FSH test should only be performed on postmenopausal females who have been postmenopausal for ≥1 year and last menstrual cycle occurred <2 years ago.**

Change #39

Table 12-4 PDILI laboratory measurements

[a] For detecting substances such as alcohol, amphetamines, benzodiazepines, opioids, marijuana, cocaine, phencyclidine, and tricyclic antidepressants. Additional tests may be performed based on the Investigator's medical judgment and patient's history.

Has been changed to

[a] For detecting substances such as ~~**alcohol,**~~ amphetamines, benzodiazepines, opioids, marijuana, cocaine, phencyclidine, and tricyclic antidepressants. Additional tests may be performed based on the Investigator's medical judgment and patient's history.

Change #40

Section 12.6.1.1 Assessment and management of TB and TB risk factors

Once withdrawn from study treatment, subjects should return for the Week 12/WD Visit, complete all Early Withdrawal Visit assessments, and complete a SFU Visit (17 weeks after the last dose of study medication).

Has been changed to

Once withdrawn from study treatment, subjects should return for the Week ~~**12**~~**36**/**E**WD Visit, complete all Early Withdrawal Visit assessments, and complete a SFU Visit (~~**17**~~**20** weeks after the last dose of study medication).

Change #41

Section 12.6.1.4 Tuberculosis management

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 Week 12/WD Visit as soon as possible but no later than the next scheduled study visit and complete all Week 12/WD Visit assessments.

Has been changed to

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 Week ~~**12**~~**36**/**E**WD Visit as soon as

possible but no later than the next scheduled study visit and complete all Week ~~12~~36/EWD Visit assessments.

Change #42

Section 12.6.2 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening and SFU Visits. The pregnancy test will be urine at all other visits.

Has been changed to

Pregnancy testing will consist of serum testing at the Screening and SFU Visits. The pregnancy test will be urine at all other visits. **If the subject is entering the extension study, a urine pregnancy test will be performed at SFU.**

Change #43

Section 12.6.4 12-lead electrocardiograms

Twelve-lead standard ECGs will be recorded at the visits specified in Table 5-1, and read by a central ECG laboratory.

Full details of ECG recording will be provided in the ECG Manual.

Has been changed to

~~**Twelve-lead standard ECGs will be recorded at the visits specified in Table 5-1, and read by a central ECG laboratory.**~~

~~**Full details of ECG recording will be provided in the ECG Manual.**~~

Standard 12-lead ECG will be recorded after 10 minutes of rest in the supine or semirecumbent position. The following ECG variables will be recorded: heart rate, PR interval, QRS duration, QT interval, Fridericia's QTc interval (QTcF), and the Investigator's interpretation of the ECG profile.

Change #44

The following section was added

Section 12.7.4 Data Monitoring Committee

The DMC membership includes experienced clinicians and a statistician, all of whom have expertise in clinical trials. Board members may not participate in the study as principal or co-Investigators, or as study subject care physicians. The duration of membership for the DMC will be inclusive of planned analyses for PS0010. The DMC may also be asked to provide a review of final study results, as deemed appropriate.

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.

The DMC procedures will ensure that data remain blind to the study team and Investigators at all times throughout the conduct of the study.

A cardiovascular (CV) Adjudication Committee will also periodically review the safety data from this study. Details will be described in a separate charter document.

Change #45

Section 13.2.1 Definition of source data

Electronic data records, such as Holter monitor records or electroencephalogram records, must be saved and stored as instructed by the Sponsor or designee.

Patient Reported Outcome (PRO) measures (eg, PtGADA) will be completed by each subject utilizing electronic data capture.

Has been changed to

Electronic data records, such as **PASI~~Holter monitor~~** records**~~or electroencephalogram records~~**, must be saved and stored as instructed by the Sponsor or designee.

~~Patient Reported Outcome (PRO) measures (eg, PtGADA) will be completed by each subject utilizing electronic data capture.~~

Change #46

Section 13.3.1 Case Report Form completion

The second paragraph was removed

~~This study will use an electronic device to capture patient reported outcomes (see Section 13.2.1).~~

Change #47

Section 14.1 Definition of analysis sets

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of the study medication and have a valid measurement of the primary efficacy variable at Baseline.

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

The Pharmacodynamics Per-Protocol Set (PD-PPS) will consist of all randomized subjects who took at least 1 dose of the study medication and provided at least 1 PD measurement post-dose without important protocol deviations affecting the measurement.

Has been changed to

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least 1 dose of the study medication and have a valid measurement of the primary efficacy variable ~~at~~**post-**Baseline.

The Per-Protocol Set (PPS) will consist of all randomized subjects who receive at least 1 dose of the study medication and have a valid measurement of the primary efficacy variable post-Baseline without important protocol deviations affecting the measurement.

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized subjects who ~~took~~**received** at least 1 dose of the study medication and provided at least 1 quantifiable plasma concentration post-dose.

The Pharmacodynamics Per-Protocol Set (PD-PPS) will consist of all randomized subjects who ~~took~~**received** at least 1 dose of the study medication and provided at least 1 PD measurement post-dose without important protocol deviations affecting the measurement.

Change #48

Section 14.1 Definition of analysis sets

The analysis of the primary efficacy variable may be repeated on the PD-PPS (if appropriate).

Has been changed to

The analysis of the primary efficacy variable may be repeated on the ~~**PD-**~~PPS (if appropriate).

Change #49

Section 14.3.3.1 Safety analyses

Treatment-emergent adverse events will be defined as events that have a start date on or following the first administration of study treatment through the final administration of study treatment +119 days (covering the 17-week SFU Period). To allow for a fair comparison across all subjects, exposure at risk for defining treatment-emergence during the 28-week treatment period will be cut off at the Week 16 Visit (for subjects who complete through the Week 16 Visit) or at 17 weeks (119 days) after the last administration of study treatment (for subjects who discontinue prior to the Week 16 Visit).

Has been changed to

Treatment-emergent adverse events will be defined as events that have a start date on or following the first administration of study treatment **up until**~~**through**~~ the final administration of study treatment +~~**119**~~**140** days (covering the ~~**17**~~**20**-week SFU Period). To allow for a fair comparison across all subjects, exposure at risk for defining treatment-emergence **during the 28-week treatment period** will be cut off at the Week 16 Visit (for subjects who complete through the Week 16 Visit) or at ~~**17**~~**20** weeks (~~**119**~~**140** days) after the last administration of study treatment (for subjects who discontinue prior to the Week 16 Visit).

Change #50

Section 14.5 Handling of dropouts or missing data

For the primary efficacy analysis, missing data will be imputed using NRI. That is, subjects with missing data at Week 28 or who discontinue study treatment prior to Week 28 will be counted as non-responders for the analysis. Sensitivity analyses may be performed and will be detailed in the SAP.

Has been changed to

For the primary efficacy analysis, missing data will be imputed using NRI. That is, subjects with missing data at Week 28 or who discontinue study treatment prior to Week 28 will be counted as non-responders for the analysis**. Imputations (such as LOCF) will be considered for missing PASI scores for summary statistics and changes from baseline. More details will be included in the SAP.** Sensitivity analyses may be performed and will be detailed in the SAP.

Change #51

Section 14.6 Planned interim analysis and data monitoring

No formal interim analysis will be performed; however, regular data cuts will be performed, and data may be evaluated

Has been changed to

No formal interim analysis will be performed; however, regular data cuts will be performed, and data may be evaluated. **Data will also be made available, as requested, to the DMC overseeing the study.**

Change #52

Section 15.1 Informed consent

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

Has been changed to

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

Change #53

Section 15.2 Subject identification cards

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

Has been changed to

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

Change #54

Section 17 References

The following reference was added

Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. National Institutes of Health, National Cancer Institute, Division of Cancer Treatment and Diagnosis. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Updated 03 Mar 2016.

18.2 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment is to revise the following:

- Serious adverse event reporting contact information included the wrong fax number for Canada and this was corrected
- The PtGADA assessment was removed from the protocol, as this assessment is not relevant for the study population of patients with psoriasis
- The PASI25 assessment was added to the study.

Specific changes

Change #1 Serious adverse event reporting

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** PPD **USA:** PPD or PPD **Canada:** PPD
Email	**Global:** PPD

Has been changed to

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** PPD **USA and Canada:** PPD or PPD ~~**Canada:**~~ PPD
Email	**Global:** PPD

Change #2 List of Abbreviations

The table row with PtGADA and its definition was deleted

Change #3 Section 4.3.1 Other efficacy variables

Original text:

- Absolute and % change from Baseline in PASI with time (Week 2 to Week 36)
- PASI50, PASI75, PASI90, and PASI100 response at Weeks 2, 4, 8, 12, 20, 24, 28, and 36
- IGA response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Weeks 2, 4, 8, 12, 20, 24, 28, and 36
- Change from Baseline in IGA score
- Absolute and percent change from Baseline in the BSA affected by psoriasis
- Change from Baseline in the Patient's Global Assessment of Disease Activity (PtGADA) for the arthritis visual analog scale (VAS)

- Change from Baseline in Hospital Anxiety and Depression Scale (HADS) HADS-A and HADS-D scores
- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores)

Has been changed to:

- Absolute and % change from Baseline in PASI with time (Week 2 to Week 36)
- ~~PASI50,~~ PASI75, PASI90, and PASI100 response at Weeks 2, 4, 8, 12, 20, 24, 28, and 36
- **PASI25 and PASI50 response (Week 2 to Week 36)**
- IGA response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Weeks 2, 4, 8, 12, 20, 24, 28, and 36
- Change from Baseline in IGA score
- ~~Absolute and percent c~~**C**hange from Baseline in the BSA affected by psoriasis
- ~~Change from Baseline in the Patient's Global Assessment of Disease Activity (PtGADA) for the arthritis visual analog scale (VAS)~~
- Change from Baseline in Hospital Anxiety and Depression Scale (HADS) HADS-A and HADS-D scores
- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores)

Change #4 Table 5-1 Schedule of assessments

The table row for the PtGADA assessment was deleted.

The footnote with PtGADA abbreviation definition was deleted.

Change #5 Section 7.6 Drug Accountability

Original text:

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

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

Has been changed to:

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

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

Change #6 Section 8.2 Baseline Visit

PtGADA assessment was deleted.

Change #7 Section 8.11 Week 36/Safety Follow-Up Visit (20 weeks after the last dose)

PtGADA assessment was deleted.

Change #8 Section 9 Assessment of Efficacy

The subsection discussing the PtGADA (Section 9.5 Patient's Global Assessment of Disease Activity for the arthritis VAS) was deleted.

In addition the following change was made to Section 9.1 Psoriasis Area and Severity Index:

Original text:

The PASI50, PASI75, PASI90, and PASI100 responses are based on at least 50%, 75%, 90%, and 100% improvement in the PASI score.

Has been changed to:

The **PASI25,** PASI50, PASI75, PASI90, and PASI100 responses are based on at least **25%,** 50%, 75%, 90%, and 100% improvement in the PASI score.

Change #9 Section 14.3.2.1 Analysis of the secondary efficacy variables

Original text:

Subjects who achieve a PASI50, PASI75, PASI90, and PASI100 response will be summarized and plotted by treatment group for each visit.

The 95% CIs for the PASI50/75/90/100 response rates will be included in the summaries and plots.

Has been changed to:

Subjects who achieve a **PASI25,** PASI50, PASI75, PASI90, and PASI100 response will be summarized and plotted by treatment group for each visit.

The 95% CIs for the PASI**25**/50/75/90/100 response rates will be included in the summaries and plots.

18.3 Protocol Amendment 3

Rationale for the amendment

The purpose of this amendment is the following:

- Add an exclusion criterion to exclude subjects that had been admitted to a mental hospital or other institution by an order of the court
- Clarify wording in the RNA, proteins, and metabolite variables section
- Add a Baseline blood sample for anti-bimekizumab antibodies
- Specify the study stopping rules
- Delete Section 4.3.4 header: Non-hereditary pharmacogenomics variables. This section had no content and the header was included in error.

Specific changes

Change #1

Section 4.1.3 Primary immunogenicity variable

The primary immunological variable is anti-bimekizumab antibody detection following study treatment.

Has been changed to

The primary immunological variable is anti-bimekizumab antibody detection **prior to and** following study treatment.

Change #2

The section header **Section 4.3.4 Non-hereditary pharmacogenomic variables** was deleted.

Change #3

Section 4.3.4 RNA, proteins, and metabolite variables

Where local regulations permit, blood and tissue biopsy samples will be collected at specific time points and stored for up to 20 years to allow for potential exploratory analyses of RNA,

proteins, and metabolites biomarkers relevant to psoriasis and the inflammatory and immune response processes.

Has been changed to

Blood and tissue biopsy samples will be collected at specific time points and stored for up to 20 years to allow for potential exploratory analyses of RNA, proteins, and metabolites biomarkers relevant to psoriasis and the inflammatory and immune response processes.

Change #4

Table 5-1 Schedule of assessments

An "X" has been added to the Baseline column for the "Blood sample for anti-bimekizumab antibodies" assessment.

Change #5

Table 5-1 Schedule of assessments, footnote n

All blood samples taken prior to dosing. PK sampling for bimekizumab: sample at each visit; to be collected predose at the dosing visits (ie, BaselineWeeks 4 and 16). Samples for detection of anti-bimekizumab antibodies will be collected at Week 4, and each visit thereafter.

Has been changed to

All blood samples taken prior to dosing.

Change #6

Section 6.2 Exclusion criteria

The following exclusion criterion was added

32. Subjects who have been admitted to a mental hospital or other institution by an order of the court

Change #7

Section 6.4 Study stopping rules has been added

6.4 Study stopping rules

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

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

- A pattern of AEs occurs that contraindicates the further dosing of enrolled/additional subjects, including (but not limited to):
  - More than 1 subject meets any individual Withdrawal Criteria 4, 8a, 9a, 10 or 11 (as provided in Section 6.3), regardless of whether they met the same or different criteria.
  - Once a second subject meets any of those criteria, referral to the DMC may not be delayed while awaiting the outcome of either case.

  If the above criteria are reached, the DMC will meet as soon as possible to determine whether discontinuation or suspension of the study should occur, and to determine what investigations, analyses, procedural amendments, or other actions should occur, before making any recommendation regarding the possibility of recommencing the study. Further details on the role of the DMC are provided in Section 12.1.11 and Section 12.7.4.
- If the Sponsor or its designees judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations, and GCP.

Change #8

Section 8.2 Baseline Visit

The following procedures or assessments will be performed/recorded prior to administration of study drug:

- Confirm inclusion/exclusion criteria
- Ensure no significant changes in medical procedure history and concomitant disease, including psoriasis disease history
- Vital signs (blood pressure, pulse rate, and temperature)
- Body weight
- Record 12-lead ECG
- TB questionnaire
- C-SSRS
- HADS
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry

  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential. (Note: A negative result must be received prior to administration of study medication.)
- Obtain skin biopsy (lesional and nonlesional)
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments completed)

Has been changed to

The following procedures or assessments will be performed/recorded prior to administration of study drug:

- Confirm inclusion/exclusion criteria
- Ensure no significant changes in medical procedure history and concomitant disease, including psoriasis disease history
- Vital signs (blood pressure, pulse rate, and temperature)
- Body weight
- Record 12-lead ECG
- TB questionnaire
- C-SSRS
- HADS
- PASI
- IGA
- BSA
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - **Anti-bimekizumab antibodies**
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry
  - RNA, proteins, and metabolites biomarkers
- Obtain urine sample for:

  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential. (Note: A negative result must be received prior to administration of study medication.)
- Obtain skin biopsy (lesional and nonlesional)
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments completed)

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 Good Clinical Practice.

PS0016 Protocol Amendment 3

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
PPD	Clinical Approval	26-Sep-2016 13:35 GMT+02
PPD	Clinical Approval	26-Sep-2016 17:45 GMT+02