PROTOCOL PS0010 AMENDMENT 2

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, DOSE RANGING STUDY TO EVALUATE THE SAFETY, EFFICACY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

PHASE 2B

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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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
CAT	Computed Axial Tomography
CDMS	clinical data management system
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRP	C-reactive protein
eCRF	electronic Case Report Form
CRO	Contract Research Organization
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DAP	data analysis plan
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	electrocardiogram
EDC	Electronic Data Capture
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 Conference on 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)
IWRS	interactive web response system
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
PCS	Physical Component Summary

PD	pharmacodynamics
PDE4	phosphodiesterase 4
PDILI	potential drug-induced liver injury
PD-PPS	Pharmacodynamics Per-Protocol Set
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetics
PK-PPS	Pharmacokinetics Per-Protocol Set
PPS	Per-Protocol Set
PRO	Patient-reported outcome
PS	Patient Safety
PSO	psoriasis
PSSI	Psoriasis Scalp Severity Index
PGADA	Patient's Global Assessment of Disease Activity
RS	Randomized Set
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SF-36	36-Item Short Form Health Survey
SFU	Safety Follow-Up
SOC	System Organ Class
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TNF	tumor necrosis factor
ToPAS	Toronto Psoriatic Arthritis Screening questionnaire
ULN	upper limit of normal
VAS	visual analog scale
WD	withdrawal
Q4W	every 4 weeks

1 SUMMARY

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to investigate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of bimekizumab (also known as UCB4940) compared with placebo 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 320 subjects will be screened in order to have 240 subjects randomized in the study. There will be approximately 40 subjects per treatment arm. For each subject, the study will last a maximum of 32 weeks and will consist of 3 periods, a Screening Period (2 to 4 weeks), a Treatment Period (12 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the last dose of study medication). After the 12-week Treatment Period, eligible subjects will be allowed to enroll in an extension study.

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

- Bimekizumab 64mg administered subcutaneously (sc) every 4 weeks (Q4W)
- Bimekizumab 160mg administered sc Q4W
- Bimekizumab 320mg loading dose administered sc at Baseline followed by 160mg dose administered sc Q4W.
- Bimekizumab 320mg administered sc Q4W
- Bimekizumab 480mg administered sc Q4W
- Placebo administered sc Q4W

Approximately 40 subjects will be randomized to each treatment arm and study medication will be administered in the clinic at Baseline, Week 4, and Week 8. Additional nondosing study visits will occur at Week 1, Week 2, and Week 6. At Week 12, all subjects enrolling in the extension study will undergo the Week 12 study assessments before receiving their first extension study dose of study treatment. All subjects not enrolling in the extension study will have the Week 12 study assessments and will enter the SFU Period.

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 12 weeks after the first dose (ie, the Week 12 Visit) and for the SFU Visit.

The primary objective of the study is to evaluate the dose response of bimekizumab administered sc every 4 weeks for 12 weeks in the treatment of subjects with moderate to severe chronic plaque psoriasis.

The secondary objectives of the study are to assess the efficacy of individual dose regimens of bimekizumab compared to placebo, the PK, safety, tolerability, and immunogenicity of bimekizumab, and to assess the exposure response relationship of bimekizumab as it relates to efficacy and safety.

The other objectives of the study are to demonstrate the effects of bimekizumab on improvement of general health-related quality of life (QOL), skin-related QOL, and psoriatic disease in nails and scalp (in subjects with nail and scalp disease at Baseline). Analyses of genomic, genetic, and proteomic biomarkers may also be performed.

The primary efficacy variable is the PASI90 response defined as a subject that achieves 90% reduction in the PASI score at Week 12. The secondary efficacy variables are IGA response at Week 12 and Week 8, PASI90 response at Week 8, PASI75 response at Week 12, and PASI100 response at Week 12. The other efficacy variables are listed in Section 4.1.3.

Pharmacokinetic and PD variables are listed in Section 4.2.1 and Section 4.2.2, respectively, immunological variables are listed in Section 4.3, and pharmacogenomics variables are listed in Section 4.2.3.

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 (Kreuger 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.

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 the study is to evaluate the dose response of bimekizumab administered sc every 4 weeks for 12 weeks in the treatment of subjects with moderate to severe chronic plaque psoriasis.

3.2 Secondary objectives

The secondary objectives of the study are to:

- Evaluate the efficacy of individual dose regimens of bimekizumab compared to placebo after 12 weeks of treatment for subjects with moderate to severe chronic plaque psoriasis
- Compare the efficacy of the bimekizumab 160mg treatment group versus the bimekizumab 160mg treatment group with a 320mg loading dose
- Assess the PK of bimekizumab following sc dosing Q4W
- Assess the safety, immunogenicity, and tolerability of bimekizumab
- Assess the exposure response relationship of bimekizumab as it relates to efficacy and safety
- Characterize the population PK of bimekizumab in the moderate to severe psoriatic population following repeat dose administration

3.3 Other objectives

The other objectives of the study are to:

- Assess the improvement of skin-related QOL
- Assess the improvement of general health-related QOL
- Assess psoriatic nail disease in subjects with nail disease at Baseline
- Assess psoriatic scalp disease in subjects with scalp psoriasis at Baseline
- 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 Efficacy variables

4.1.1 Primary efficacy variables

The primary efficacy variable is the PASI90 response defined as a subject that achieves 90% reduction from Baseline in the PASI score at Week 12.

4.1.2 Secondary efficacy variable

The secondary efficacy variables are:

- IGA response (Clear or Almost Clear with at least 2 category improvement from Baseline) at Week 12
- IGA response (Clear or Almost Clear with at least 2 category improvement from Baseline) at Week 8
- PASI90 response at Week 8
- PASI75 response at Week 12
- PASI100 response at Week 12

4.1.3 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 5–1. This excludes the primary and secondary variables as specified in Section 4.1.1 and Section 4.1.2.

- PASI50, PASI75, PASI90, and PASI100 response
- IGA response (Clear or Almost Clear with at least 2 category improvement from Baseline)
- Absolute and percent change from Baseline in PASI score
- Shift from Baseline in IGA score
- Change from Baseline in Dermatology Life Quality Index (DLQI)
- Percentage of subjects achieving a DLQI score of 0 or 1

- Percentage of subjects achieving a minimal clinically important difference (MCID) (improvement from Baseline of 5 or more) in the DLQI
- Time to PASI50 response
- Time to PASI75 response
- Time to PASI90 response
- Time to PASI100 response
- Absolute and percent change from Baseline in the BSA affected by psoriasis
- Change from Baseline in modified Nail Psoriasis Severity Index (mNAPSI) score (in the subgroup of subjects with psoriatic nail disease at Baseline)
- Change from Baseline in the Patient's Global Assessment of Disease Activity (PGADA) for the arthritis visual analog scale (VAS)
- Change from Baseline in the Psoriasis Scalp Severity Index (PSSI) (in the subgroup of subjects with scalp psoriasis at Baseline)
- Change from Baseline in Short Form 36 item Health Survey (SF-36) Physical Component Summary (PCS) score, and Mental Component Summary (MCS) score, and individual domains
- Change from Baseline in the Patient Symptom Diary responses (for subjects at sites in selected countries)
- Patient Global Impression of Change (PGIC)
- Change from Baseline in Patient Global Impression of Severity (PGIS)
- 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)

4.2 Pharmacokinetic, pharmacodynamic, and pharmacogenomic variables

4.2.1 Pharmacokinetic variables

The PK variables are listed below:

- Plasma concentration of bimekizumab and population PK (CL/F, V/F)
- Dose-exposure response characterizing the relationship between PASI score and bimekizumab concentration and dose, including EC50/ED50 and E_{max} to support dose selection for subsequent Phase 3 studies

4.2.2 Pharmacodynamic variable

The PD variable is to determine the 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.

4.2.3 Pharmacogenomic variables

4.2.3.1 Genomic, genetic, and metabolite variables

Where local regulations permit, additional blood samples will be collected from consenting subjects at specific time points and stored at -80°C for up to 20 years to allow for potential, exploratory analyses of genomic, genetic, and proteomic biomarkers relevant to the inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available.

4.3 Immunological variable

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

4.4 Safety variables

Safety variables to be assessed are:

- Severity and frequency of AEs
- 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

5 STUDY DESIGN

5.1 Study description

This is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the safety, efficacy, PK, and PD 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 (2 to 4 weeks), a Treatment Period (12 weeks), and a SFU Period (20 weeks after the last dose of study medication). After the 12-week Treatment Period, eligible subjects will be allowed to enroll in an extension study (PS0011).

Screening Period

The Screening Period will last 2 weeks, but can be extended 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 1:1:1:1:1:1 to receive the following blinded study treatment regimens:

- Bimekizumab 64mg administered sc Q4W
- Bimekizumab 160mg administered sc Q4W
- Bimekizumab 320mg loading dose administered sc at Baseline followed by 160mg dose administered sc Q4W
- Bimekizumab 320mg administered sc Q4W
- Bimekizumab 480mg administered sc Q4W
- Placebo administered sc Q4W

Approximately 320 subjects will be screened in order to have 240 subjects randomized in the study. There will be approximately 40 subjects per treatment arm and study medication will be administered in the clinic at Baseline, Week 4, and Week 8. Additional nondosing study visits will occur at Week 1, Week 2, and Week 6.

At Week 12, all subjects enrolling in the extension study (PS0011) will undergo the Week 12 study assessments and then receive their first extension study dose of study treatment. All subjects not enrolling in the extension study will have the Week 12 study assessments and will enter the SFU Period.

Subjects who withdraw early from study treatment will be asked to return for study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and for the SFU Visit.

Subjects withdrawing early from the study will undergo the early Withdrawal Visit assessments 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.

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 32 weeks. This includes the following study period durations:

- Screening Period: 2 to 4 weeks
- Double-blind, placebo-controlled Treatment Period: 12 weeks
- Safety Follow-Up Period: a SFU Visit is planned 20 weeks after the last dose of study medication

After the 12-week Treatment Period, subjects will be allowed to enroll in an extension study. The SFU Visit will not be conducted in PS0010 for subjects who enroll in the extension study.

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

Approximately 320 subjects will be screened in order to have 240 subjects randomized in the study. There will be approximately 40 subjects per treatment arm. The planned number of study sites is approximately 40.

5.1.4 Anticipated regions and countries

The regions planned for study conduct are Europe, Canada, and the US, 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 study assessments

Visit[a]/ Week / Protocol activity	Screening	Baseline (first dose)	Double-blind Treatment Period (Time after the first dose)						SFU[b]
			1	2	4	6	8	12/WD	
Informed consent[c]	X						X[d]	X[d]	
Inclusion/exclusion	X	X							
Demographic data	X								
Psoriasis history	X								
Toronto Psoriatic arthritis screening questionnaire	X								
Significant past medical history and concomitant diseases	X	X[e]							
Physical exam[f]	X							X	X
Height	X								
Body Weight	X	X						X	X
Vital signs[g]	X	X	X	X	X	X	X	X	X
HADS	X	X			X		X	X	X
eC-SSRS	X	X	X	X	X	X	X	X	X
Hematology/biochemistry/urinalysis	X	X	X	X	X	X	X	X	X
Central ECG	X	X		X	X	X		X	X
Pregnancy testing[h]	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing [i]	X								
HIV testing	X								
Chest x-ray[j]	X								

Table 5–1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Baseline (first dose)	Double-blind Treatment Period (Time after the first dose)						SFU[b]
			1	2	4	6	8	12/WD	
IGRA tuberculosis test[k]	X						X		
Tuberculosis questionnaire	X	X						X	
Blood sample for bimekizumab plasma concentrations[l]		X	X	X	X		X	X	X
Blood sample for anti-bimekizumab antibodies[l]		X			X		X	X	X
Blood sample for cytokines, complement, candidate biomarker analysis, and flow cytometry[l]		X		X		X	X	X	
Blood sample genomic, genetic/epigenetic proteomic, and metabolomics analyses[c l]		X		X		X		X	
PASI	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X
BSA affected by psoriasis	X	X			X		X	X	X
mNAPSI		X			X		X	X	
DLQI		X	X	X	X		X	X	X
PGADA		X						X	
Psoriasis Scalp Severity Index		X		X	X		X	X	
Patient Symptom Diary responses (for subjects at sites in selected countries)		X	X	X	X	X	X	X	
PGIS		X	X	X	X	X	X	X	
PGIC		X	X	X	X	X	X	X	
SF-36		X		X	X		X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X[m]
IXRS[n]	X	X	X	X	X	X	X	X	X
Bimekizumab or placebo administration[o]		X			X		X		

BSA=body surface area; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; 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; mNAPSI=modified Nail Psoriasis Severity Index; PASI=Psoriasis Area and Severity Index; PGADA=Patient's Global Assessment of Disease Activity; PGIC=Patient Global

Impression of Change; PGIS=Patient Global Impression of Severity; SF-36=36-Item Short Form Health Survey; SFU=Safety Follow-Up; TB=tuberculosis; WD=withdrawal

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

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

[c] A separate Informed Consent Form will be required for subjects who decide to participate in the genomics, genetics, and proteomics substudy. The Informed Consent Form must be signed prior to collecting any samples for the substudy.

[d] A separate Informed Consent Form is required to be completed for the extension study (PS0011) at Week 8 or Week 12. The sites are encouraged to begin the PS0011 consent process at Week 8.

[e] Ensure no significant changes in medical history.

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

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

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

[i] 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+); or, 2) positive for anti-hepatitis B core antibody (HBcAb+) are excluded; a positive test for HCV is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab), and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction) are also excluded. Subjects will also be tested for anti-hepatitis B surface antibody.

[j] 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.

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

[l] All blood samples taken prior to dosing.

[m] Including assessment for the development of different forms of psoriasis at the SFU visit.

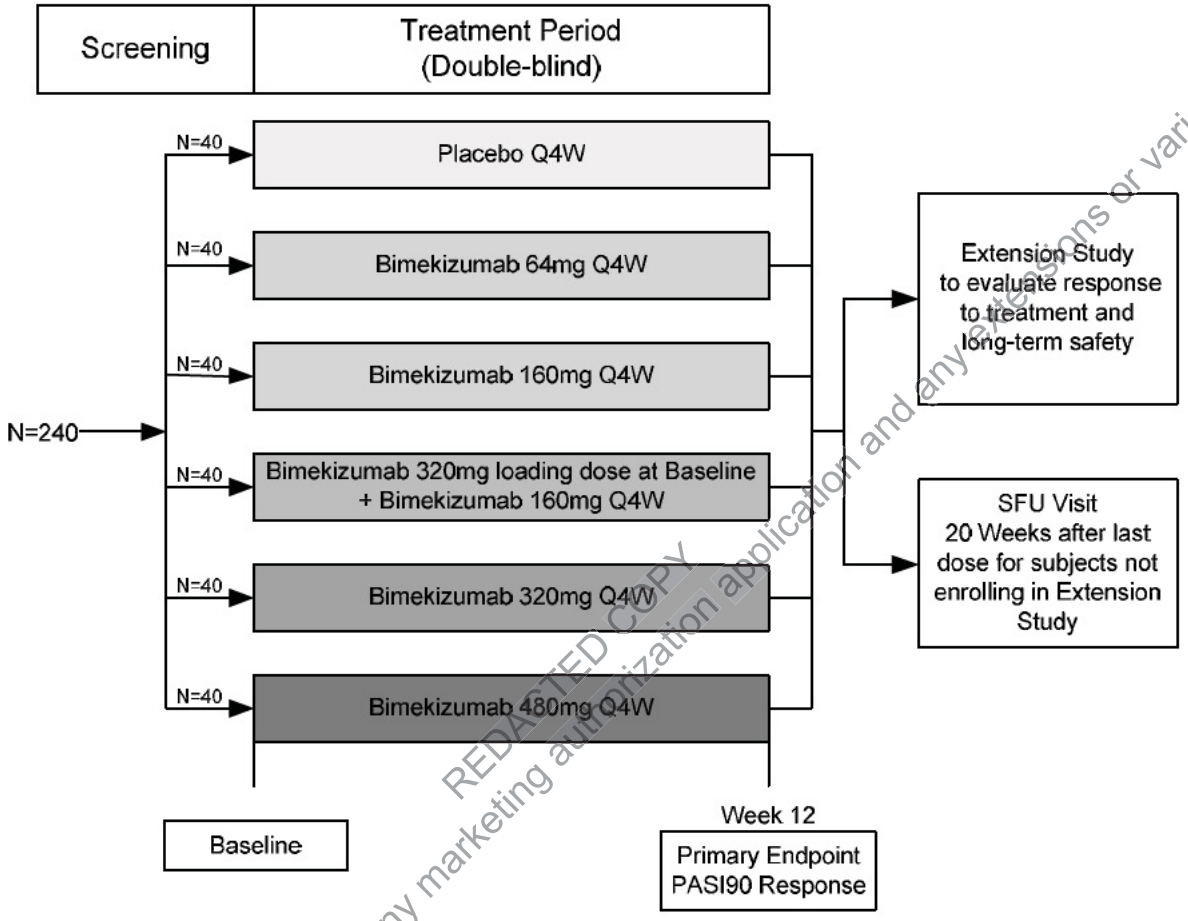
[n] Drug administration is based on randomization.

[o] The time between doses should be no less than 24 days and no more than 32 days.

5.3 Schematic diagram

The study schematic diagram for PS0010 is presented in Figure 5–1.

Figure 5–1: Schematic diagram of PS0010



Q4W=every 4 weeks; SFU=Safety Follow-Up

5.4 Rationale for study design and selection of dose

PS0010 is a Phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study. For each subject, the study will last a maximum of up to 32 weeks and will consist of a Screening Period (2 to 4 weeks), a double-blind, placebo-controlled Treatment Period (12 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 different doses and different dosing regimens of bimekizumab as shown below:

- Bimekizumab 64mg administered sc Q4W

- Bimekizumab 160mg administered sc Q4W
- Bimekizumab 320mg loading dose administered sc at Baseline followed by 160mg dose administered sc Q4W
- Bimekizumab 320mg administered sc Q4W
- Bimekizumab 480mg administered sc Q4W
- Placebo administered sc Q4W

These doses were chosen based on the efficacy and safety data from the 3 completed clinical studies of bimekizumab (UP0008, RA0124, and PA0007). These doses support the maximum likelihood of confirmation of efficacy for bimekizumab in subjects with moderate to severe chronic plaque psoriasis while presenting a high likelihood of an acceptable safety profile.

The study duration of 12 weeks is considered appropriate to show the separation between the doses studied to assess dose-response relationship. Twelve weeks is an appropriate duration to determine the induction of efficacy in patients with plaque psoriasis who are starting a biologic therapy.

The study is double-blind in order to avoid subjective bias in the reporting and assessment of the efficacy, safety, and tolerability effects of bimekizumab. Placebo will be administered as a control in order to provide a comparison of inactive treatment to bimekizumab and to establish the frequency and/or magnitude of changes in clinical endpoints that may occur in the absence of active treatment.

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:

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. Male or female at least 18 years of age.

4. Chronic plaque psoriasis for at least 6 months prior to Screening.

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

6. Candidates 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 till 20 weeks after last administration of study drug, and have a negative pregnancy test at Visit 1

(Screening) and immediately prior to first dose. The following methods are considered highly effective when used consistently and correctly.

- combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner (where postvasectomy testing had demonstrated sperm clearance).
- sexual abstinence if it is in accordance with a subject's preferred and common lifestyle. Subjects who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse until 20 weeks after the 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).

1. Patient 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 judgement, 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) for psoriatic arthritis or psoriasis 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.

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. 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 are allowed to take stable doses of NSAIDs to treat their psoriatic arthritis symptoms during the study. Subjects are allowed to use acetaminophen/paracetamol and mild opioids, as needed.

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 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 or Anxiety score ≥15

30. Subjects are Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

31. Subjects are UCB employees or are employees of third-party organizations involved in the study.

6.3 Withdrawal criteria

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

Subjects should be withdrawn from the study 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 study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and 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.
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.

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.

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. [redacted]

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 3 sc injections. Suitable areas for sc injections are the lateral abdominal wall and upper outer thigh. During each dosing visit, each of the 3 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.

Study medication will be administered at Baseline, Week 4, and Week 8. Study medication will also be administered at Week 12 for all subjects entering the extension study. The minimum of time between doses should be no less than 24 days and no more than 32 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 Conference on 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, 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.

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.

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

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 relative 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
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 (including 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 #0, 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 and study sites will have blinded and unblinded personnel.

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 double-blind 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.

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

7.9.1 Procedures for maintaining and breaking the treatment blind

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

7.10 Randomization and numbering of subjects

An IXRS will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by the 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. Subject treatment assignment will be stratified by region and prior biologic exposure (yes/no). The IXRS will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Efforts should be made to limit the enrollment of subjects with prior biologic exposure to approximately 30% of the total study population.

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

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.
- The minimum of time between doses should be no less than 24 days and no more than 32 days.
- 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.

Where local regulations permit, subjects will also be given the option to participate in the genomics, genetics, and proteomics substudy. Subjects agreeing to participate in the substudy will be required to complete a separate Informed Consent Form. The Informed Consent Form must be signed prior to collecting any samples for the substudy. The substudy will only be conducted where ethically accepted and authorized by the regulatory agencies. Refusal to participate in the substudy will not affect a subject's ability to participate in the main PS0010 study.

Subjects may also be asked about their willingness to participate in a study exit interview near the end of the study. Subjects may decide to participate in the genomic, genetic and proteomic substudy, or the interview, or neither.

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)
- HADS
- Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)
- Record 12-lead ECG
- Chest x-ray (not necessary if performed within 3 months prior to Screening Visit and report is available)
- TB questionnaire
- Toronto Psoriatic Arthritis Screening 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
- Obtain urine sample for standard safety laboratory tests
- Record AEs
- Contact the IXRS

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
- Vital signs (blood pressure, pulse rate, and temperature)
- Body weight
- Record 12-lead ECG
- TB questionnaire
- eC-SSRS
- HADS
- PASI
- IGA
- BSA
- DLQI
- mNAPSI
- PGADA
- PSSI
- SF-36
- Patient Symptom Diary responses (for subjects at sites in selected countries)
- PGIC (for subjects at sites in selected countries)
- PGIS (for subjects at sites in selected countries)
- 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 (serum and plasma)
  - Genomic, genetic/epigenetic, proteomic, and metabolomics analyses (for subjects in the substudy)
- 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)

8.3 Week 1 (+/-3 days)

The following procedures or assessments will be performed/recorded:

- Vital signs (blood pressure, pulse rate, and temperature)
- eC-SSRS
- PASI
- IGA
- DLQI
- Patient Symptom Diary responses (for subjects at sites in selected countries)
- PGIC (for subjects at sites in selected countries)
- PGIS (for subjects at sites in selected countries)
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
- Obtain urine sample for:
  - standard safety laboratory tests
  - urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS

8.4 Week 2 (+/- 3 days)

The following procedures or assessments will be performed/recorded:

- Vital signs (blood pressure, pulse rate, and temperature)
- eC-SSRS
- Record 12-lead ECG
- PASI
- IGA
- DLQI
- PSSI
- SF-36

- Patient Symptom Diary responses (for subjects at sites in selected countries)
- PGIC (for subjects at sites in selected countries)
- PGIS (for subjects at sites in selected countries)
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry (serum and plasma)
  - Genomic, genetic/epigenetic, proteomic, and metabolomics analyses (for subjects in the substudy)
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS

8.5 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)
- eC-SSRS
- HADS
- Record 12-lead ECG
- PASI
- IGA
- BSA
- DLQI
- mNAPSI
- PSSI
- SF-36
- Patient Symptom Diary responses (for subjects at sites in selected countries)
- PGIC (for subjects at sites in selected countries)

- PGIS (for subjects at sites in selected countries)
- 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)

8.6 Week 6 (+/- 3 days)

The following procedures or assessments will be performed/recorded:

- Vital signs (blood pressure, pulse rate, and temperature)
- eC-SSRS
- Record 12-lead ECG
- PASI
- IGA
- Patient Symptom Diary responses (for subjects at sites in selected countries)
- PGIC (for subjects at sites in selected countries)
- PGIS (for subjects at sites in selected countries)
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry (serum and plasma)
  - Genomic, genetic/epigenetic, proteomic, and metabolomics analyses (for subjects in the substudy)
- Obtain urine sample for:
  - standard safety laboratory tests
  - urine pregnancy test for women of childbearing potential
- Concomitant medications

- Record AEs
- Contact the IXRS

8.7 Week 8 (+/- 3 days)

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

- Obtain written informed consent for subjects planning to enter the extension study (PS0011). The sites are encouraged to begin the PS0011 consent process at Week 8.
- Vital signs (blood pressure, pulse rate, and temperature)
- eC-SSRS
- HADS
- PASI
- IGA
- BSA
- DLQI
- mNAPSI
- PSSI
- SF-36
- Patient Symptom Diary responses (for subjects at sites in selected countries)
- PGIC (for subjects at sites in selected countries)
- PGIS (for subjects at sites in selected countries)
- Obtain blood sample(s) for:
  - TB test (interferon gamma release assay; IGRA)
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Cytokines, complement, candidate biomarker analysis, and flow cytometry (serum and plasma)
- 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)

8.8 Week 12 (+/- 3 days) Study Exit/Early Withdrawal

The following procedures or assessments will be performed:

- Obtain written informed consent for subjects planning to enter the extension study (PS0011) if not obtained at Week 8. The sites are encouraged to begin the PS0011 consent process at Week 8.
- Vital signs (blood pressure, pulse rate, and temperature)
- eC-SSRS
- HADS
- Body weight
- Physical examination
- Record 12-lead ECG
- TB questionnaire
- PASI
- IGA
- BSA
- DLQI
- mNAPSI
- PGADA
- PSSI
- SF-36
- Patient Symptom Diary responses (for subjects at sites in selected countries)
- PGIC (for subjects at sites in selected countries)
- PGIS (for subjects at sites in selected countries)
- 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 (serum and plasma)

  - Genomic, genetic/epigenetic, proteomic, and metabolomics analyses (for subjects in the substudy)
- Obtain urine sample for:
  - standard safety laboratory tests
  - urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS

8.9 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 Safety Follow-up 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)
- eC-SSRS
- HADS
- Body weight
- Physical examination
- Record 12-lead ECG
- PASI
- IGA
- BSA
- DLQI
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
  - Serum pregnancy test for women of childbearing potential
- Obtain urine sample for standard safety laboratory tests
- Concomitant medications
- Record AEs

- Contact the IXRS

8.10 Early Withdrawal Visit

Subjects withdrawing early from the study (see Section 6.3) will undergo the same assessments as the Week 12 Visit (see Section 8.8) and will enter the SFU Period.

Subjects that withdrawal from study treatment early will be asked to return for the study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and for the SFU Visit (20 weeks after the last received dose).

8.11 Unscheduled Visit

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

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

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

- Vital signs
- eC-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 PASI50, PASI75, PASI90, and PASI100 responses are based on at least 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 Dermatology Life Quality Index

The DLQI is a questionnaire designed for use in adult subjects with psoriasis. The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect patients' health related QOL. This instrument asks subjects about symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. It has been shown to be valid and reproducible in psoriasis patients. The DLQI score ranges from 0 to 30 with higher scores indicating lower health related QOL. A 5-point change in the DLQI score (DLQI response) has been reported to be meaningful for the patient (within-patient minimal important difference); while a DLQI absolute score of 0 or 1 indicates no or small impact of the disease on health related QOL. Subjects will be asked to complete the DLQI as outlined in the Schedule of Study Assessments (Table 5–1). Study site personnel should ensure that each subject completes the instrument prior to leaving the study site.

9.5 Hospital Anxiety and Depression Scale

The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with chronic plaque psoriasis (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 wheras a score of 15 and above is considered severe (Snaith and Zigmond, 1994).

9.6 Modified Nail Psoriasis Severity Index Score

Psoriatic nail disease will be evaluated at the Baseline Visit using the modified Nail Psoriasis Severity Index (mNAPSI). All affected nails will be scored (0 to 3) for onycholysis/oil drop dyschromia, nail plate crumbling, and pitting and will be scored (0 for "no" or 1 for "yes") for leukonychia, nail bed hyperkeratosis, splinter hemorrhages and red spots in the lunula. The score for an individual nail ranges from 0 to 13 with higher scores indicative of more severe nail disease. The total mNAPSI score is the sum of the scores for each individual nail. If a nail is unaffected, it will be recorded as such and will not contribute to the total mNAPSI score. Subjects with nail disease at Baseline are defined as those with an mNAPSI score >0 at Baseline.

The mNAPSI will be assessed at the visits specified in Table 5–1.

9.7 Patient's Global Assessment of Disease Activity for the arthritis visual analog scale

The PGADA for the arthritis visual analog scale (VAS) will be used to provide an overall evaluation of arthritis disease symptoms. Subjects will respond to the question, "Considering all the ways your arthritis affects you, please mark a vertical line on the scale below to show how you are feeling today", using a VAS where 0 is "very good, no symptoms" and 100 is "very poor, severe symptoms.

Each subject will complete the PGADA at the visits specified in Table 5–1.

9.8 Patient Global Impression of Change

The PGIC will be assessed at Baseline and on a weekly basis following the completion of all the patient symptom diary items. Only patients in selected countries who participate in the completion of the patient symptom diary will participate in the completion of the PGIC.

The PGIC is a 5-item instrument that will ask the participants to think about their psoriasis-related symptoms (including itching, pain, scaling, and sleep loss) since they started this study. Each item has 7 response categories ranging from "Very much improved," "Much improved," "Minimally improved," "No change," "Minimally worse," "Much worse," to "Very much worse."

9.9 Patient Global Impression of Severity

The PGIS will be completed at Baseline and on a weekly basis following the completion of all patient symptom diary items. Only patients in selected countries who participate in the completion of the patient symptom diary will participate in the completion of the PGIS.

The PGIS is a 5-item instrument that will ask the participants to think about their psoriasis-related symptoms (including itching, pain, scaling, and sleep loss) over the past week and an additional 5 items asking about the same set of symptoms at the current point in time. Each item has 5 response categories ranging from "No (symptoms)," "Mild (symptoms)," "Moderate (symptoms)," "Severe (symptoms)," to "Very severe (symptoms)."

Both PGIC and PGIS will be used to evaluate participants overall sense of the status and perceived improvement in relevant symptoms and to aid the interpretation of the changes in the patient symptom diary.

9.10 Psoriasis Scalp Severity Index

The PSSI considers both the extent of the area of involvement and the severity based on the scoring scales outlined in Table 9–3. The assessment considers erythema, induration and desquamation on the scalp. For each of these 3 elements, the scores of the area and severity are multiplied. Then, the score from each element is totaled to obtain the PSSI score. As with the PASI, the PSSI score ranges from 0 to 72 with a higher score indicating increased scalp disease severity.

The PSSI will be assessed at the visits specified in Table 5–1.

Table 9–3: Parameters assessed for the PSSI

Assessment of extent of scalp psoriasis	
Score	**Definition**
1	<10%
2	10-29%
3	30-49%
4	50-69%
5	70-89%
6	90-100%
Assessment of clinical symptoms (erythema, induration, and desquamation)	
Score	**Definition**
0	Absent
1	Slight
2	Moderate
3	Severe
4	Severest possible

PSSI= Psoriasis Scalp Severity Index

9.11 Patient Symptom Diary responses

UCB is developing a new PRO measure that will be used to assess key symptoms relevant to patients with moderate to severe chronic plaque psoriasis. PS0010 will use the draft PRO measure in selected countries to enable psychometric validation of the PRO. Site staff will train the participating subjects on the use of the electronic PRO (ePRO) diary at the Screening Visit, following which the device will be dispensed to the subject for home use until the Week 12 Visit. The ePRO diary will be administered on a daily basis from Screening to the Week 12 Visit.

Item content of the ePRO diary will be finalized prior to study initiation and will include a variety of psoriasis-related characteristics, reported as relevant by patients in the published literature and planned concept elicitation interviews. The ePRO diary will also administer appropriate anchor items (eg, patient global impression of change, and patient global impression of concept) at the end of every study week. The ePRO diary software will be programmed such that the subjects will be given a window of opportunity to complete the ePRO diary each evening. The data collected on the ePRO diary will be uploaded to a central server database and will be 21 CFR Part 11 compliant. Appropriate GCP procedures (including subject/site training and testing) will be performed at the study sites

9.12 36-Item Short Form Health Survey

The SF-36 (Version 2, standard recall) is a 36-item generic health related QOL instrument that uses a recall period of 4 weeks. Items are grouped into 8 domains as follows: Physical Functioning (10 items), Role Physical (4 items), Bodily Pain (2 items), General Health (5 items), Vitality (4 items), Social Functioning (2 items), Role Emotional (3 items), Mental Health (5 items), and 1 item for perceived stability or change in health (Health Transition) during the last year. The concepts represented by these domains contribute to physical, mental, and social aspects of health-related QOL. In addition to domain scores, the PCS and MCS scores are calculated from the 8 domains (excluding the Health Transition item). Component scores appreciate the impact of each domain on physical and mental health status (Maruish, 2011). Each of the 8 domain scores and the component summary scores range from 0 to 100, with a higher score indicating a better health status. The domains and the 2 component summary scores are standardized with a mean of 50 and a standard deviation (SD) of 10 in the general USA population. The minimally important differences (MIDs), in terms of T-score points, for SF-36 domains and component summaries are the following: PCS, 2; MCS, 3; Physical Functioning, 3; Role-Physical, 3; Bodily Pain, 3; General Health, 2; Vitality, 2; Social Functioning, 3; Role-Emotional, 4; and Mental Health, 3.

The SF-36 will be completed by the subject the visits specified in Table 5–1.

10 ASSESSMENT OF PHARMACOKINETICS/ PHARMACODYNAMICS/PHARMACOGENOMICS

10.1 Pharmacokinetic and pharmacodynamic variables

Blood samples for measurement of PK and PD variables (Section 4.2) will 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 will include, but is not limited to: CD3, CD19, CD4, CD8, and CD69.

Candidate biomarkers will 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 Pharmacogenomic variables

10.2.1 Genomics, genetics, and proteomics variables

For individuals consenting to the biomarker substudy, blood samples will be drawn for exploratory genetic/epigenetic, genomic, proteomic and metabolomics analysis 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. The nature and format of these tentative analyses will be determined when the results of the main study are made available.

A separate Informed Consent Form will be required for those subjects who agree to participate in the genomics, genetics, and proteomics substudy. The substudy will only be conducted where ethically accepted and authorized by the regulatory agencies. Refusal to participate in the substudy will not affect a subject's ability to participate in the main study.

The samples will be stored at -80°C at the central biorepository 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 eC-SSRS), depression-and anxiety (assessed using the HADS, see Section 9.5), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 12.5.1), 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.

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.

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

12.5 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]

Table 12–2: Laboratory measurements

Hematology	Chemistry	Urinalysis
MCH	Creatinine	
MCHC	ALP	
MCV	AST	
Platelet count	ALT	
RBC count	GGT	
WBC count	Total bilirubin	
	LDH	
	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.

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]

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

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

The following additional 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 (2 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 (2 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 12/WD 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 8/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 (2 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 be completed at Screening, Baseline, and the Week 12/WD Visit. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question "[redacted]" at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has LTB or active TB (see Exclusion Criterion 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 12/WD Visit as soon as possible but no later than the next scheduled study visit and complete all Week 12/WD 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.

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, axillary, 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

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.

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 Screening, the Week 12/WD Visit, and the SFU Visit. 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 Screening, Baseline, the Week 12/WD Visit, and at the SFU Visit.

12.6.7 Assessment of suicidal ideation and behavior

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

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

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

12.7 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 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.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

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

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

13.2 Monitoring

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

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

The Investigator will allow UCB (or designee) to periodically review all CRFs and corresponding source documents (eg, hospital and laboratory records for each study participant). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of 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 Holter monitor records or electroencephalogram records, must be saved and stored as instructed by the Sponsor or designee.

Patient Reported Outcome (PRO) measures (eg, DLQI, SF-36, and PGADA) will be completed by each subject utilizing electronic data capture.

The ePRO diary data will be entered into an electronic diary by the subject. The data collection and database management system will be supplied by a vendor and will be compliant with the FDA Part 11. The data collected on the ePRO diary will be uploaded to a central server database and will be sent electronically to UCB (or a designated CRO).

13.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 13.2.1.

13.3 Data handling

13.3.1 Case Report Form completion

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

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

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 at Baseline.

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

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized subjects who 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.

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 dose-response relationship between treatment and PASI90 response will be assessed using a logistic regression model which will include fixed effects for treatment, region, and prior biologic exposure (yes/no). This will be evaluated using a linear contrast in which equal spacing between each of the doses is assumed. The coefficients for this linear contrast will be -2, -1, 0, 1, and 2 for placebo, bimekizumab 64mg Q4W, bimekizumab 160 Q4W, bimekizumab 320mg Q4W, and bimekizumab 480mg Q4W, respectively. While the bimekizumab 320mg loading dose followed by bimekizumab 160mg Q4W has been left out of the linear contrast for evaluating dose response, it will remain a part of the logistic regression model and will be compared to the bimekizumab 160mg Q4W dose. Prior biologic exposure was selected as a fixed effect in the logistic regression model as it is a stratification variable for randomization and because it may have an impact on efficacy. The use of region as a fixed effect in the model is also based on its use as a stratification variable in randomization and is intended to combine study centers into similar geographic regions. The geographic regions to be used will be defined in the IXRS and in the SAP. If the logistic regression model is unable to converge, then prior biologic exposure may be dropped from the model to facilitate convergence. The linear contrast from the logistic regression model will be evaluated at a 2-sided significance level of α=0.05. This evaluation of dose-response will constitute the primary efficacy analysis.

As a supportive analysis for the primary efficacy variable, the same logistic regression model described above will be used to assess the effect of each individual dose vs placebo on PASI90 response. Comparisons will be made for each dose vs placebo at a 2-sided significance level of α=0.05. For each dose, the odds ratio vs placebo, the 95% confidence interval, and the corresponding p-value will be calculated.

The pairwise comparisons of bimekizumab versus placebo will be formally evaluated for statistical significance only if the primary dose response efficacy analysis is statistically significant. Once the dose response has been established, pairwise testing of each bimekizumab dose versus placebo will account for multiplicity by using a fixed sequence testing procedure with each bimekizumab dose being tested sequentially from the highest dose to the lowest dose. Each test will only be conducted if the previous test reaches significance at a 2-sided significance level of α=0.05. This procedure will control the overall Type I error rate. A pairwise comparison will also be made for the bimekizumab 160mg Q4W group versus the bimekizumab 320mg loading dose followed by bimekizumab 160mg Q4W group, but this evaluation will not be part of the sequential testing procedure described above (ie, the p-value will be nominal).

Non-responder imputation (NRI) will be used to account for missing data in the primary analysis. That is, subjects with a missing PASI score at Week 12 or who discontinued study treatment prior to the Week 12 Visit will be considered non-responders for the primary analysis.

14.3.1.1 Sensitivity analyses

The primary dose response analysis and pairwise comparisons will be repeated for all subjects in the PPS to evaluate the effect of important protocol deviations on the analysis.

An ordered categorical analysis using a non-parametric correlation statistic of Mantel and Haenszel (1959) and modified ridit scores will be performed as a sensitivity analysis to the primary dose-response evaluation based on the logistic regression model. This analysis will include region and prior biologic exposure as stratification factors to adjust for potential differences in the dose response based on these variables, and will be evaluated at a 2-sided significance level of α=0.05.

Additional sensitivity analyses to evaluate the assumptions related to the handling of missing data for the primary efficacy variable will be performed and are described in greater detail in Section 14.6.

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.

All categorical variables (ie, PASI75/90/100 response, IGA response [clear, almost clear]) will be analyzed for treatment effects using pairwise comparisons based on the same method as that described for the primary efficacy variable.

Dose and exposure response will be assessed using a non-linear model assessing the relationship between dose/exposure and PASI score. The model will include fixed effects for dose/exposure and test the clinical and statistical relevance of covariate effects. Further details will be given in a separate data analysis plan (DAP) and reported in a separate document.

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.

Time to PASI50, PASI75, PASI90, and PASI100 response will be estimated and presented using the Kaplan-Meier product-limit method for each treatment. Time to a given response will be defined as the length in days from Baseline until the first date when the response is achieved. Subjects who discontinue study treatment prior to achieving a response will be censored at the date of study treatment discontinuation. Subjects who reach the Week 12 Visit without achieving the given response will be censored at the date of the Week 12 Visit. The median time to response, including the 2-sided 95% confidence interval, will be calculated for each treatment. Between group differences (each bimekizumab dose vs placebo) will be analyzed with the log-rank statistic.

All other efficacy variables will be summarized based on imputed data (NRI and last observation carried forward [LOCF] for binary and continuous variables, respectively) and observed case data (ie, subjects with missing data or who have prematurely discontinued study treatment are treated as missing).

14.3.3 Subgroup analyses

Subgroup analyses will be performed on the primary and secondary efficacy variables. The following variables for subgroup analyses will be defined: age, gender, disease duration, region, body weight, BMI, prior systemic phototherapy or chemophototherapy, prior nonbiologic systemic therapy, prior biologic systemic exposure, any prior systemic therapy, and antibody positivity. These summaries will be based on imputed data (NRI) and will include descriptive statistics only.

14.4 Planned safety and other analyses

14.4.1 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.

TEAEs 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 +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 12-week treatment period will be cut off at the Week 12 visit (for subjects who complete through the Week 12 visit) or at 12 weeks (84 days) after the first administration of study treatment (for subjects who discontinue prior to the Week 12 visit). Adverse events that emerge following the 12-week treatment period will be summarized separately.

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

14.4.2 Pharmacokinetics/pharmacodynamics analyses

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

Pharmacokinetic and PD analyses will be detailed in a separate DAP and reported in a separate document.

An analysis will be performed based on data through Week 8 to confirm the dose selection for Phase 3. Details will be described in the DAP and linked with the Operational Plan and SAP.

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

Anti-bimekizumab antibody data will be summarized for each treatment at each scheduled visit.

IL-17A, IL-17F, IL-6, and IL-23 data will be summarized for each treatment at each scheduled visit.

14.5 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.

14.6 Handling of dropouts or missing data

For the primary efficacy analysis based on evaluating dose response, missing data will be imputed using NRI. That is, subjects with missing data at Week 12 or who discontinue double-blind study treatment prior to Week 12 will be counted as non-responders for the analysis. Two sensitivity analyses will be performed for the primary analysis:

1. An analysis will be performed in which all available data at Week 12 will be considered. This analysis will be based on the logistic regression model to evaluate dose-response as specified in the primary analysis. However, in this case, subjects will be analyzed according to their randomized treatment, even if they discontinued prior to Week 12 and were no longer on the randomized study treatment when the assessment was performed at Week 12. Even though efforts will be made to collect the primary outcome data for all subjects at Week 12, there may still be some subjects for whom Week 12 efficacy data cannot be obtained. In this case, the subjects will be assumed to be non-responders. The estimand here is the difference in outcome improvement at the planned endpoint for all randomized participants (Mallinckrodt, 2012). This is an estimand of effectiveness to evaluate the de facto hypothesis. It should be noted that this measures something different from the primary analysis and could be confounded by placebo subjects who withdraw and are subsequently on another active medication at the time of the Week 12 assessment. Therefore, the results of this analysis should be interpreted in the appropriate context.
2. An additional sensitivity analysis will be based on observed data only for subjects who are still on the initially randomized treatment at Week 12. Subjects with missing data or who have prematurely discontinued study treatment will be treated as missing. The same procedure described for the primary efficacy analysis of dose response will be used.

Sensitivity analyses will also be performed for the pairwise comparisons of bimekizumab doses versus placebo based on PASI90 at Week 12. The following sensitivity analysis will be conducted:

1. Missing data will be addressed by using multiple imputation (MI) based on the Markov-Chain Monte Carlo (MCMC) method for intermittent missing data, followed by monotone regression for monotone missing data. The actual PASI scores will be imputed and then dichotomized to obtain the PASI90 response status. The multiply imputed data sets will be analyzed using a logistic regression model with factors of treatment group, prior biologic exposure (yes/no), and region. Finally, SAS PROC MIANALYZE will be used to combine the results into a single inference. This procedure assumes a missing at random (MAR)

pattern of missingness and corresponds to an estimand of what has been called the difference in outcome improvement if all subjects tolerated or adhered to treatment (Mallinckrodt, 2012). This is an estimand of efficacy to evaluate the de jure hypothesis.

2. The logistic regression model will be applied where all available data at Week 12 will be considered, as described in sensitivity analysis #1 for the primary dose-response efficacy analysis.
3. The logistic regression model will be applied where only observed data for subjects still on the initially randomized treatment at Week 12 will be considered, as described in sensitivity analysis #2 for the primary dose-response efficacy analysis.

For the dose/exposure response model, missing data will not be imputed. If a subject drops out, this will be used as a covariate in the model.

Other categorical efficacy variables will be imputed using NRI.

Other continuous efficacy variables will be imputed using LOCF where the last observed value of a variable is used to impute the missing data.

14.7 Planned interim analysis and data monitoring

After all enrolled subjects have completed 8 weeks of treatment, an interim analysis will be performed to analyze the dose-exposure response for PASI, including the PASI90 response, in each dose group to determine the optimal therapeutic dose(s) for subsequent studies. Decisions related to the conduct of the PS0010 study will not be impacted by these analyses as they will be conducted by individuals that are not part of the clinical study team, and they will not be shared with any clinical study team members until after the lock of Week 12 data, at which point the study will be unblinded. Further details related to this interim analysis will be outlined in a separate DAP.

14.8 Determination of sample size

A total of 240 subjects (40 in each treatment group) are planned to be randomized in this study. The primary efficacy analysis will be based on the FAS. While some randomized subjects may not be in the FAS, it is expected that this number will not impact the following calculations.

The sample size is calculated based on published PASI90 response data from the secukinumab psoriasis program (ERASURE and FIXTURE studies) and from a Phase 2 bimekizumab study in subjects with psoriatic arthritis (PA0007). As an IL-17A inhibitor, the secukinumab data are important in the estimation of the response of bimekizumab, an IL-17A/F inhibitor. In the ERASURE and FIXTURE studies, PASI90 responses at Week 12 were reported to be 59.2% and 54.2% for the 300mg treatment group and 39.1% and 41.9% for the 150mg treatment group versus 1.2% and 1.5% in the placebo group, respectively (Langley et al, 2014). Limited data from a subset of subjects with psoriasis BSA >3% in the PA0007 study indicate a PASI90 response of 86.7% after 8 weeks of treatment for the combined top 3 doses versus no response in the placebo group.

For the sample size calculation, responder rates of 60%, 50%, and 2% at the end of a 12-week Treatment Period for bimekizumab 480mg Q4W, bimekizumab 320mg Q4W, and placebo have been assumed, respectively. These assumptions are similar to the results observed in the ERASURE and FIXTURE studies and conservative relative to the PA0007 study in order to

account for uncertainty in the estimates. The PASI90 responder rates for the 160mg Q4W, and 64mg Q4W doses are assumed to decrease, using estimates of 40% and 20%, respectively. Note that the bimekizumab 320mg loading dose followed by bimekizumab 160mg Q4W has been left out of this sample size calculation as it will not be included in the test for dose response, but will rather be compared separately to the bimekizumab 160mg Q4W dose.

The sample size for the primary objective of evaluating the dose response relationship was calculated using a 2-sided test for detecting a linear trend across proportions (Nam, 1987) at a significance level of 0.05. With 40 subjects in each treatment group, the test for detecting the overall dose response based on PASI90 response is powered at >99%.

The sample size calculations were performed using the software nQuery Advisor® 7.0.

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.

A separate Informed Consent Form will be required for subjects participating in the substudy for genomics, genetics, and proteomics blood sampling.

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:

- 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.
- Clarify the exclusion criterion regarding laboratory values
- 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 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 timing of the optional study exit interview
- 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 subgroup analyses that will be performed

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.
- The maximum study duration for enrolled subjects was changed from 29 weeks to 32 weeks.
- The List of Abbreviations was revised
- The term “photochemotherapy” was changed to “chemophototherapy” throughout for consistency
- Minor editorial revisions were made

Specific changes

Change #1

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 currently under regulatory review. 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~~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**, **~~an~~** IL-17A inhibitor**s** approved for treatment of moderate to severe psoriasis**~~; and ixekizumab, an IL-17A inhibitor currently under regulatory review~~**. 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 #2

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 #3

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 #4

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 #5

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 #6

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 #7

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 #8

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 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 **Q**4question 4 or **Q**5question 5 of the "Screening/Baseline" version of the eC-SSRS at screening.

    – HADS Depression score **>10 <u>or</u>** Anxiety score ≥15

Change #9

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 #10

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 #11

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 #12

Section 6.3 Withdrawal criteria

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

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 #13

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 #14

Section 8.1 Screening Visit

Subjects will also be asked about their willingness to participate in a post-study interview process. Subjects may decide to participate in the genomic, genetic and proteomic substudy, or the interview, or neither.

Has been changed to

Subjects **may** ~~**will**~~ also be asked about their willingness to participate in a ~~**post-**~~study **exit** interview **near the end of the study** ~~**process**~~. Subjects may decide to participate in the genomic, genetic and proteomic substudy, or the interview, or neither.

Change #15

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 9.5), 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 eC-SSRS), depression-and anxiety (assessed using the HADS, see Section 9.5), 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 #16

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 #17

Table 12-4 PDILI laboratory measurements

[a] For detecting substances (ie, 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 (ie, ~~**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 #18

Section 14.3.3 Subgroup analyses

Subgroup analyses will be performed on the primary and secondary efficacy variables. The following variables for subgroup analyses will be defined: age, gender, disease duration, region, body weight, BMI, prior systemic chemotherapy or chemophototherapy, prior biologic exposure, and antibody positivity. These summaries will be based on imputed data (NRI) and will include descriptive statistics only.

Has been changed to

Subgroup analyses will be performed on the primary and secondary efficacy variables. The following variables for subgroup analyses will be defined: age, gender, disease duration, region, body weight, BMI, prior systemic **phototherapy or** ~~**chemotherapy or**~~ chemophototherapy, **prior nonbiologic systemic therapy,** prior biologic **systemic** exposure, **any prior systemic therapy,** and antibody positivity. These summaries will be based on imputed data (NRI) and will include descriptive statistics only.

Change #19

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 #20

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 #21

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 the following:

- To revise the references to PS0011 as an "open-label extension study." Because of changes to the study design of PS0011, the PS0011 study is no longer planned to be an "open-label" study.
- Clarify that the SFU Visit will not be conducted in PS0010 for subjects who enroll in the extension study.
- Clarify and correct text regarding the analyses of safety.

Modifications and changes

Global changes

The reference to PS0011 as an "open-label extension study" was changed throughout the document. "Open-label" was deleted and, instead, the PS0011 study is being referred to as an "extension study."

Specific changes

Change #1

Section 1 Summary

Approximately 40 subjects will be randomized to each treatment arm and study medication will be administered in the clinic at Baseline, Week 4, and Week 8. Additional nondosing study visits will occur at Week 1, Week 2, and Week 6. At Week 12, all subjects enrolling in the open-label extension study will undergo the Week 12 study assessments before receiving their first open-label dose of bimekizumab. All subjects not enrolling in the open-label extension study will have the Week 12 study assessments and will enter the SFU Period.

Has been changed to

Approximately 40 subjects will be randomized to each treatment arm and study medication will be administered in the clinic at Baseline, Week 4, and Week 8. Additional nondosing study visits will occur at Week 1, Week 2, and Week 6. At Week 12, all subjects enrolling in the ~~**open-label**~~ extension study will undergo the Week 12 study assessments before receiving their first **extension study**~~**open-label**~~ dose of ~~**bimekizumab**~~**study treatment**. All subjects not enrolling in the ~~**open-label**~~ extension study will have the Week 12 study assessments and will enter the SFU Period.

Change #2

Section 5.1.1 Study Periods

At Week 12, all subjects enrolling in the open-label extension study (PS0011) will undergo the Week 12 study assessments and then receive their first open-label dose of bimekizumab. All subjects not enrolling in the open-label extension study will have the Week 12 study assessments and will enter the SFU Period.

Has been changed to

At Week 12, all subjects enrolling in the ~~**open-label**~~ extension study (PS0011) will undergo the Week 12 study assessments and then receive their first **extension study**~~**open-label**~~ dose of ~~**bimekizumab**~~**study treatment**. All subjects not enrolling in the ~~**open-label**~~ extension study will have the Week 12 study assessments and will enter the SFU Period.

Change #3

Section 5.1.2 Study duration per subject

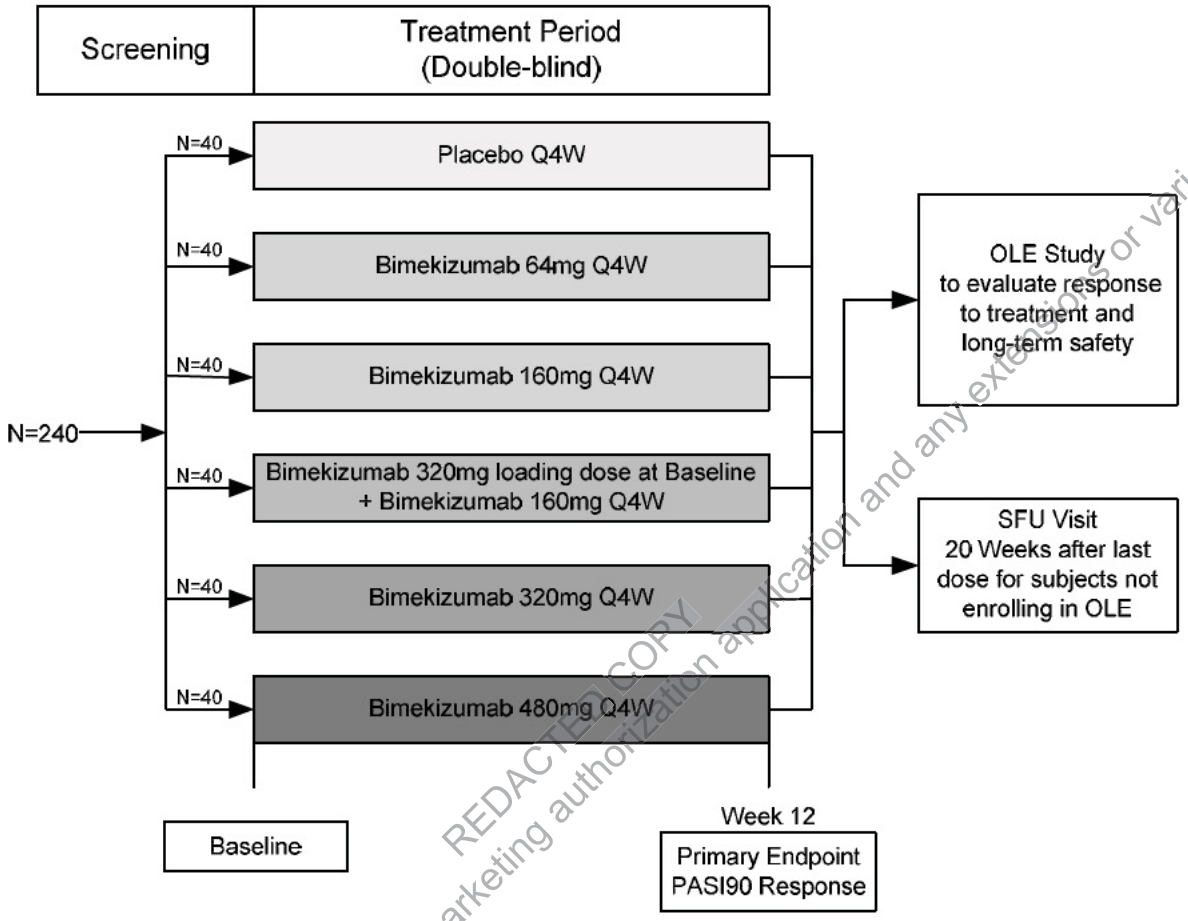
After the 12-week Treatment Period, subjects will be allowed to enroll in an extension study. The SFU Visit will not be required for subjects who enroll in the extension study.

Has been changed to

After the 12-week Treatment Period, subjects will be allowed to enroll in an extension study. The SFU Visit will not be ~~**required**~~**conducted in PS0010** for subjects who enroll in the extension study.

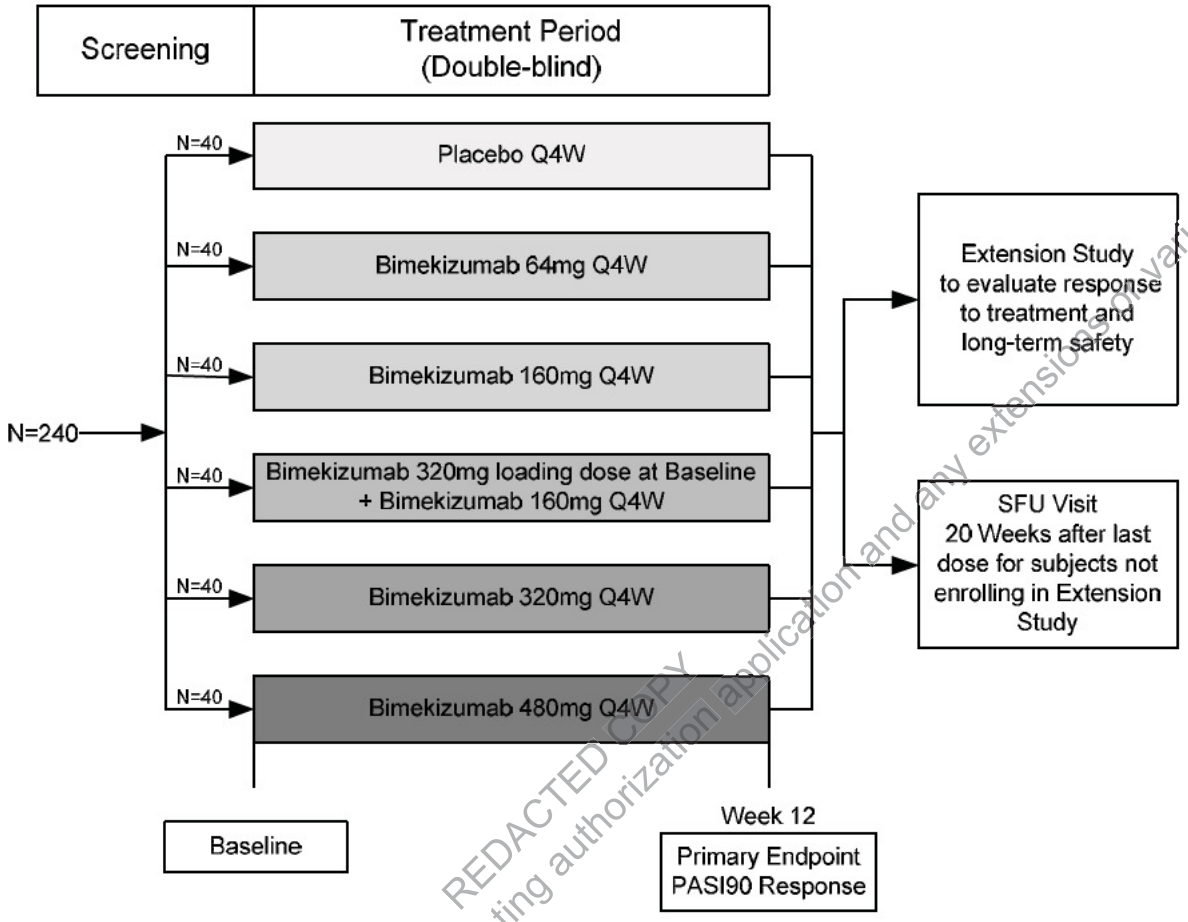
Change #4

Figure 5-1 Schematic diagram of PS0010



OLE=open-label extension; Q4W=every 4 weeks; SFU=Safety Follow-Up

Has been changed to



~~**OLE=open label extension;**~~ Q4W=every 4 weeks; SFU=Safety Follow-Up

Change #5

Section 14.4.1 Safety analyses

TEAEs 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 +140 days (covering the 20-week SFU period). To allow for a fair comparison across all subjects, exposure at risk for defining treatment-emergence will be cut off at the Week 12 visit (for subjects who complete through the Week 12 visit) or at 20 weeks (140 days) after the first administration of study treatment (for subjects who discontinue prior to the Week 12 visit). Adverse events that emerge following the 12-week treatment period will be summarized separately.

Has been changed to

TEAEs 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 +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 12-week treatment period** will be cut off at the Week 12 visit (for subjects who complete through the Week 12 visit) or at ~~**20**~~**12** weeks (~~**140**~~**84** days) after the first administration of study

treatment (for subjects who discontinue prior to the Week 12 visit). Adverse events that emerge following the 12-week treatment period will be summarized separately.

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.

PS0010 Protocol Amendment 2

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	18-Jul-2016 22:51 GMT+020
[redacted]	Clinical Approval	18-Jul-2016 22:56 GMT+020