PROTOCOL PS0009 AMENDMENT 4

A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE COMPARATOR-CONTROLLED, PARALLEL-GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

PHASE 3

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SERIOUS ADVERSE EVENT REPORTING

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AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMS	Active Medication Set
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
BA	bioavailability
BP	blood pressure
BSA	body surface area
cAMP	cyclic adenosine monophosphate
CDC	Centers for Disease Control
CDMS	clinical data management system
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPM	Clinical Project Manager
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report Form
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
ePRO	electronic patient-reported outcome
EQ-5D-3L	Euro-Quality of Life 5-Dimensions, 3 levels
FAS	Full Analysis Set
GCP	Good Clinical Practice

GI	gastrointestinal
GMP	Good Manufacturing Practices
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBcAb	anti-hepatitis B core antibody
HBsAg	anti-hepatitis B surface antigen
HCP	healthcare practitioner
HCV	hepatitis C virus
HCV Ab	hepatitis C antibody
HIV	human immunodeficiency virus
HLT	High Level Term
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGA	Investigator's Global Assessment
IGRA	interferon-gamma release assay
IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
iv	intravenous
LOCF	last observation carried forward
LTB	latent tuberculosis
LTBI	latent tuberculosis infection
mAb	monoclonal antibody
MAR	missing at random
MCMC	Markov-Chain Monte Carlo
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation

mNAPSI	Modified Nail Psoriasis Severity Index Score
NRI	Nonresponder imputation
NSAID	non-steroidal anti-inflammatory drugs
NTMB	nontuberculous mycobacterium
PASE	Psoriatic Arthritis Screening and Evaluation
PASI	Psoriasis Area Severity Index
PCS	Physical Component Summary
PD	pharmacodynamics
PDE4	phosphodiesterase 4
PDILI	potential drug-induced liver injury
PEOT	Premature End of Treatment
PFS	prefilled syringe
PGADA	Patient's Global Assessment of Disease Activity
PHQ-9	Patient Health Questionnaire
PK	pharmacokinetics
PK-PPS	Pharmacokinetics Per-Protocol Set
pp-IGA	palmoplantar Investigator's Global Assessment
PPS	Per-Protocol Set
PRO	patient-reported outcome
PS	Patient Safety
PsA	psoriatic arthritis
PSO	psoriasis
Q4W	every 4 weeks
QOL	quality of life
RS	Randomized Set
SAE	serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
scalp IGA	scalp-specific IGA
SD	standard deviation
SF-36	Short Form 36-item Health Survey
SFU	Safety Follow-Up

SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
ULN	upper limit of normal
VAS	visual analog scale
WBC	white blood cell
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire-specific health problem

1 SUMMARY

This is a Phase 3, multicenter, randomized, double-blind, placebo- and active comparator-controlled, parallel-group, study to evaluate the efficacy, safety, and pharmacokinetics (PK) of bimekizumab compared with placebo and ustekinumab in adult subjects with moderate to severe chronic plaque psoriasis (PSO).

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

Approximately 750 subjects will be screened in order to have 560 subjects randomized in the study. For each subject, the study will last a maximum of 73 weeks and will consist of 4 periods, a Screening Period (2 to 5 weeks), a double-blind, placebo- and active comparator-controlled Initial Treatment Period (16 weeks), a double-blind, active comparator-controlled Maintenance Treatment Period (36 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the final dose of investigational medicinal product (IMP). After the 36-week Maintenance Treatment Period, eligible subjects will be allowed to enroll in an open-label study.

Eligible subjects will be randomized 4:2:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered subcutaneously (sc) every 4 weeks (Q4W)
- Ustekinumab (45mg or 90mg, depending on subject weight) administered sc at Baseline and 4 weeks later, followed by ustekinumab sc every 12 weeks
- Placebo administered sc Q4W for 16 weeks during the Initial Treatment Period, followed by bimekizumab 320mg administered sc Q4W during the Maintenance Treatment Period

Approximately 320 subjects will be randomized to bimekizumab 320mg, 160 subjects will be randomized to ustekinumab, and approximately 80 subjects will be randomized to placebo. Investigational medicinal product will be administered in the clinic at Baseline and Q4W thereafter, until Week 16 (Initial Treatment Period). Additional nondosing study visits will occur at Week 1 and Week 2. At Week 16, subjects will enter the Maintenance Treatment Period. The Maintenance Treatment Period will include Q4W dosing for subjects receiving bimekizumab and Q12W dosing for subjects receiving ustekinumab.

At Week 52, all subjects enrolling in the open-label study will undergo the Week 52 study assessments before receiving their first treatment dose in the open-label study. All subjects not enrolling in the open-label study will have the Week 52 study assessments and will enter the SFU Period.

Subjects withdrawing early from the study will undergo the Premature End of Treatment (PEOT) Visit assessments and will enter the SFU Period.

The primary objective of the study is to compare the efficacy of bimekizumab administered sc for 16 weeks versus placebo in the treatment of subjects with moderate to severe chronic plaque PSO. The secondary objectives of the study are listed in Section 3.2.

The co-primary efficacy variables are the PASI90 response (defined as a subject that achieves 90% reduction from Baseline in the PASI score) at Week 16 and the IGA response (defined as Clear or Almost Clear with at least a 2-category improvement relative to Baseline) at Week 16. The secondary efficacy variables are listed in Section 4.2.

Pharmacokinetic variables are listed in Section 4.3.3. Pharmacogenomic variables are listed in Section 4.3.4. Immunological variables are listed in Section 4.3.5.

Pharmacokinetic, 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 PSO is not fully understood, the importance of T-cells and inflammatory cytokines has been demonstrated by the clinical benefit provided by therapies directed at these targets (Krueger and Ellis, 2005).

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

In addition to the impact on skin, PSO 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 PSO, especially with more severe PSO. Psoriatic arthritis (PsA), cardiovascular (CV) disease, metabolic syndrome, chronic pulmonary disease, peptic ulcer disease, renal disease, and diabetes have all been demonstrated to have an increased prevalence in PSO 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 US adult 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 PSO 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 PSO. Plaque PSO is the most common form of the disease therefore reported estimates of the magnitude of this condition are likely weighted heavily by this subtype. Both the incidence and prevalence of PSO 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 PSO 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 phototherapy, methotrexate, cyclosporine, the oral phosphodiesterase 4 (PDE4) inhibitor apremilast, or biologic agents, such as tumor necrosis factor (TNF) antagonists, interleukin (IL) 12/23 inhibitors, IL-23p19 inhibitors and IL-17A inhibitors. The effectiveness of TNF inhibitors in the treatment of PSO 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 PSO. Interleukin inhibitors approved for this indication include the IL-12/23 antagonist ustekinumab, the IL-23p19 antagonist guselkumab, the IL-17A inhibitors secukinumab and ixekizumab, and the IL-17 receptor antagonist brodalumab.

Standard therapies for PSO are listed below:

- Topical steroids (eg, triamcinolone, mometasone, clobetasol, betamethasone, hydrocortisone) are generally used as first-line treatment of PSO. 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 PSO, and work best within the mild patients. They are safe but lack efficacy for more severe disease.
- Phototherapy 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 PSO patients. Toxicity concerns, particularly in older patients, are a major drawback.
- Cyclosporine is a systemic immunosuppressant used in patients with severe, recalcitrant, PSO who have failed at least one systemic therapy or in whom other systemic therapies are contraindicated. In recommended dosages cyclosporine can cause systemic hypertension and nephrotoxicity, therefore, renal function must be monitored during therapy.
- Apremilast is an oral small-molecule inhibitor of PDE4 that is also approved for treatment of adults with moderate to severe plaque PSO. Phosphodiesterase 4 inhibitors work intracellularly to modulate a network of proinflammatory and anti-inflammatory mediators. Phosphodiesterase 4 is a cyclic adenosine monophosphate (cAMP)-specific PDE and the dominant PDE in inflammatory cells. Phosphodiesterase 4 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), the IL-23p19 antagonist (guselkumab), the IL-17A

inhibitors (secukinumab and ixekizumab), and the IL-17 receptor antagonist brodalumab are the treatment options of choice for patients with moderate to severe plaque PSO who are candidates for systemic therapy or phototherapy. These products are injected sc or delivered via intravenous (iv) infusion. 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.

- TNFα inhibitors, while effective, 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 PSO is attributed to their inhibition of Th17-T cells.
- Ustekinumab has been approved in the US and the EU for the treatment of patients with moderate to severe plaque PSO who are candidates for phototherapy or systemic therapy. Ustekinumab is a human immunoglobulin (Ig) G1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines, naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation.
- Secukinumab and ixekizumab have been approved in the US and the EU for the treatment of moderate to severe plaque PSO in adult patients who are candidates for systemic therapy or phototherapy. Secukinumab is a human IgG1 monoclonal antibody that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. Ixekizumab is a humanized IgG4 monoclonal antibody that selectively binds with the interleukin 17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Both drugs inhibit the release of proinflammatory cytokines and chemokines.
- Guselkumab has been approved in the US and EU for the treatment of adult patients with moderate to severe plaque PSO who are candidates for systemic therapy or phototherapy. It is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.
- Brodalumab has been approved in the US for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. In the EU, brodalumab is indicated for the treatment of moderate to severe plaque PSO in adult patients who are candidates for systemic therapy. Brodalumab is a human monoclonal IgG2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25. Blocking IL-17RA inhibits IL-17 cytokine-induced responses including the release of proinflammatory cytokines and chemokines. Brodalumab has a black box warning regarding suicidal ideation and behavior.

2.2 Bimekizumab

Bimekizumab (UCB4940) is an engineered, humanized full length monoclonal antibody (mAb) of immunoglobulin (Ig) G1 subclass of approximately 150,000 Daltons which is expressed in a genetically engineered Chinese hamster ovary cell line. Bimekizumab has high affinity for human IL-17A and human IL-17F and selectively and potently inhibits the activity of both isoforms in vitro. Interleukin-17A and IL-17F are key proinflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases. Bimekizumab is being developed for the treatment of patients with inflammatory diseases such as PsA, PSO, and axial spondyloarthritis (axSpA).

While anti-IL-17A antibodies have demonstrated efficacy in patients with PSO, PsA, and ankylosing spondylitis, as yet, no therapeutic approach selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro. Bimekizumab is an engineered, humanized, full-length IgG1 mAb which has been designed to inhibit the activity of IL-17A and IL-17F subtypes of IL-17. This property makes bimekizumab distinct from the other IL-17-targeting agents, like secukinumab and ixekizumab (selective anti-IL-17-A mAb), or brodalumab (anti-IL-17 receptor mAb).

Overexpression of IL-17A, IL-17C, and IL-17F in lesion tissue suggests that broader IL-17 blockade may be more beneficial in the treatment of plaque PSO. However, blocking all IL-17 isoforms (including the IL-17E isoform, also known as IL-25) may not be the optimal approach. The role of IL-25 in PSO and other IL-17 mediated diseases has not been well established, however it has been suggested that IL-25 may play a beneficial role in inflammatory conditions associated with type 1 T helper (Th-1) mediated immune responses, such as PSO (as opposed to type 2 T helper (Th-2) mediated) (Valizadeh et al, 2015). Thus, it can be hypothesized that inhibition of both IL-17A and IL-17F is associated with additional benefits in PSO compared to the selective IL-17A inhibition or a broader IL-17 blockade.

2.2.1 Clinical

2.2.1.1 Completed studies

Five clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, UP0031 in 12 healthy volunteers, and UP0042 in 48 healthy volunteers.

UP0008 was a Phase 1, single ascending dose study in adults with mild to moderate PSO 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 PSO 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 (BA) 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 BA 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 PsA. 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 IMP. The exploratory analysis showed clinically relevant improvement in activity of PsA and in skin involvement in those subjects with concomitant active psoriatic lesions.

UP0031 was a Phase 1, open-label, parallel-group, randomized, single-dose study to evaluate the BA, PK, and tolerability of 2 different formulations of bimekizumab in healthy subjects. Subjects receiving Formulation A ([redacted]) were administered two 1mL injections of 80mg each of bimekizumab and subjects receiving Formulation B [redacted]) were administered a single injection of bimekizumab 160mg given as a 1mL injection. Six subjects were randomized to each bimekizumab formulation. The geometric means (GeoMeans) for area under the curve were similar between bimekizumab 2x80mg and 1x160mg groups and the relative BA for Formulation B vs Formulation A was 96.1% (95% confidence interval [CI]: 72.7%, 127.0%). Administration of the 2 formulations of bimekizumab used in this study identified no new safety issues. There were no treatment-emergent adverse events (TEAEs) leading to discontinuation, and no serious adverse events (SAEs) or fatalities were reported. The only preferred term experienced by more than 1 subject in either treatment group was injection site pain (5 subjects [83.3%] and 3 subjects [50%] in the 2x80mg and 1x160mg groups, respectively). The most frequently reported TEAE considered related to the IMP was injection site pain, experienced by 5 subjects [83.3%] and 3 subjects [50.0%] in the 2x80mg and 1x160mg groups, respectively. There were no clinically significant laboratory values reported in the study.

UP0042 was a randomized double-blind, placebo-controlled, single-dose, parallel-group study to evaluate the safety, tolerability, and PK of bimekizumab administered as an sc injection to Japanese and Caucasian healthy subjects. This study demonstrated that the PK profiles following single administration of 80mg, 160mg, and 320mg with an sc injection were dose proportional with a linear elimination in both Japanese and Caucasian subjects and that the PK profiles of Japanese and Caucasian subjects were considered to be generally similar. A single dose of bimekizumab (80mg, 160mg, or 320mg) administered as an sc injection was generally safe and well tolerated in healthy Japanese and Caucasian subjects and no major differences in safety findings were observed between Japanese and Caucasian subjects.

2.2.1.2 Ongoing studies

Four additional studies of bimekizumab in the treatment of PSO are ongoing**.**

- PS0010 is a Phase 2b, double-blind, placebo-controlled, dose ranging study to evaluate the safety, efficacy, PK, and pharmacodynamics (PD) of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PS0011 is a long-term extension study for subjects who completed PS0010 to assess the long-term safety, tolerability, and efficacy of bimekizumab.
- PS0016 is a Phase 2a, subject-blind, investigator-blind study to evaluate the time course of PD response, safety, and PK of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PS0018 is a long-term extension study for eligible subjects from PS0016 to assess the safety, tolerability, and efficacy of bimekizumab.

Bimekizumab is also being evaluated in the treatment of other indications (eg, PsA, axSpA, hidradenitis suppurativa). 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 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 OBJECTIVE(S)

3.1 Primary objective

The primary objective of the study is to compare the efficacy of bimekizumab administered sc for 16 weeks versus placebo in the treatment of subjects with moderate to severe chronic plaque PSO.

3.2 Secondary objectives

The secondary objectives of the study are to:

- Evaluate the efficacy of bimekizumab compared to placebo at achieving complete clearance (PASI100) after 16 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to placebo after 4 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to ustekinumab after 4 weeks, 12 weeks, 16 weeks, and 52 weeks of treatment
- Evaluate the change in itch, pain, and scaling of bimekizumab compared to placebo after 16 weeks of treatment as reported by subjects using the Patient Symptom Diary
- Evaluate the change in psoriatic scalp disease of bimekizumab compared to placebo after 16 weeks of treatment in subjects with scalp PSO at Baseline
- Assess TEAEs, SAEs, and TEAEs leading to withdrawal adjusted by duration of subject exposure to study treatment

3.3 Other objectives

The other objectives of the study are to demonstrate the effects of bimekizumab on aspects of the disease:

- Assess the efficacy of bimekizumab over time
- Assess the change of skin-related quality of life (QOL)
- Assess the change of general health-related QOL
- Assess the change in nail PSO over time in subjects with nail PSO at Baseline
- Assess the change in scalp PSO over time in subjects with scalp PSO at Baseline
- Assess the change in palmoplantar PSO over time in subjects with palmoplantar PSO at Baseline
- Assess the change in physical function (as measured by the Health Assessment Questionnaire-Disability Index [HAQ-DI]) over time in subjects with PsA at Baseline
- Assess the symptoms of PsA as measured by the Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire
- Assess the change of patient-reported joint symptoms in subjects with PsA at Baseline

- Assess the change in symptoms of PSO as reported by subjects using the Patient Symptom Diary (all items) through Week 16
- Assess depression
- Assess the PK of bimekizumab
- Assess the immunogenicity of bimekizumab
- Assess work productivity
- Assess the effect of bimekizumab on gene and protein expression, and explore the relationship between genomic, genetic, and proteomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (from consenting subjects who agree to participate in the biomarker substudy)
- Assess the safety and tolerability of bimekizumab

4 STUDY VARIABLES

4.1 Primary efficacy variables

The co-primary efficacy variables are the PASI90 response (defined as a subject that achieves 90% reduction from Baseline in the PASI score) at Week 16 and the IGA response (defined as Clear or Almost Clear with at least a 2-category improvement relative to Baseline) at Week 16.

4.2 Secondary variables

4.2.1 Secondary efficacy variables

The secondary efficacy variables are:

- PASI100 response at Week 16
- PASI75 response at Week 4
- Patient Symptom Diary responses for itch, pain, and scaling at Week 16
- Scalp IGA response (Clear or Almost Clear with at least a 2-category improvement from Baseline) at Week 16 for subjects with scalp PSO at Baseline
- PASI90 response at Week 12 and 52
- IGA response at Week 12 and 52

4.2.2 Secondary safety variables

- TEAEs adjusted by duration of subject exposure to study treatment
- SAEs adjusted by duration of subject exposure to study treatment
- TEAEs leading to withdrawal adjusted by duration of subject exposure to study treatment

4.3 Other variables

The other variables are listed below and will be evaluated according to the planned assessments (Table 5–1).

4.3.1 Other efficacy variable(s)

The other efficacy variables are listed below and will be evaluated according to the planned assessments (Table 5–1). This excludes the timepoints for the primary and secondary variables specified above in Section 4.1 and Section 4.2.1, respectively.

Change from Baseline variables evaluated during the Initial Treatment Period are relative to the Baseline (first dose) Visit. For subjects who switch treatment at the Week 16 Visit, change from Baseline variables during the Maintenance Treatment Period may be evaluated relative to both the Baseline (first dose) Visit and the Week 16 Visit.

For simplicity, "change from Baseline" is used below for all such variables. Greater detail on the definition of Baseline for different summaries will be provided in the Statistical Analysis Plan (SAP). Unless otherwise stated PASI responders will be calculated relative to the Baseline Visit (first dose).

The other efficacy variables are:

- PASI50, PASI75, PASI90, and PASI100 response
- Time to PASI75, PASI90, and PASI100 response during the Initial Period
- Absolute and percent change from Baseline in PASI score
- IGA response (Clear with at least a 2-category improvement from Baseline)
- IGA response (Clear or Almost Clear with at least 2 category improvement relative to Baseline)
- Shift from Baseline in IGA score
- Absolute and percent change from Baseline in the BSA affected by PSO
- Absolute and percent change from Baseline in the product of IGA and BSA (IGAxBSA)
- Change from Baseline in Dermatology Life Quality Index (DLQI)
- Percent of subjects achieving a DLQI total score of 0 or 1
- Percent of subjects achieving a minimal clinically important difference (improvement from Baseline of 4 or more) in the DLQI
- Change from Baseline in the Patient's Global Assessment of Disease Activity (PGADA) for the arthritis visual analog scale (VAS) in subjects with PsA at Baseline
- Change from Baseline in Patient Global Assessment of PSO score
- Patient Symptom Diary responses
- Scalp-specific Investigator's Global Assessment (scalp IGA) response (Clear or Almost Clear with at least a 2-category improvement from Baseline) for subjects with scalp PSO at Baseline
- Change from Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) score for subjects with nail PSO at Baseline

- Palmoplantar Investigator's Global Assessment (pp-IGA) response (Clear or Almost Clear) for subjects with palmoplantar PSO at Baseline
- Change from Baseline in the HAQ-DI for subjects with PsA at Baseline
- Change from Baseline in the PASE questionnaire scores (function score, symptom score, and total score)
- Shift from Baseline in PASE score suggestive of PsA (<47 versus ≥47)
- 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
- Responses to Euro-Quality of Life 5-Dimensions, 3 levels (EQ-5D-3L), absolute and changes from Baseline in EQ-5D-3L VAS scores
- Change from baseline in Patient Health Questionnaire (PHQ)-9 scores
- Change from Baseline in Work Productivity and Activity Impairment Questionnaire-specific health problem (WPAI-SHP) V2.0 adapted to PSO scores

4.3.2 Other safety variables

Safety variables to be assessed are:

- Severity and frequency of AEs
- Change from Baseline in vital signs
- ECG results
- Change from Baseline in clinical laboratory values (chemistry, hematology, and urinalysis)

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

4.3.3 Pharmacokinetic variable

The PK variable is the plasma concentration of bimekizumab.

4.3.4 Pharmacogenomic variables

Additional blood samples will be collected from subjects who consent to participate in the substudy at specific time points and stored at -80°C for up to 20 years.

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

The candidate exploratory variables are the blood or blood derivative (eg, serum) concentrations of cytokines and chemokines of relevance to IL-17A/F signaling pathway and PSO biology. Additional variables may include but will not be limited to serum complement concentrations.

4.3.5 Immunological variable

The immunological variable is the anti bimekizumab antibody level prior to and following IMP.

5 STUDY DESIGN

5.1 Study description

PS0009 is a randomized, double-blind, placebo- and active comparator-controlled study to evaluate the efficacy and safety of bimekizumab administered sc to subjects with PSO. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe plaque PSO (PASI ≥12 and BSA ≥10% and IGA score ≥3 [on a 5-point scale]) who are a candidate for ustekinumab, or for systemic PSO therapy and/or phototherapy. Subjects may have been previously exposed to a biologic therapy (see Exclusion Criterion #23).

5.2 Study periods

This study will include 4 periods, a Screening Period (2 to 5 weeks), an Initial Treatment Period (16 weeks), a Maintenance Treatment Period (36 weeks), and a SFU Period (20 weeks after the final dose of IMP). After completion of the Maintenance Treatment Period, eligible subjects will be allowed to enroll in an open-label study. Subjects enrolling into the open-label study will not have the PS0009 SFU Visit.

5.2.1 Screening Period

The Screening Period will last 2 weeks, but can be extended up to a total of 5 weeks in cases where a laboratory assessment needs to be repeated or to allow washout of prohibited medications. During this time, eligible subjects will be informed about the study and sign the Informed Consent Form (ICF), laboratory data (hematology, urine, and biochemistry tests) will be obtained, and the doses of medications used to treat PsA, will be verified as stable. The Screening Period will also enable washout of any medications not permitted for use during the study. Subjects who require prophylaxis for latent tuberculosis (LTB) infection must be on treatment for at least 8 weeks prior to their first dose of IMP. These subjects may be rescreened once they have completed the first 8 weeks of prophylaxis treatment.

One rescreening may be allowed after consultation with the Medical Monitor.

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

5.2.2 Initial Treatment Period

During the 16-week Initial Treatment Period, approximately 560 subjects will be randomized 4:2:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered sc Q4W (320 subjects)
- Ustekinumab (160 subjects):
  - For subjects weighing ≤100kg (220lbs) at Baseline, 45mg sc initially and 4 weeks later
  - For subjects weighing >100kg (220lbs) at Baseline, 90mg sc initially and 4 weeks later
- Placebo administered sc Q4W (80 subjects)

Investigational medicinal product will be administered in the clinic by sc injection at the time points specified in the schedule of assessments (Table 5–1).

Subjects withdrawing early from the study will undergo the PEOT Visit assessments and will enter the SFU Period. Subjects withdrawing early from the study will not be eligible for inclusion in the open-label study.

Subjects will be followed in a double-blind fashion. Subjects may receive placebo injections at certain visits in order to blind the IMP.

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

5.2.3 Maintenance Treatment Period

After the 16-week Initial Treatment Period, subjects will enter the 36-week Maintenance Treatment Period. The Maintenance Treatment Period will start at Week 16 and subjects will return to the clinic Q4W through Week 52.

Treatment during the Maintenance Treatment Period will be based on initial treatment, per the following rules:

- Subjects in the bimekizumab 320mg treatment arm will continue to receive bimekizumab 320mg Q4W.
- Subjects in the ustekinumab treatment arm will continue on ustekinumab (subjects weighing ≤100kg [220lbs] at Baseline will receive 45mg sc every 12 weeks; subjects weighing >100kg [220lbs] at Baseline will receive 90mg sc every 12 weeks).
- Subjects in the placebo arm will receive bimekizumab 320mg Q4W.

Subjects may receive placebo injections at certain visits in order to blind the IMP (see Section 7.2).

At the end of the Maintenance Treatment Period, all subjects enrolling in the open-label study will, after signing a new ICF, undergo the Week 52 study assessments and then receive their first dose of bimekizumab in the open-label study. All subjects not enrolling in the open-label study will have the Week 52 study assessments and will enter the SFU Period.

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

5.2.4 Safety Follow-Up

All subjects not continuing in the open-label study, including those withdrawn from IMP, will have a SFU Visit 20 weeks after their final dose of IMP.

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

5.2.5 Premature End of Treatment

Subjects withdrawing early from the study will undergo PEOT Visit assessments (see Section 8.4) and will enter the SFU Period.

5.3 Study duration per subject

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

- Screening Period: 2 to 5 weeks
- Double-blind, placebo- and active comparator-controlled Initial Treatment Period: 16 weeks

- Double-blind, active comparator-controlled Maintenance Treatment Period: 36 weeks
- Safety Follow-Up Period: a SFU Visit is planned 20 weeks after the final dose of IMP (for subjects not enrolling in the open-label study)

After the 36-week Maintenance Treatment Period, subjects will be allowed to enroll in an open-label study, in which case subjects will undergo the Week 52 study assessments before receiving their first open-label IMP dose. The SFU Visit will not be required for subjects who enroll in the open-label study.

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

5.4 Planned number of subjects and site(s)

Approximately 750 subjects will be screened in order to have 560 subjects randomized in the study. There will be approximately 320 subjects in the bimekizumab 320mg treatment arm, 160 subjects in the ustekinumab treatment arm, and 80 subjects in the placebo treatment arm. The planned number of study sites is approximately 100. Every eligible subject who signs an ICF will be randomized.

5.5 Anticipated regions and countries

The regions planned for study conduct are North America, Western Europe, Central/Eastern Europe, and Asia/Australia, with possible extension to other regions and countries.

5.6 Schedule of study assessments

The schedule of study assessments is presented in Table 5–1. At each visit, all study assessments should be performed prior to administration of IMP.

Table 5–1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Informed consent[c]	X															X[d]		
Inclusion/exclusion	X	X																
Urine drug screen	X																X	
Demographic data	X																	
Psoriasis history	X																	
Significant past medical history and concomitant diseases	X	X[e]																
Physical exam[f, g]	X	X					X			X			X				X	X
Height		X																
Body weight		X					X			X			X				X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X	X	X	X	X	X	X	X	X	X		X		X		X	X	X
Urinalysis	X	X						X		X		X		X		X	X	X
ECG	X						X					X					X	
Pregnancy testing[i]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing[j]	X																	
HIV testing[k]	X																	
Chest x-ray[l]	X																	

Table 5–1: Schedule of study assessments

Protocol activity / Visit[a] / Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
IGRA Tuberculosis test	X															X		
Tuberculosis questionnaire	X	X					X			X			X				X	X
Blood sample for bimekizumab plasma concentrations[m]		X	X	X	X	X	X	X			X			X			X	X
Blood sample for anti-bimekizumab antibodies[m]		X			X	X	X	X			X			X			X	X
Blood sample genomic, proteomic, metabolomics, and candidate biomarker analyses[c,m]		X	X			X	X	X									X	
Blood sample genetic/epigenetic analysis[c,m]		X															X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Percentage of BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X			X			X			X	
PHQ-9	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (daily)	X	X	X	X	X	X	X	X										
scalp IGA		X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X[n]			X[n]			X[n]	
mNAPSI		X			X[o]	X[o]	X[o]	X[o]			X[o]			X[o]			X[o]	

Table 5–1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
pp-IGA		X			X[p]	X[p]	X[p]	X[p]			X[p]			X[p]			X[p]	
EQ-5D-3L		X			X	X	X	X			X			X			X	
SF-36		X			X	X	X	X			X			X			X	
Patient Global Assessment of psoriasis[q]											X			X			X	
PASE		X															X	
PGADA[r]		X			X		X	X			X			X			X	
HAQ-DI[r]		X			X	X	X	X			X			X			X	
WPAI-SHP V2.0		X						X		X				X			X	
Photographs of skin and nails (subset of sites)		X	X	X	X	X	X	X			X			X			X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT[s,t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bimekizumab, ustekinumab, or placebo administration[s,t]		X			X	X	X	X	X	X	X	X	X	X	X	X		

Table 5–1: Schedule of study assessments

Protocol activity / Visit[a] / Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	

BSA=body surface area; CV=cardiovascular; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; eCRF=electronic Case Report Form; EQ-5D-3L=Euro-Quality of Life 5-Dimensions 3-level; GI=gastrointestinal; HAQ-DI=Health Assessment Questionnaire-Disability Index; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=Informed Consent Form; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; mNAPSI=Modified Nail Psoriasis Severity Index Score; PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area Severity Index; PEOT=Premature End of Treatment; PGADA=Patient's Global Assessment of Disease Activity; PHQ-9=Patient Health Questionnaire 9; pp-IGA=palmoplantar Investigator's Global Assessment; PsA=psoriatic arthritis; SF-36=Short Form 36-item Health Survey; SFU=Safety Follow-Up; scalp IGA=scalp-specific Investigator's Global Assessment; TB=tuberculosis; WPAI-SHP=Work Productivity and Activity Impairment Questionnaire-specific health problem

[a] Visit windows of ±3 days from the first dose to the Week 24 visit. Visit windows of ±7 days from the Week 28 visit to the Week 52 visit. The SFU Visit window is ±7 days from last dose.

[b] The SFU Visit will occur 20 weeks after the final dosefor subjects who do not enroll in the open-label study.

[c] All genomic, proteomic, and metabolomics samples will be stored at -80°C at the central biorepository for up to 20 years.

[d] A separate ICF is required to be completed for the open-label study.

[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] The physical examination will be performed as per Section 12.3.5.

[h] Vital signs (sitting systolic and diastolic blood pressure, pulse rate, and body temperature) are to be measured prior to blood sampling, and prior to dosing, where applicable.

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

[j] Subjects who have evidence of or test positive for hepatitis B by any of the following criteria: 1) positive for hepatitis B surface antigen (HBsAg+); 2) positive for anti-hepatitis B core antibody (HBcAb+) 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.

[k] The HIV test results will not be recorded in the eCRF.

[l] Screening chest x-ray must occur within 3 months prior to Screening Visit.

[m] All blood samples taken prior to dosing.

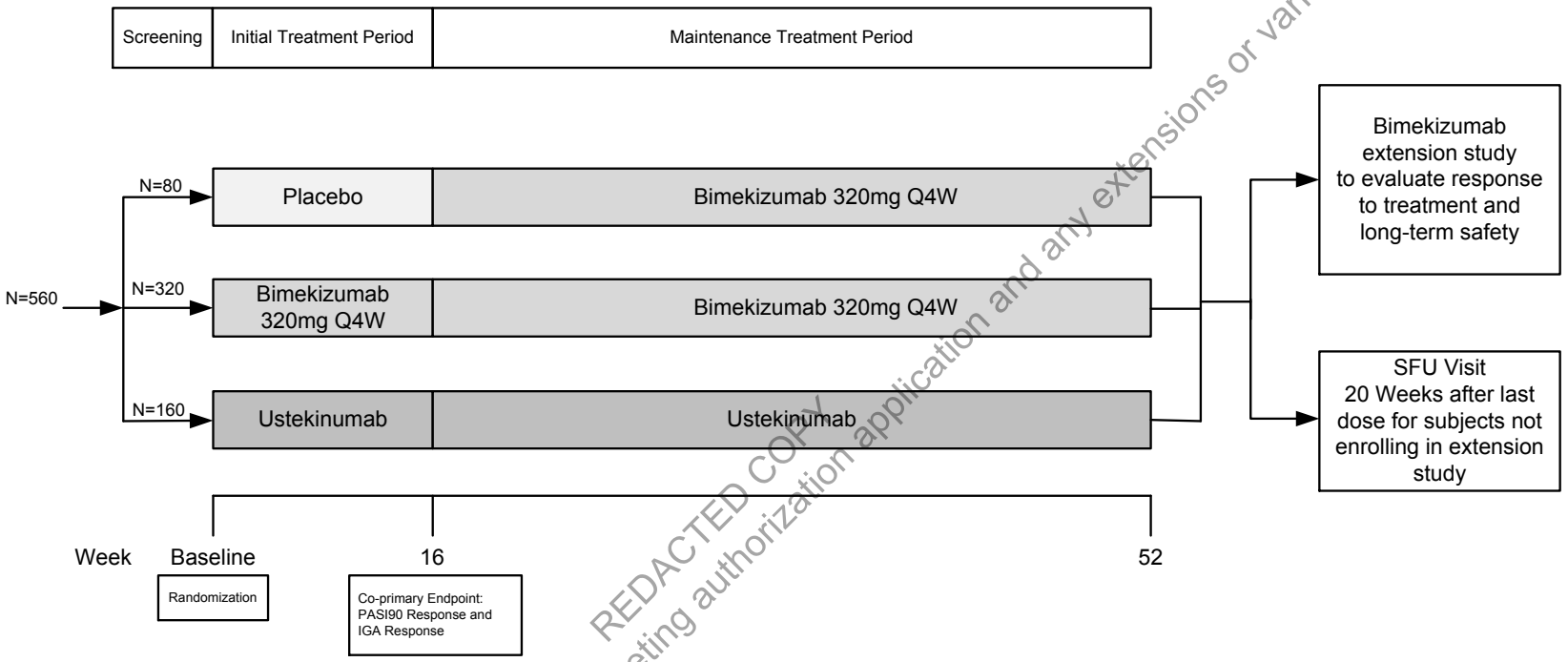
[n] The scalp IGA will only be assessed for those subjects with scalp involvement (scalp IGA score >0) at Baseline.

[o] The mNAPSI will be assessed only in subjects with nail involvement (mNAPSI score >0) at Baseline.
[p] The pp-IGA will only be assessed in subjects with palmoplantar involvement (pp-IGA score >0) at Baseline.
[q] The Patient Global Assessment of psoriasis will be performed as part of the patient symptoms diary on a weekly basis from baseline through the initial treatment period. During the Maintenance Treatment Period this assessment will be completed at the specified clinic visits.
[r] The PGADA and HAQ-DI are assessed for all subjects at Baseline. At all subsequent visits, the PGADA and HAQ-DI are assessed only for subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47).
[s] IMP administration is based on randomization.
[t] The dosing window is ±3 days relative to the scheduled dosing visit through Week 24. The dosing window is ±7 days from Week 28 through the end of the study.

5.7 Schematic diagram

The study schematic diagram for PS0009 is presented in Figure 5–1.

Figure 5–1: Schematic diagram



IGA=Investigator's Global Assessment; N=number; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks; SFU=Safety Follow-Up
Note: At Week 24 and all following visits, subjects on continuous treatment with the same IMP for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period are defined as nonresponders and should discontinue IMP.

5.8 Rationale for study design and selection of dose

5.8.1 Study design

A randomized, double-blind, placebo- and active-controlled study design has been selected to demonstrate efficacy and safety of bimkeizumab for regulatory approval. The study population will include adults with moderate to severe chronic plaque PSO and allow subjects who have received previous biologic treatment as well as those who are biologic treatment naïve. The primary efficacy outcome measures (based on PASI and IGA) and other efficacy assessments included in this study are consistent with those used for other PSO studies and are considered appropriate for establishing efficacy of bimekizumab. An initial treatment period of 16 weeks will be used to demonstrate the efficacy of bimekizumab over PBO and ustekinumab. The study duration extends beyond the initial treatment period (to 52 weeks) to collect information on dosing beyond initial treatment.

5.8.2 Dose selection

Bimekizumab doses ranging from 64mg to 480mg were evaluated in the Phase 2b multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study PS0010. Bimekizumab 320mg was found to have an acceptable safety profile, only required 2 injections per treatment administration, and achieved significant PASI responses at Week 12 (summarized in the IB). Furthermore, data from the Phase 2a multicenter, randomized, subject-blind, investigator-blind study PS0016 and PK/PD modeling in this PSO population indicates improved responses through Week 16. Therefore, a bimekizumab dose of 320mg Q4W was selected for this study.

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 at the Baseline Visit:

1. Subject has provided informed consent.
2. 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 PSO for at least 6 months prior to the Screening Visit.
5. PASI ≥12 and BSA affected by PSO ≥10% and IGA score ≥3 on a 5-point scale.

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

7. Subject must be considered, in the opinion of the Investigator, to be a suitable candidate for treatment with ustekinumab per regional labeling and has no contraindications to receive ustekinumab as per the local label.
8. Female subjects must be:
   - Postmenopausal: Menopause is defined as 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause.

- Permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy)
- Or, if of childbearing potential (and engaged in sexual activity that could result in procreation), must be willing to use a highly effective method of contraception throughout the duration of the study until 20 weeks after last administration of IMP, and have a negative pregnancy test at 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
  - Intrauterine hormone-releasing system
  - Vasectomised partner
  - Abstinence as a form of birth control is generally not allowed in the study unless abstinence is in accordance with a subject's preferred and common lifestyle. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.

9. Subject agrees not to change their usual sun exposure during the course of the study and to use ultraviolet A/ultraviolet B sunscreens if unavoidable exposure occurs.

6.2 Exclusion criteria

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

1. Female subject who is breastfeeding, pregnant, or plans to become pregnant during the study or within 20 weeks following the final dose of IMP.
2. Subject previously participated in a bimekizumab clinical study who received at least 1 dose of the IMP (including placebo).

3a. Subject is currently participating in another study of a medication (systemic) under investigation. Subject must be washed out of the medication for 12 weeks or at least 5 half-lives prior to the Baseline Visit, whichever is greater.

4a. Subject is currently participating in another study of a topical medication under investigation. Subject must be washed out of the medication for 4 weeks prior to the Baseline Visit.

5a. Subject is currently, or was within the 4 weeks prior to the Baseline Visit, participating in another study of a medical device under investigation.

6. Subject has a known hypersensitivity to any excipients of bimekizumab or ustekinumab.
7. Subject has a form of PSO other than chronic plaque-type (eg, pustular, erythrodermic and guttate PSO, or drug-induced PSO).
8. Subject has an active infection or history of infection(s) as follows:

- Any active infection (except common cold) within 14 days prior to Baseline
- A serious infection, defined as requiring hospitalization or iv anti-infective(s) within 2 months prior to the Baseline Visit
- A history of opportunistic, recurrent, or chronic infections that, in the opinion of the Investigator, might cause this study to be detrimental to the subject. Opportunistic infections are infections caused by uncommon pathogens (eg, pneumocystis jirovicii, cryptococcosis) or unusually severe infections caused by common pathogens (eg, cytomegalovirus, herpes zoster)

9. Subject has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Subjects who have evidence of, or tested positive for hepatitis B or hepatitis C are excluded. A positive test for the hepatitis B virus is defined as: 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).
10. Subject has received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline visit (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted).
11. Subject has received Bacillus Calmette-Guerin vaccinations within 1 year prior to the Baseline Visit.
12. Subject has known tuberculosis (TB) infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection. A subject with LTB (a positive interferon-gamma release assay [IGRA] and diagnosis confirmed by TB specialist) may be rescreened once and enrolled after receiving at least 8 weeks of appropriate LTB infection therapy and if no evidence of therapy-related hepatotoxicity has occurred prior to the first injection (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] remain ≤3 times the upper limit of normal [ULN]).

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

    Refer to Section 12.3.1 for details on determining full TB exclusion criteria.
13. Subject has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.

14a. Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer.

15. Subject has a diagnosis of inflammatory conditions other than PSO or PsA, 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.

16. Subject has had major surgery (including joint surgery) within the 3 months prior to the Baseline Visit, or has planned major surgery within 6 months after entering the study.

17a. Subject has any systemic disease (ie, cardiovascular, neurological, renal, liver, metabolic, gastrointestinal, hematological, immunological, etc.) considered by the Investigator to be uncontrolled, unstable, or likely to progress to a clinically significant degree during the course of the study.

18. Subject has had myocardial infarction or stroke within the 6 months prior to the Screening Visit.

19. Subject has laboratory abnormalities at Screening, including any of the following:
    a. ≥3.0x ULN of any of the following: ALT, AST, alkaline phosphatase (ALP); or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome).
    b. White blood cell (WBC) count <$3.00x10^3$/µL
    c. Absolute neutrophil count <$1.5x10^3$/µL
    d. Lymphocyte count <500 cells/µL
    e. Hemoglobin <8.5g/dL
    f. Any other laboratory abnormality, which, in the opinion of the Investigator, will prevent the subject from completing the study or will interfere with the interpretation of the study results

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

20. Subject has any other condition, including medical or psychiatric, which, in the Investigator's judgment, would make the subject unsuitable for inclusion in the study.

21. Subject has had previous exposure to ustekinumab.

22. Criterion deleted

23. Subject has experienced primary failure (no response within 12 weeks) to 1 or more IL-17 biologic response modifier (eg, brodalumab, ixekizumab, secukinumab) OR more than 1 biologic response modifier other than an IL-17.

24. Subject is taking PsA medications other than stable doses (ie, stable for at least 1 week prior to the Screening Visit) of nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics (see Section 7.8.1.2).

25. Subject has a history of chronic alcohol or drug abuse within 6 months prior to Screening as evaluated by the Investigator based on medical history, site interview, and/or results of the specified urine drug screen.

26. Presence of active suicidal ideation, or positive suicide behavior using the "Screening" version of the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) and with either of the following criteria:

- History of a suicide attempt within the 5 years prior to the Screening Visit. Subjects with a history of a suicide attempt more than 5 years ago should be evaluated by a mental healthcare practitioner (HCP) before enrolling into the study.
- Suicidal ideation in the past month prior to the Screening Visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the "Screening" version of the eC-SSRS.

27a. Subject has presence of moderately severe major depression or severe major depression, indicated by a score of ≥15 using the screening PHQ-9. Medication used to treat depression should be stable for 8 weeks prior to baseline.

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

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

30. Subject is taking or has taken prohibited psoriasis medications without meeting the mandatory washout period relative to the Baseline Visit (Table 7–2).

6.3 Withdrawal criteria

Subjects are free to withdraw from the study at any time, without prejudice to their continued care. Subjects who withdraw from the study should complete the PEOT Visit (see Section 8.4).

Subjects should be withdrawn from the study and will be encouraged to come back for the SFU Visit 20 weeks after final dose of IMP if the subject withdraws his/her consent or the Sponsor or a regulatory agency requests withdrawal of the subject.

A subject should be withdrawn from IMP and will be asked to come back for the SFU visit 20 weeks after final dose of IMP if any of the following events occur:

1. Subject develops an illness that in the opinion of the Investigator would interfere with his/her continued participation if the risk of continuing IMP outweighs the potential benefit.
2. Subject develops erythrodermic, guttate, or pustular form of PSO.
3. Criterion deleted
4. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
5. 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 or the integrity of the study data, in the opinion of the Investigator and/or the Medical Monitor.
6. Subject has a clinical laboratory value meeting any of the following criteria:
   a. Hepatotoxicity as described in Section 6.3.1
   b. A laboratory value meeting any of the following criteria:
      - Absolute neutrophil count <$1.0x10^3/\mu L$
      - Absolute lymphocyte count <$0.2x10^3/\mu L$

Subjects may remain in the study if the result is transient. A retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat absolute neutrophil count or absolute lymphocyte count is still below the allowable values, the subject must be withdrawn. If the repeat absolute neutrophil count or absolute lymphocyte count is above the allowable values, the subject may continue in the study.

7. The subject experiences a severe AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the Investigator, merits the discontinuation of the investigational product and appropriate measures being taken.
8. At Week 24 and all following visits, subjects on continuous treatment with the same IMP for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period are defined as nonresponders and should discontinue IMP.
9. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test (see Section 12.1.4 for more information regarding pregnancies).
10. A subject considered as having either a suspected new LTB infection or who develops active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by IGRA or other diagnostic means) must be immediately discontinued from IMP and a PEOT Visit must be scheduled as soon as possible, but not later than the next regular visit.

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

    Confirmed active TB is an SAE and must be captured 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 is provided in Section 12.3.1.
11. Subjects with newly diagnosed inflammatory bowel disease (IBD) or with IBD flares during the study must:

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

    If IBD flares increase in severity or frequency during the study, the Investigator should use clinical judgement in deciding whether the subject should continue in the study and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.
12. Subjects **must be referred** immediately to a mental health care professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk for:

    – Active suicidal ideation as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the eC-SSRS.

- Moderately severe major depression as indicated by a PHQ-9 score of 15 to 19 if this represents an increase of 3 points compared to last visit.

13. Subjects must be referred immediately to a mental healthcare professional and must be withdrawn in case of:
    - Active suicidal ideation as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the eC-SSRS
    - Any suicidal behavior since last visit.
    - Severe major depression as indicated by a PHQ-9 score ≥20.

The mental health consultation must be recorded in source documentation.

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

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

6.3.1 Potential drug-induced liver injury IMP discontinuation criteria

Subjects with 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 for subjects with either of the following:

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

The PDILI criterion below requires immediate discontinuation of IMP for:

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

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

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

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

  Evaluation of PDILI must be initiated as described in Section 12.2.1 with repeat tests performed in two weeks. Upon re-test, if ALT or AST values have reduced to <5xULN, the subject can continue with the study. However, if ALT or AST remains ≥5xULN and <8xULN after re-test, IMP should be temporarily withheld and subject should undergo a repeat test in two weeks. If ALT or AST values remain ≥5xULN even after the second re-test, then the subject should be permanently withdrawn from the study and should be followed for possible drug-induced liver injury.

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

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

7 STUDY TREATMENT(S)

7.1 Description of investigational medicinal product(s)

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

- Bimekizumab will be supplied in a [redacted] for sc injection.
- Placebo will be supplied as 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (USP/Ph.Eur) quality in a 1mL PFS for sc injection.
- Ustekinumab is commercially available and will be supplied in a 0.5mL PFS at a concentration of 45mg/0.5mL.

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

7.2 Treatment(s) to be administered

Unblinded study staff will be responsible for preparation of the clinical trial material, including recording the administration information on source documents, and administration of the IMP as sc injections. 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.

Suitable areas for sc injections are the lateral abdominal wall, upper outer thigh, or upper arm. During each dosing visit, each of the injections should be administered at a separate injection site. Injection sites should be rotated at each visit and injections should not be given into a PSO plaque or areas where the skin is tender, bruised, erythematous, or indurated. The injection should last approximately 10 to 15 seconds.

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

Double-blind Initial Treatment Period dosing

Because of differences in the dosing schedule between bimekizumab and ustekinumab, all subjects will receive 2 injections sc Q4W based on the following dosing scheme:

- Subjects randomized to receive placebo will receive 2 placebo injections sc Q4W.
- Subjects randomized to receive bimekizumab 320mg Q4W will receive 2 bimekizumab 160mg injections sc Q4W.
- Subjects randomized to receive ustekinumab will receive ustekinumab sc at Baseline and Week 4, followed by placebo (2 placebo injections sc) at Week 8 and Week 12. Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) at Baseline will receive 1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) at Baseline will receive 2 ustekinumab 45mg sc injections.

Maintenance Treatment Period dosing

Investigational medicinal product treatment during the Maintenance Treatment Period will be based on initial treatment as described in Section 5.2.3.

- Subjects who received bimekizumab or placebo in the Initial Treatment Period will receive 2 bimekizumab 160mg injections sc Q4W.
- Subjects randomized to receive ustekinumab will have received ustekinumab sc at Baseline and Week 4, and will continue to receive ustekinumab sc every 12 weeks (Weeks 16, 28, and 40). Subjects will receive placebo (2 placebo injections sc) on non-ustekinumab treatment weeks (Weeks 20, 24, 32, 36, 44, and 48). Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) at Baseline will receive 1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) at Baseline will receive 2 ustekinumab 45mg sc injections.

The dosing scheme is depicted in Table 7–1.

Table 7–1: Dosing scheme

Week Dose Assignment	Baseline (first dose)	4	8	12	16	20	24	28	32	36	40	44	48
Bimekizumab 320mg Q4W	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●
Ustekinumab 45mg (subjects ≤100kg)	▲○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○
Ustekinumab 90mg (subjects >100kg)	▲▲	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○
Placebo/ bimekizumab 320mg Q4W	○○	○○	○○	○○	●●	●●	●●	●●	●●	●●	●●	●●	●●

Q4W=every 4 weeks

Notes: A bimekizumab 160mg injection is depicted by a black circle (●). A placebo injection is depicted by a white circle (○). A ustekinumab 45mg injection is depicted by a black triangle (▲).

7.3 Packaging

Bimekizumab, ustekinumab, 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

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

7.5 Handling and storage requirements

Refer to the IMP Handling Manual for the storage conditions of the IMP.

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

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

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

The IMP 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, damaged (eg, due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

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

Unblinded study staff will be delegated the responsibility to receive, inventory and destroy the used kits. The packaging identifies each kit by a unique number, but due to the commercial packaging of the comparator, the unblinded study staff will be responsible in order to maintain the blind. Unblinded study staff will be responsible for preparation (breaking tamper proof sticker on kit, etc) of the clinical trial material, including recording the administration information on source document.

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

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

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

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures (SOPs) or returned to UCB (or designee). Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

Investigational medicinal product 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)

Any treatment administered from the time of informed consent to the final study visit will be considered concomitant medication. This includes medications that were started before the study and are ongoing during the study.

7.8.1 Permitted concomitant treatments (medications and therapies)

7.8.1.1 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 PSO of the scalp are also permitted.

Mild and low potency topical steroids will be permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not be used within approximately 24 hours prior to study visits requiring IGA and PASI measures.

7.8.1.2 Other medications

Subjects who are already receiving an established NSAID regimen for PsA or symptoms of arthritis and have been on a stable dose for at least 1 week prior to the Screening Visit 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 gastrointestinal (GI) intolerance to NSAIDs or a history of GI ulceration) should not occur prior to Week 16 and should not happen within 2 weeks of the Week 52 Visit.

Subjects may take mild pain relievers (acetaminophen/paracetamol, mild opiates) as needed for arthritis pain but preferably not within 24 hours of the Baseline and Week 52 Visits.

Intra-articular steroid injections of any joint and hyaluronic acid injections are allowed after Week 16.

Subjects who are receiving an established regimen for depression should remain on stable dosing prior to Baseline and throughout the study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

Table 7–2 presents the list of prohibited PSO medications.

Table 7–2: Prohibited psoriasis medications

Drug	Washout period relative to Baseline Visit
Topicals except for those permitted (Section 7.8.1.1)	2 weeks
Systemic retinoids	3 months
Systemic treatment (non-biological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) fumaric acid esters specifically used for the treatment of PSO systemic corticosteroids phototherapy	1 month
Anti-TNFs: etanercept (including biosimilar) infliximab (including biosimilar), golimumab, certolizumab pegol, adalimumab (including biosimilar)	 1 month for etanercept 3 months for everything other than etanercept
Other biologics and other systemic therapies, eg: ustekinumab apremilast, tofacitinib alefacept, efalizumab, guselkumab tildrakizumab, risankizumab briakinumab rituximab	 Any exposure for ustekinumab 2 weeks for apremilast and tofacitinib 3 months for alefacept, efalizumab, and guselkumab 5 months for tildrakizumab and risankizumab 6 months for briakinumab 12 months for rituximab
Anti-IL-17 therapy: secukinumab ixekizumab brodalumab	3 months (bimekizumab is excluded per exclusion criteria)

Table 7–2: Prohibited psoriasis medications

Drug	Washout period relative to Baseline Visit
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)	3 months or 5 half-lives, whichever is greater
Any other antipsoriatic agent (topical) under investigation	1 month

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

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

7.8.2.1 Vaccines

Administration of live (including attenuated) vaccines is not allowed during the conduct of the study and for 20 weeks after the final dose of IMP (see Exclusion Criterion #10, Section 6.2). Administration of inactivated vaccines is allowed during the study at the discretion of the Investigator.

7.9 Blinding

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

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

- 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 documents, and administration of the IMP as sc injections. 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.
- Bioanalytical staff analyzing blood samples for bimekizumab and anti-bimekizumab antibody determination.

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. Unblinded study site personnel need to be available in order to resolve queries. Study monitors and study site personnel, blinded to treatment assignment, will not discuss or have access to any drug related information.

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. Sites will be instructed to keep study subjects blind to the IMP as detailed in the site blinding plan.

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

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of IMP blind

All subject treatment details (bimekizumab, ustekinumab, or placebo) will be allocated and maintained by the IRT system.

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 IRT. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor or equivalent should be consulted prior to unblinding, whenever possible.

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

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subject treatment assignment will be stratified by region (North America, Western Europe, Central/Eastern Europe, and Asia/Australia) and prior biologic exposure (yes/no).

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 IRT regarding a particular subject.

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

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

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.

- From the Week 1 visit to the Week 24 visit, 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. From the Week 28 visit to the Week 52 visit, visit windows are ±7 days. Changes to the dosing schedule outside of the visit window must be discussed with the Medical Monitor.

- The dosing window is ±3 days relative to the scheduled dosing visit through Week 24. The dosing window is ±7 days relative to the scheduled dosing visit from Week 28 through the end of the study.
- For the SFU Visit (20 weeks after the last dose), the visit window is ±7 days relative to the scheduled visit date.

8.1 Screening Visit (2 to 5 Weeks)

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and that complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent procedure, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

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 ICF. The ICF must be signed prior to collecting any samples for the substudy. The substudy will only be conducted where ethically accepted and authorized by the regulatory agencies. Refusal to participate in the substudy will not affect a subject's ability to participate in the main PS0009 study.

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

- Informed consent
- Inclusion/exclusion
- Urine drug screen
- Demographic data (age, gender, race and ethnicity [according to local regulations])
- Psoriasis history including the date of onset and past treatments
- Significant past medical history including clinically relevant past or coexisting medical conditions and surgeries
- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Vital signs (sitting systolic and diastolic blood pressure [BP), pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests:
  - Hematology and biochemistry
  - Urinalysis
  - Serum pregnancy test
  - Hepatitis B and Hepatitis C
  - HIV

  - IGRA Tuberculosis test
- Record 12-lead ECG
- Chest x-ray (not necessary if performed within 3 months prior to Screening Visit and report is available)
- Tuberculosis questionnaire
- PASI
- IGA
- Percentage of BSA
- PHQ-9
- eC-SSRS
- Patient Symptom Diary (daily)
- Concomitant medication
- AEs
- Confirm subject eligibility and contact IRT

8.2 Initial Treatment Period

8.2.1 Baseline Visit

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

- Inclusion/exclusion
- Significant past medical history and concomitant diseases to ensure no significant changes since screening
- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Height
- Body weight
- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urinalysis
  - Urine pregnancy test
  - Bimekizumab plasma concentrations

  - Anti-bimekizumab antibodies
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses (participating subjects only)
  - Genetic/epigenetic analysis (participating subjects only)
- Tuberculosis questionnaire
- PASI
- IGA
- Percentage of BSA
- DLQI
- PHQ-9
- eC-SSRS
- Patient Symptom Diary (daily)
- scalp IGA
- mNAPSI
- pp-IGA
- EQ-5D-3L
- SF-36
- PASE
- PGADA
- HAQ-DI
- WPAI-SHP V2.0
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, bimekizumab, ustekinumab, or placebo administration will occur.

8.2.2 Week 1 Visit (±3 days relative to Baseline)

The following procedures/assessments will be performed/recorded:

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:

  - Hematology and biochemistry
  - Bimekizumab plasma concentrations
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses
- PASI
- IGA
- Percentage of BSA
- DLQI
- eC-SSRS
- Patient Symptom Diary (daily)
- scalp IGA for subjects with scalp involvement at Baseline
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

8.2.3 Week 2 Visit (±3 days relative to Baseline)

The following procedures/assessments will be performed/recorded:

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Bimekizumab plasma concentrations
- PASI
- IGA
- Percentage of BSA
- DLQI
- eC-SSRS
- Patient Symptom Diary (daily)
- scalp IGA for subjects with scalp involvement at Baseline
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs

- Contact IRT

8.2.4 Week 4 Visit (±3 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
- PASI
- IGA
- Percentage of BSA
- DLQI
- PHQ-9
- eC-SSRS
- Patient Symptom Diary (daily)
- scalp IGA for subjects with scalp involvement at Baseline
- mNAPSI for subjects with nail involvement at Baseline
- pp-IGA for subjects with palmoplantar involvement at Baseline
- EQ-5D-3L
- SF-36
- PGADA (only for subjects with PsA)
- HAQ-DI (only for subjects with PsA)
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab, ustekinumab, or placebo will occur.

8.2.5 Week 8 Visit (±3 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses
- PASI
- IGA
- Percentage of BSA
- DLQI
- PHQ-9
- eC-SSRS
- Patient Symptom Diary (daily)
- scalp IGA for subjects with scalp involvement at Baseline
- mNAPSI for subjects with nail involvement at Baseline
- pp-IGA for subjects with palmoplantar involvement at Baseline
- EQ-5D-3L
- SF-36
- HAQ-DI (only for subjects with PsA)
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.2.6 Week 12 Visit (±3 days relative to Baseline)

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

- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Body weight
- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses (participating subjects only)
- Record 12-lead ECG
- Tuberculosis questionnaire
- PASI
- IGA
- Percentage of BSA
- DLQI
- PHQ-9
- eC-SSRS
- Patient Symptom Diary (daily)
- scalp IGA for subjects with scalp involvement at Baseline
- mNAPSI for subjects with nail involvement at Baseline
- pp-IGA for subjects with palmoplantar involvement at Baseline
- EQ-5D-3L
- SF-36
- PGADA (only for subjects with PsA)
- HAQ-DI (only for subjects with PsA)
- Photographs of skin and nails (participating centers only)

- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.2.7 Week 16 Visit (±3 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urinalysis
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses (participating subjects only)
- PASI
- IGA
- Percentage of BSA
- DLQI
- PHQ-9
- eC-SSRS
- Patient Symptom Diary (daily)
- scalp IGA for subjects with scalp involvement at Baseline
- mNAPSI for subjects with nail involvement at Baseline
- pp-IGA for subjects with palmoplantar involvement at Baseline
- EQ-5D-3L
- SF-36
- PGADA (only for subjects with PsA)
- HAQ-DI (only for subjects with PsA)

- WPAI-SHP V2.0
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, the Maintenance Treatment Period will begin with administration of bimekizumab, ustekinumab, or placebo.

8.3 Maintenance Treatment Period

8.3.1 Week 20 Visit (±3 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urine pregnancy test
- PASI
- IGA
- Percentage of BSA
- PHQ-9
- eC-SSRS
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.3.2 Week 24 Visit (±3 days relative to Baseline)

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

- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Body weight

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urinalysis
  - Urine pregnancy test
- Tuberculosis questionnaire
- PASI
- IGA
- Percentage of BSA
- PHQ-9
- eC-SSRS
- WPAI-SHP V2.0
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.3.3 Week 28 Visit (±7 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
- PASI
- IGA
- Percentage of BSA
- DLQI

- PHQ-9
- eC-SSRS
- scalp IGA for subjects with scalp involvement at Baseline
- mNAPSI for subjects with nail involvement at Baseline
- pp-IGA for subjects with palmoplantar involvement at Baseline
- EQ-5D-3L
- SF-36
- Patient Global Assessment of PSO
- PGADA (only for subjects with PsA)
- HAQ-DI (only for subjects with PsA)
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab, ustekinumab, or placebo will occur.

8.3.4 Week 32 Visit (±7 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urinalysis
  - Urine pregnancy test
- Record 12-lead ECG
- PASI
- IGA
- Percentage of BSA
- PHQ-9
- eC-SSRS
- Concomitant medication

- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.3.5 Week 36 Visit (±7 days relative to Baseline)

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

- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Body weight
- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Urine pregnancy test
- Tuberculosis questionnaire
- PASI
- IGA
- Percentage of BSA
- PHQ-9
- eC-SSRS
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.3.6 Week 40 Visit (±7 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry

  - Urinalysis
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
- PASI
- IGA
- Percentage of BSA
- DLQI
- PHQ-9
- eC-SSRS
- scalp IGA for subjects with scalp involvement at Baseline
- mNAPSI for subjects with nail involvement at Baseline
- pp-IGA for subjects with palmoplantar involvement at Baseline
- EQ-5D-3L
- SF-36
- Patient Global Assessment of psoriasis
- PGADA (only for subjects with PsA)
- HAQ-DI (only for subjects with PsA)
- WPAI-SHP V2.0
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab, ustekinumab, or placebo will occur.

8.3.7 Week 44 Visit (±7 days relative to Baseline)

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

- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Urine pregnancy test

- PASI
- IGA
- Percentage of BSA
- PHQ-9
- eC-SSRS
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.3.8 Week 48 Visit (±7 days relative to Baseline)

The following procedures/assessments will be performed/recorded:

- Informed consent (to be completed for the open-label study, if applicable)
- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urinalysis
  - Urine pregnancy test
  - IGRA Tuberculosis test
- PASI
- IGA
- Percentage of BSA
- PHQ-9
- eC-SSRS
- Concomitant medication
- AEs
- Contact IRT

After completion of the above-mentioned procedures, administration of bimekizumab or placebo will occur.

8.3.9 Week 52 Visit (±7 days relative to Baseline)

The following procedures/assessments will be performed/recorded:

- Urine drug screen
- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Body weight
- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urinalysis
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses (participating subjects only)
  - Genetic/epigenetic analysis (participating subjects only)
- Record 12-lead ECG
- TB questionnaire
- PASI
- IGA
- Percentage of BSA
- DLQI
- PHQ-9
- eC-SSRS
- scalp IGA for subjects with scalp involvement at Baseline
- mNAPSI for subjects with nail involvement at Baseline
- pp-IGA for subjects with palmoplantar involvement at Baseline
- EQ-5D-3L
- SF-36
- Patient Global Assessment of PSO
- PASE
- PGADA (only for subjects with PsA)

- HAQ-DI (only for subjects with PsA)
- WPAI-SHP V2.0
- Photographs of skin and nails (participating centers only)
- Concomitant medication
- AEs
- Contact IRT

8.4 Premature End of Treatment Visit

If a subject is withdrawn from the study:

- The subject will be withdrawn from IMP, will undergo the same assessments as the Week 52 visit (see Section 8.3.9), and will enter the SFU Period.
- The subject will be encouraged to return for the SFU Visit (20 weeks after the last received dose; see Section 8.5).

8.5 Safety Follow-Up Visit (20 weeks after last dose, ±7 days)

All subjects not continuing in the open-label study, including those withdrawn from IMP, will have a SFU Visit 20 weeks after their final dose of IMP.

The following procedures/assessments will be performed/recorded:

- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Vital signs (sitting systolic and diastolic BP, pulse rate, and body temperature) should be obtained prior to blood sampling
- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry
  - Urinalysis
  - Urine pregnancy test
  - Bimekizumab plasma concentrations
  - Anti-bimekizumab antibodies
- Tuberculosis questionnaire
- PASI
- IGA
- Percentage of BSA
- eC-SSRS
- Concomitant medication

- AEs
- Contact IRT

8.6 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, 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 assessment may be performed, as needed, depending on the reason for the visit.

9 ASSESSMENT OF EFFICACY

The PASI, BSA, IGA, scalp IGA, mNAPSI, and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. The same assessor should evaluate the subject at each assessment.

9.1 Psoriasis Area and Severity Index

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

The percent area of involvement (BSA%) is estimated across 4 body areas; head, upper extremities, trunk, and lower extremities. Assessors will enter the degree of involvement for a given region on a scale of 0 to 6 (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) (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 extremities	Left, right, upper lower, flexor surface, extensor surface	20%	0 to 6
Trunk	Front, back, groin	30%	0 to 6

Lower extremities	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, respectively.

The total BSA affected by PSO will be entered as a percentage from 0 to 100.

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

9.2 Investigator's Global Assessment

A static IGA for PSO 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 PSO using the following 5-point scale presented in Table 9–2.

Table 9–2: Five-point IGA

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

IGA=Investigator's Global Assessment; PSO=psoriasis

9.3 Dermatology Life Quality Index

The DLQI is a questionnaire designed for use in adult subjects with PSO. The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect subjects' 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 subjects with PSO. The DLQI score ranges from 0 to 30 with higher scores indicating lower health related QOL. A 4-point change in the DLQI score (DLQI response) has been reported to be meaningful for the subject (within-subject 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).

9.4 Patient Health Questionnaire 9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression (Kroenke et al, 2001). The PHQ-9 scores for depression range from 0 to 27, with higher scores indicating worse state. A score of 5-9 is considered to be minimal symptoms of depression. A score of 10 to 14 is considered minor depression, dysthymia, or mild major depression. A score of 15 to 19 is considered to indicate moderately severe major depression, and a score ≥20 is considered to be severe major depression.

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

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

9.5 Scalp IGA

A static IGA for scalp PSO will be used to assess disease severity on the scalp.

All subjects will complete the scalp IGA at Baseline. Only subjects with scalp involvement at Baseline will complete the scalp IGA at the other visits specified in Table 5–1. Subjects with scalp involvement at Baseline are defined as those with a scalp IGA score >0 at Baseline.

Scalp lesions will be assessed in terms of clinical signs of redness, thickness, and scaliness using a 5-point scale (Table 9–3).

Table 9–3: Scalp IGA

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

PSO=psoriasis; scalp IGA=scalp-specific Investigator's Global Assessment

9.6 mNAPSI

Nail PSO will be evaluated using the 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 PSO. 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 PSO at Baseline are defined as those with a mNAPSI score >0 at Baseline.

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

9.7 pp-IGA

A static IGA for palmoplantar PSO will be used to assess palmoplantar disease severity.

All subjects will complete the pp-IGA at Baseline. Only subjects with palmoplantar involvement at Baseline will complete the pp-IGA at the other visits specified in Table 5–1. Subjects with palmoplantar involvement at Baseline are defined as those with a pp-IGA score >0 at Baseline.

Palmoplantar disease will be assessed in terms of clinical signs of redness, thickness, and scaliness using a 5-point scale (Table 9–4).

Table 9–4: pp-IGA

Score	Short Descriptor	Detailed Descriptor
0	Clear	Palmoplantar areas have no signs of PSO; post-inflammatory hyperpigmentation may be present
1	Almost clear	Palmoplantar areas have no thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Palmoplantar areas have just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Palmoplantar areas have clearly distinguishable to moderate thickening; dull to bright red and clearly distinguishable coloration; moderate scaling
4	Severe	Palmoplantar areas have severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions; numerous fissures

PSO=psoriasis; pp-IGA=palmoplantar-specific Investigator's Global Assessment

9.8 Euro Quality of Life 5-Dimensions, 3-Level

The Euro Quality of life 5-Dimensions 3-Level (EQ-5D-3L) health questionnaire provides a descriptive profile and a single index value for health status. The instrument is comprised of a 5-item health status measure and a VAS. The EQ-5D-3L VAS records the respondent's self-rated health status on a vertical 20cm scale, graduated from 0 to 100 (0=worst imaginable health status, 100=best imaginable health status).

The EQ-5D-3L will be assessed at the visits specified in Table 5–1.

9.9 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 at a group level, 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 at the visits specified in Table 5–1.

9.10 Patient Global Assessment of psoriasis

The Patient Global Assessment of PSO is a PSO-specific item in which the patient responds to the multiple-choice question, "How severe are your psoriasis-related symptoms right now?" Possible responses to the question are "no symptoms," "mild symptoms," "moderate symptoms", "severe symptoms," or "very severe symptoms."

The Patient Global Assessment of PSO will be performed as part of the patient symptoms diary from Screening through the Initial Treatment Period.

During the Maintenance Treatment Period, this assessment will be completed at the visits specified in Table 5–1.

9.11 Patient Symptom Diary responses

UCB developed a new patient-reported outcome (PRO) measure that will be used to assess key symptoms relevant to patients with moderate to severe chronic plaque PSO. PS0010 used 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 daily until the Week 16 Visit. The ePRO diary will be administered on a daily basis from Screening to the Week 16 Visit.

The ePRO diary will also administer the patient global assessment of PSO as noted above appropriate anchor items 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. 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.

The Patient Symptom Diary responses for itch, pain, and scaling at Week 16 will be computed based on the responder definition as well as the absolute and percent change from Baseline. Each of the Patient Symptom Diary response scores included in the statistical testing procedure (itch, pain, and scaling) will be characterized in terms of the cumulative percent of subjects demonstrating a pre-specified point improvement at Week 16. The threshold for the Patient Symptom Diary response score of itch, pain, and scaling is 2.39, 1.98, and 2.86, respectively. The responder analysis will be limited to the subjects with a Baseline Patient Symptom Diary response score at or above the applicable threshold score (ie, at least 2.39, 1.98, and 2.86 for itch, pain, and scaling, respectively).

9.12 PASE questionnaire

The PASE questionnaire is a self-administered tool to screen for active PsA in patients with PSO (Husni et al, 2014). The questionnaire consists of 15 items that are divided into a 7-item

symptoms subscale and an 8-item functions subscale. Standardized responses are based on 5 categories relating to agreement (strongly agree [5], agree [4], no idea [3], disagree [3], and strongly disagree [1]). The total maximum score is 75 points (symptom score: 35 points and function score: 40 points). Psoriatic Arthritis Screening and Evaluation questionnaire scores ≥47 points are indicative of active PsA. Subjects with scores ≥47 should be referred to a rheumatologist for evaluation.

If a subject with a PASE score ≥47 points is referred to a rheumatologist, the referral will be recorded in the eCRF. Subjects with PsA, defined as a past medical history of PsA or PASE ≥47, are required to receive the additional PsA assessments (PGADA and HAQ-DI) as noted in Section 9.13 and Section 9.14.

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

9.13 PGADA for arthritis visual analog scale

The PGADA for the arthritis 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."

All subjects will complete the PGADA at Baseline. Subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47) will complete the PGADA at the visits specified in Table 5–1.

9.14 HAQ-DI score

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

All subjects will complete the HAQ-DI at Baseline. Subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47) will complete the HAQ-DI at the visits specified in Table 5–1.

9.15 WPAI-SHP V2.0

The WPAI-SHP V2.0 is a patient-reported questionnaire that assesses subject's employment status, work absenteeism, work impairment while working (presenteeism), overall work, and daily activity impairment attributable to a specific health problem (WPAI:SHP) (Reilly et al, 1993). It has been used in several clinical studies of biologic therapy in subjects with plaque PSO (Kimball et al, 2012; Vender et al, 2012).

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

The WPAI-SHP V2.0 will be assessed at the visits specified in Table 5–1.

9.16 Photographs

At certain clinical sites, representative photographs of the changes in skin and nail appearance will be captured. Subjects will have full body (anterior and posterior views) photographs taken. Only those subjects with nail disease at Baseline will have nail photographs taken. Only those subjects with palmoplantar disease at Baseline will have photographs of their palms or soles of their feet taken. Only those subjects with scalp disease at Baseline will have scalp photographs taken. Photographs will be anonymized.

Study sites selected for photography will be trained and receive standardized photographic equipment by a centralized photographic vendor. Photographs will be electronically transferred from the site to the vendor.

At the end of the study, the site will receive an electronic file of all subject photographs for archiving.

The central photography vendor will tabulate and transfer all subject photos to the Sponsor at the end of the study.

10 ASSESSMENT OF PHARMACOKINETIC AND PHARMACOGENOMIC VARIABLE(S)

10.1 Pharmacokinetic variables

Blood samples for measurement of PK assessments (Section 4.3.3) 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.

Pharmacokinetic samples from subjects receiving ustekinumab will not be analyzed, but stored for potential future PK analysis and anti-drug antibody determination.

10.2 Pharmacogenomic variables

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

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

For individuals consenting to the genomics, genetics, and proteomics substudy, blood samples will be drawn for exploratory genetic/epigenetic, genomic, proteomic, metabolomics analysis, and for candidate biomarker analyses. Candidate biomarker evaluations may include, but are not

limited to, IL-17A/IL-17F pathway signaling and PSO biology (eg, IL-17A, IL-17F, IL-23, IL-6, tumor necrosis factor, dendritic cell-specific transmembrane protein, and circulating osteoclast precursors).

Collection of these samples will occur at the time points specified in the schedule of study assessments (Table 5–1). At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF. The samples will be stored at -80°C at the central biorepository for up to 20 years.

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.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLE(S)

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.

12 ASSESSMENT OF SAFETY

12.1 Adverse events

12.1.1 Definitions

12.1.1.1 Adverse event

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

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

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

12.1.1.2 Serious adverse event

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

- Death
- Life-threatening

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

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 12.1.1.1], 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.)

Confirmed active TB must be reported as an SAE. The Investigator is to complete and submit the TB Follow-Up Form provided.

12.1.1.2.1 Anticipated serious adverse events

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

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

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

12.1.1.1 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.

12.1.1.2 Other safety topics of interest

Pre-specified safety topics of interest for the study are: infections (serious, opportunistic, fungal, and TB), neutropenia, hypersensitivity, suicidal ideation and behavior, depression, major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel diseases (with gastroenterology referral, as appropriate).This is based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action. There are no specific AE reporting requirements for these topics, however special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB) are in place.

12.1.2 Procedures for reporting and recording adverse events

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

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

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

12.1.2.1 Description of adverse events

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

When recording the severity of an AE in the eCRF (ie, mild, moderate, or severe), the Investigator may refer to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) for additional guidance as needed. Details for completion of the Adverse Event eCRF (including judgment of relationship to IMP) are described in the eCRF Completion Guidelines.

12.1.2.2 Rule for repetition of an adverse event

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

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

12.1.2.3 Additional procedures for reporting serious adverse events

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

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

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

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

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

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

12.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AESIs; further details regarding follow up of PDILI events is provided in Section 12.2.1.4.

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

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

12.1.4 Pregnancy

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

- The subject should return for an early discontinuation visit.
- The subject should immediately stop the intake of the IMP.
- A 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 Serious Adverse Event 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 a SAE in the following circumstances: miscarriage, elective abortion when medically indicated (e.g. when pregnancy is endangering life or health of woman or when fetus will be born with severe abnormalities), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

Should a subject become pregnant while participating in the study, the subject may be offered the option to enroll in a separate observational pregnancy follow-up study sponsored by UCB and conducted independently from study PS0009. If the study is available locally, the PS0009 PI will be provided with the locally approved information about the observational pregnancy follow-up study to inform the subject at the time the pregnancy is reported. Participation in this separate study will be voluntary and will not impact therapeutic management of the subject nor interfere with termination and follow-up procedures as described in study protocol PS0009.

12.1.5 Suspected transmission of an infectious agent via a medicinal product

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

12.1.6 Overdose of investigational medicinal product

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

12.1.7 Safety signal detection

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

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

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

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 Laboratory measurements

Clinical laboratory assessments consist of serum chemistry, hematology, urinalysis, and urine drug screen. 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 #9, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12–2.

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

The following laboratory parameters will be measured:

Table 12–2: Laboratory measurements

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

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=gamma glutamyltransferase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PEOT=Premature End of Treatment; RBC=red blood cell; WBC=white blood cell

a A urine microscopic examination will be performed if the result for albumin (protein), leukocyte esterase, blood or nitrite is abnormal. A urine microscopic examination will include: WBC, RBC, epithelial cells (squamous, transitional and renal tubular), hyaline casts, WBC casts, RBC casts, waxy casts, granular casts, calcium oxalate crystals, uric acid crystals, triphosphate crystals, yeast, bacteria, amorphous urates, and amorphous phosphates.

[b] Pregnancy testing will consist of serum testing at the Screening Visit. The pregnancy test will be urine at all other visits.
[c] Urine drug screen will be performed at Screening Visit, and Week 52 or PEOT Visit.

12.2.1 Evaluation of PDILI

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 12.1.1.1), and, if applicable, also reported as an SAE (see Section 12.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 12–3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 12.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 12.2.1.4).

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

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

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

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

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

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 12.2.1.3); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within baseline values.[d]
≥3xULN	NA	Yes				
≥8xULN	NA	NA	Need for hepatology consult to be discussed.(required if ALT or AST ≥8xULN) Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation		
≥5xULN (and ≥2x baseline) and <8xULN	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow	Further investigation – immediate IMP discontinuation not required (see Section 12.2.1.2). IMP discontinuation	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site	Monitoring of liver chemistry values at least twice per week for 2 weeks.[d] • Immediate IMP discontinuation required if liver

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**
			up requirements).[c]	required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥5xULN (and ≥2x baseline) after 4 weeks of monitoring without evidence of resolution	with HCP (see Section 12.2.1.3).	chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • ALT or AST remains ≥5xULN <8xULN, IMP should be temporarily withheld and subject should undergo repeat test in 2 weeks. Continue IMP if ALT or AST values <5xULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values. If ALT or AST remains ≥5xULN after second re-test, immediate,

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**
						permanent IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[d]

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

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

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

[c] Details provided in Section 12.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

12.2.1.1 Consultation with Medical Monitor and local hepatologist

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

12.2.1.2 Immediate action: determination of IMP discontinuation

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

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

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

12.2.1.2.1 IMP restart/rechallenge

Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 12.2.1.3 and Section 12.2.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- The subject has shown clear therapeutic benefit from the IMP.
- Subject's ALT or AST elevations do not exceed ≥5xULN.
- Subject's total bilirubin is <2xULN.
- Subject has no signs or symptoms of hypersensitivity or hepatitis.
- The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.
- Subject agrees to the Investigator-recommended monitoring plan.

12.2.1.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 12–4 (laboratory measurements) and Table 12–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other

assessments not included below, these additional assessments should be completed and submitted, as applicable.

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

The following measurements are to be assessed:

Table 12–4: PDILI laboratory measurements

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

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

Table 12–4: PDILI laboratory measurements

[a] Tests in addition to the specified analytes may be performed based on the Investigator's medical judgment and subject 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).
[c] For women of childbearing potential.

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

12.2.1.4 Follow-up evaluation

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

12.3 Other safety measurements

12.3.1 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 12.3.1.2), laboratory testing (Section 12.3.1.1), and subject questionnaire (Section 12.3.1.3).

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

a. Known TB infection:

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

b. High risk of acquiring TB infection:

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

c. Latent TB infection (unless appropriate prophylaxis is initiated at least 8 weeks prior to IMP dosing and continued to completion of prophylaxis):

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

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

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

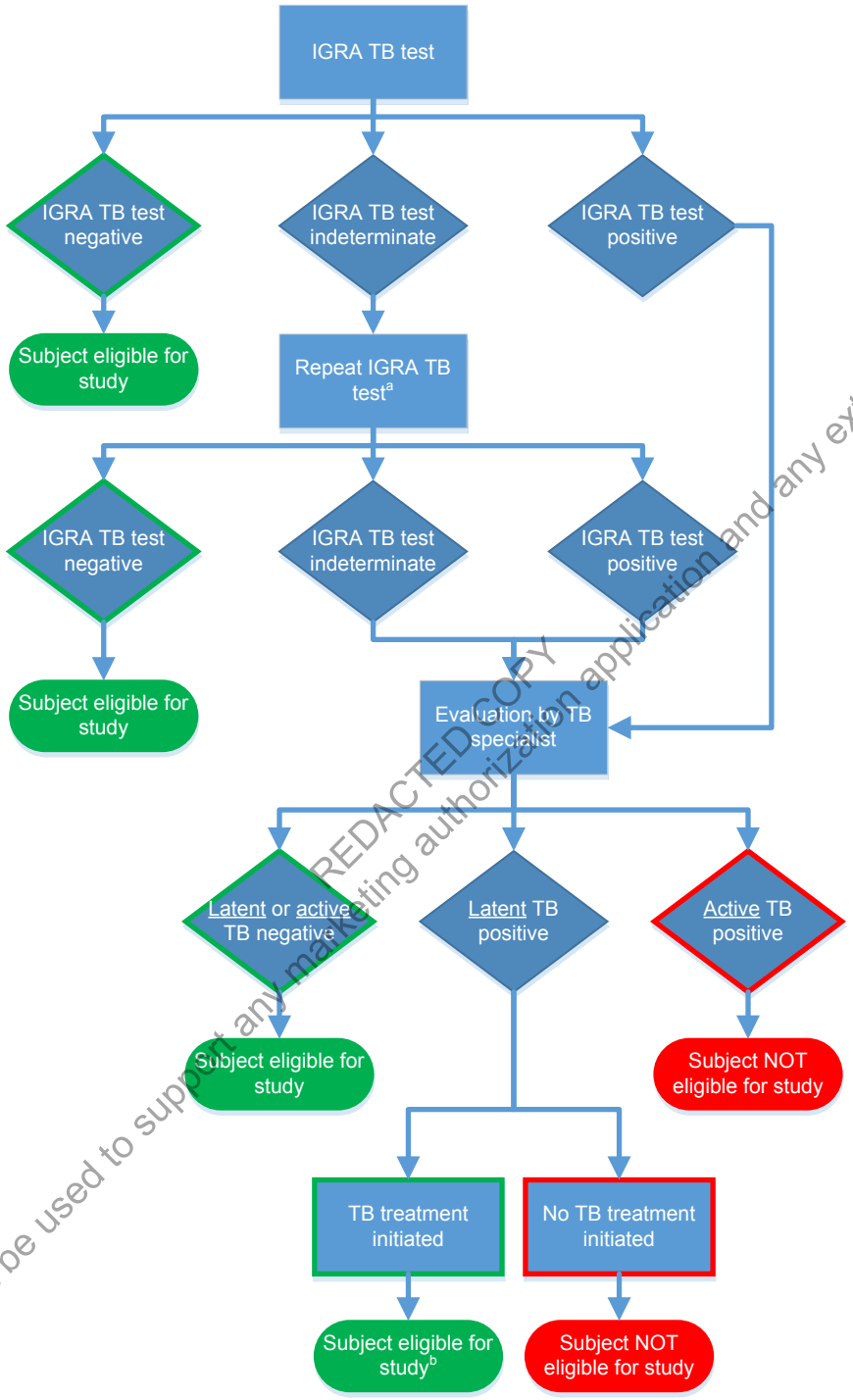
e. Tuberculosis test conversion:

- A positive IGRA result for the current test when previous IGRA test results were negative. All subjects with TB test conversion must immediately stop IMP administration and be referred to a TB specialist for further evaluation. Confirmed TB test conversions

should be classified as due to LTBI, active TB infection, or NTMB, and reported to the UCB PS function.

Subject eligibility, retesting requirements, and treatment requirements are depicted in Figure 12-1.

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



IGRA=interferon-gamma release assay; TB=tuberculosis
[a] IGRA retest must be done during the protocol-defined Screening window
[b] Subjects with LTBI may enter the study only after they have completed at least 8 weeks of appropriate prophylactic therapy and thereafter, will continue and complete the entire regimen.

12.3.1.1 Tuberculosis assessment by IGRA

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

12.3.1.2 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 of the Chest) must be clear of signs of TB infection (previous or current) before first IMP administration. All chest imaging (particularly x-rays) should be available for review by the Investigator before randomization of the subject. The chest x-ray reading should be repeated if the TB test was confirmed positive. If the second read of the pretreatment chest x-ray is confirmed to be clear, the subject may be included in the study 8 weeks after the start of the TB prophylactic treatment. If the pretreatment chest x-ray is not available for a re-read, it should be repeated after notification to the radiologist that this subject is IGRA positive, and confirmed to be clear for signs of TB.

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

12.3.1.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed as described in Table 5–1. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at Screening is excluded. A "Yes" response to any of the other questions within the questionnaire at Screening should trigger further careful assessment to determine if subject has LTB or active TB (see Exclusion Criterion #12, Section 6.2). A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection.

12.3.1.4 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 IMP and will be referred to an appropriate TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Evidence of LTB infection is defined as subject's IGRA test converts to positive or indeterminate (and confirmed indeterminate on repeat), or the subject's questionnaire or history and physical

indicates that TB infection or exposure may have occurred. Evidence of active TB includes, in addition to the aforementioned tests, signs and symptoms of organ involvement. In either situation, the subject should be carefully assessed by a TB specialist for active TB. Subjects diagnosed with active TB should be withdrawn from the study and receive appropriate TB or prophylaxis therapy.

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

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

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

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

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

12.3.2 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening. 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 IMP at the visits specified in Table 5–1. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

12.3.3 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.

12.3.4 12-lead electrocardiograms

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

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

12.3.5 Physical examination

A physical examination will be performed at the visits specified in Table 5–1. The physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; CV; GI; musculoskeletal; hepatic; neurological (including limb reflexes); and mental

status. All physical examinations will also include evaluation of signs and symptoms of active TB and risk for exposure to TB. Findings considered clinically significant changes since the physical examination at the Screening Visit will be recorded as AEs.

12.3.6 Height and body weight

Height will be measured at Baseline only.

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

12.3.7 Assessment of suicidal ideation and behavior

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

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

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

12.4 Other study measurements

12.4.1 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.

12.4.2 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.

12.4.3 Psoriasis history

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

12.4.4 Data Monitoring and Adjudication Committees

The DMC membership includes experienced clinicians and a statistician, all of whom have expertise in clinical trials. Cardiovascular and Neuropsychiatric Adjudication Committees will also periodically review data from this trial. Both Data Monitoring and Adjudication Committee members may not participate in the study as principal or co-Investigators, or as study subject care physicians. The duration of membership for the committees will be inclusive of planned analyses for PS0009. Detailed role, scope, responsibilities, and complete procedures, as well as the identity of members, are described in the separate committee charters.

13 STUDY MANAGEMENT AND ADMINISTRATION

13.1 Adherence to protocol

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

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

13.2 Monitoring

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

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

The Investigator will allow UCB (or designee) to periodically review all eCRFs and corresponding source documents (eg, hospital and laboratory records for each subject). Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

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

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

Source documents that are computer generated and stored electronically must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

Patient-reported outcome measures (eg, DLQI, EQ-5D-3L, SF-36, Patient Global Assessment of PSO, and PGADA) and ePRO diary data will be entered electronically by the subject.

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 US Food and Drug Administration 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

The Investigator is responsible for prompt reporting of accurate, complete, and legible data in the electronic eCRFs and in all required reports.

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

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

The Investigator should maintain a list of personnel authorized to enter data into the electronic eCRF.

Detailed instructions will be provided in the eCRF Completion Guidelines.

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 Electronic Data Capture: the data are entered into the eCRFs once and are subsequently verified.

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

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 (Committee for Proprietary Medicinal Products [CPMP]/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the sponsor's trial master file.

13.6 Audit and inspection

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

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

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

13.7 Good Clinical Practice

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

14 STATISTICS

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

14.1 Definition of analysis sets

The Enrolled Set 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 that received at least 1 dose of the IMP.

The Maintenance Set will consist of all subjects who have received at least 1 dose of active IMP (bimekizumab or ustekinumab) in the Maintenance Treatment Period.

The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the IMP and have a valid measurement for each of the co-primary efficacy variables at Baseline.

The Active Medication Set (AMS) will consist of all subjects who have received at least 1 dose of active IMP (bimekizumab or ustekinumab). The AMS will be used for summaries of safety that include all data from the Initial Treatment Period and/or Maintenance Treatment Period.

The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding of the data.

The Pharmacokinetics Per-Protocol Set (PK-PPS) consists of all randomized subjects who received at least 1 dose of the IMP and provided at least 1 quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration.

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, SD, median, minimum, and maximum unless stated otherwise.

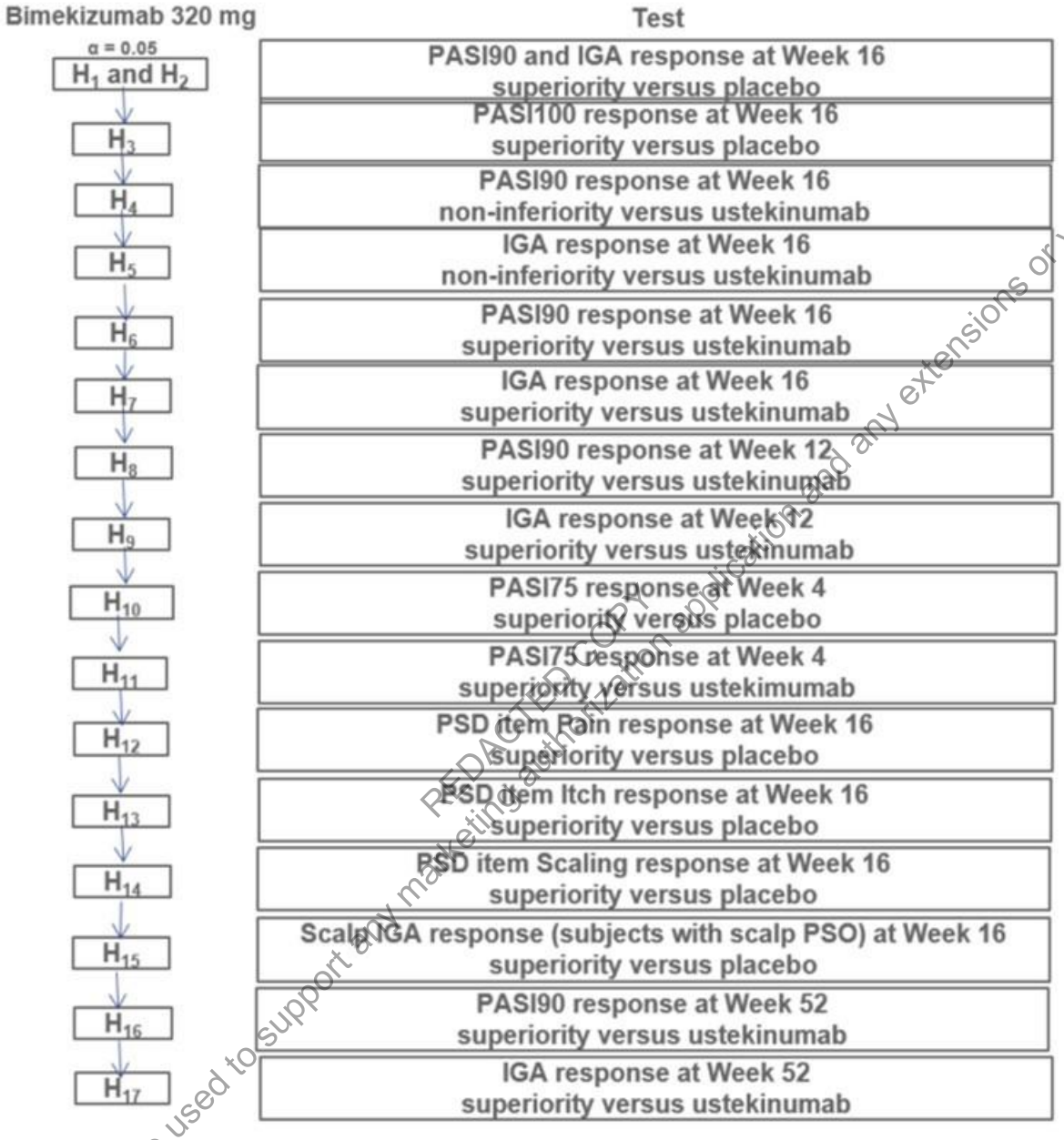
The statistical analysis of the co-primary efficacy variables and selected secondary efficacy variables will account for multiplicity and control the familywise Type I error rate at a 2-sided alpha level of 0.05 by using a fixed sequence testing procedure.

The hypotheses (H_1, H_2, H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{10}, H_{11}, H_{12}, H_{13}, H_{14}, H_{15}, H_{16}, and H_{17}) comparing bimekizumab vs. placebo or bimekizumab vs. ustekinumab will be tested at a 2-sided alpha level of 0.05.

The first 2 hypotheses (H_1 and H_2) test whether bimekizumab is superior to placebo for PASI90 response and IGA response at Week 16. These are the hypothesis tests corresponding to the co-primary endpoints. If both are rejected at a 2-sided alpha level of 0.05, that alpha will be passed to the next test in the sequence, allowing the testing procedure to proceed.

The hypotheses associated with the subsequent tests are for secondary efficacy endpoints and are based on testing for non-inferiority/superiority relative to ustekinumab or for superiority relative to placebo. Note that while subjects randomized to ustekinumab may receive either the 45mg or 90mg dose (according to weight at Baseline), all subjects randomized to ustekinumab will be analyzed as a single group (and not broken out by dose) since the proposed strategy is consistent with the recommended weight-based dosing for ustekinumab. See Figure 14-1 for details on this procedure.

Figure 14-1: Sequence of testing



IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; PSD=Patient Symptom Diary; PSO=psoriasis

14.3 Planned efficacy analyses

14.3.1 Analysis of the primary efficacy variable

The co-primary efficacy variables for this study will be PASI90 response and IGA response at Week 16, and the corresponding analyses will be based on the RS. A subject will be classified as a PASI90 responder if the PASI score at Week 16 has improved at least 90% from Baseline, and an IGA responder will be any subject with a score of 0 or 1 (Clear or Almost Clear) with at least a 2-category improvement from Baseline in the IGA score. The primary analyses will be based

on the stratified Cochran-Mantel-Haenszel (CMH) test where region and prior biologic exposure (yes/no) will be used as stratification variables. Region and prior biologic exposure have been selected as stratification variables in the analysis because they are stratification variables in the randomization and because they may have an impact on efficacy. Pairwise treatment comparisons will be made based on the CMH test using the p-value for the general association.

Nonresponder imputation (NRI) will be used to account for missing data in the primary analysis. Specifically, any subject who withdraws from IMP prior to Week 16 or who has missing data for the co-primary efficacy variables at the Week 16 time point will be considered a nonresponder. Based on previous studies of biologics in subjects with moderate to severe chronic plaque PSO, it is expected that the number of subjects who discontinue prior to Week 16 will be low. For the small percentage of subjects for whom primary endpoint data are unavailable at Week 16, this lack of data is suggestive of an ineffective IMP, thereby supporting the imputation of nonresponse. Therefore, NRI is considered an appropriate method for handling missing data since achieving the clinical response and making it through 16 weeks of IMP are both critical components of the primary outcome.

14.3.1.1 Sensitivity analyses

The primary efficacy analysis described in Section 14.3 will be repeated based on the FAS and the PPS.

As a sensitivity analysis to the primary analysis method, logistic regression based on the RS will be used. The odds ratio of the responder rates at Week 16 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and prior biologic exposure (yes/no). The odds ratio, associated CI, and p-value based on the Wald test will be presented. If the logistic regression model is unable to converge, then prior biologic exposure may be dropped from the model to facilitate convergence. If the model is still unable to converge, then region may be removed from the model as well. In addition, if the logistic regression model cannot converge due to lack of any placebo responders, then Fisher's exact test will be used for inferential comparisons to placebo. As with the primary analysis, missing data will be handled using NRI.

The center-by-treatment interaction will be tested by replacing region with center in the logistic regression model described above and adding a center-by-treatment interaction term. In the model, center will be based on the original centers prior to pooling. However, if the model is unable to converge due to a low number of subjects at a given center, a pooling (to be described in the SAP) will be applied in order to allow the model to converge.

In order to obtain reasonable estimates of variability for a treatment arm at a given center, a minimum of 21 subjects will be considered acceptable for a center to be included in the model without pooling. Given the 4:2:1 randomization allocation scheme, this should provide a minimum of about 12 subjects in the bimekizumab arm, 6 subjects in the ustekinumab arm, and 3 subjects in the placebo arm. Centers with fewer than 21 subjects will be eligible for pooling.

The following center pooling algorithm will be used for each geographic region:

- If a center has 21 or more subjects, then no pooling will be done for that center.
- Centers with fewer than 21 subjects will be ordered from largest to smallest with pooling proceeding in the following manner:

- Two or more centers will be combined until the cumulative subject total is at least 21.
- Once a pooled center has at least 21 subjects, the process will continue in an iterative fashion for the subsequent centers in the ordered list, where a new pooled center begins each time at least 21 subjects has been reached in the previous pool.
- If this iterative process reaches the end of the ordered list of centers where the final pooled center has fewer than 21 subjects, then the subjects from the centers in that pool will be combined with the pooled center formed in the previous iteration.

This procedure is only to be performed within a geographic region – there will be no pooling of centers across regions.

If the center-by-treatment interaction is not found to be significant (α=0.10), then no further analyses will be performed. On the other hand, if the interaction is significant, further analyses will be conducted to determine which center or centers may be the source of the interaction. This will be done by running the logistic regression model (including the interaction term) where each center will be systematically removed from the model. The impact of a given center will be based on the change in the interaction p-value when that center is removed. The center or centers that appear to be driving the significant interaction effect will then be removed from the model to verify that conclusions remain the same with or without the influential center(s).

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

14.3.2 Other efficacy analyses

14.3.2.1 Analysis of the secondary efficacy variables

14.3.2.1.1 Initial Treatment Period

The secondary efficacy variables for time points during the initial Treatment Period will be analyzed for all subjects in the RS.

For binary secondary efficacy variables, the stratified CMH test as specified for the primary analysis will be implemented to test for superiority. As in the primary analysis, NRI will be used to account for missing data. For the assessment of non-inferiority, a non-inferiority margin of 10% will be used and evaluated based on the confidence interval for the stratified Mantel-Haenszel risk difference between bimekizumab and ustekinumab. A non-inferiority margin of 10% has been selected as this is considered to be a clinically relevant difference that could influence the choice of interventions used to treat chronic plaque PSO. Therefore, a difference within the 10% non-inferiority margin would suggest a similar impact on efficacy between the treatments.

For continuous change from Baseline efficacy variables, an analysis of covariance (ANCOVA) model will be used with fixed effects of treatment, region, and prior biologic exposure and Baseline value as a covariate. Missing data for these variables will be imputed using multiple imputation (MI) and is further described in Section 14.7.

Sensitivity analyses for the handling of missing data will be performed for the secondary efficacy variables during the Initial Treatment Period that are part of the fixed sequence testing procedure. These analyses are described in Section 14.7.

14.3.2.1.2 Maintenance Treatment Period

Because all placebo subjects will receive bimekizumab treatment starting at Week 16, statistical comparisons against placebo after Week 16 will not be performed. However, bimekizumab will be compared to ustekinumab at Week 52 for the RS. The analysis of PASI90 and IGA at Week 52 will be based on a stratified CMH test where region and prior biologic exposure will be used as stratification variables. Pairwise treatment comparisons will be made based on the p-value for the general association.

Missing data will be imputed using NRI. All subjects with missing data at Week 52 or who discontinue study treatment prior to Week 52 will also be treated as non-responders for this secondary efficacy analysis.

14.3.2.2 Analysis of the other efficacy variables

The other efficacy variables in the Initial Treatment Period will be analyzed for all subjects in the RS. For the Maintenance Treatment Period, summaries will primarily be based on the RS. Full details will be specified in the SAP.

Binary (responder) variables will be summarized using frequency tables by treatment group for each visit.

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

Time to PASI75/90/100 response during the Initial Treatment Period 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 the first dose of IMP until the first date when the response is achieved. Subjects who discontinue IMP prior to achieving a response will be censored at the date of IMP discontinuation. Subjects who reach the Week 16 Visit without achieving the given PASI response will be censored at the date of the Week 16 Visit. The median time to response, including the 2-sided 95% CI, will be calculated for each treatment. Between group differences (bimekizumab vs placebo and bimekizumab vs ustekinumab) will be analyzed with the log-rank statistic.

All other efficacy variables during the Initial Treatment Period will be summarized based on imputed data (NRI and multiple imputation for binary and continuous variables, respectively, unless otherwise stated in the SAP). In some cases, variables may also be summarized based on observed case data (ie, subjects with missing data or who have prematurely discontinued IMP are treated as missing). There may be cases where the multiple imputation model fails to converge. In such situations, the last observation carried forward (LOCF) approach will instead be used to impute the missing data. If LOCF is used instead of multiple imputation for this reason, this will be clearly specified in the corresponding table summary. Should there be no missing data for a study variable, then only observed case data will be presented. Note that for LOCF imputation, any missing data or data collected following discontinuation of IMP will be imputed with the most recent previous value. See Section 14.7 for further details.

For other efficacy variables during the Maintenance Treatment Period, summaries will include the bimekizumab and ustekinumab treatment groups. Details of these summaries will be described further in the SAP, but there will be 2 key approaches for understanding the data in the Maintenance Treatment Period:

1. Summary of data for the RS through Week 52 based on randomized treatment group.
2. Summary of Maintenance Treatment Period data among responders only.

14.4 Subgroup analyses

Subgroup analyses will be performed on the primary and secondary efficacy variables that are part of the fixed sequence testing procedure described in Section 14.3. The following variables for subgroup analyses will be defined: age, gender, disease duration, region, weight, body mass index, prior systemic chemotherapy or phototherapy, prior biologic exposure, prior systemic therapy of any kind, Baseline disease severity, and antibody positivity. These summaries will be based on imputed data (NRI or MI) and will include descriptive statistics only. Note that the approach for deriving descriptive statistics using MI is outlined in Section 14.7.

14.5 Planned safety and other analyses

14.5.1 Safety analyses

Safety variables will be analyzed for all subjects in the SS. The AMS will be used for summaries of safety that include data from the Initial Treatment Period and/or Maintenance Treatment Period.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized descriptively by treatment group, primary system organ class, High Level Term (HLT), and preferred term. Additional tables will summarize AEs by intensity and relationship to IMP, AEs leading to withdrawal from the study, SAEs, and deaths. Specific safety topics of interest will be summarized and will be described in greater detail in the SAP.

For subjects who switch treatment, AEs will be allocated to the treatment the subject was on the day the event occurred. If the event occurs on the day of the switch, it will be attributed to the initial treatment, unless the event has a HLT of "Injection Site Reactions, in which case it will be attributed to the new treatment.

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

14.5.2 Pharmacokinetic analyses

Pharmacokinetic variables will be analyzed for all subjects in the PK-PPS. Bimekizumab plasma concentrations will be summarized for each treatment at each scheduled visit.

14.5.3 Immunogenicity analyses

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

14.6 Handling of protocol deviations

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

14.7 Handling of dropouts or missing data

Study variables with multiple components may have rules to account for partial missing data of 1 or more components. Such rules will be defined in the SAP. The following rules are outlined for cases where variables are completely missing, including partial missing data where the data handling rules conclude that the variable should be treated as completely missing.

The analysis of the co-primary efficacy variables will use NRI for handling of missing data. That is, subjects with missing data or who have discontinued IMP prior to Week 16 will be considered as nonresponders for the primary analysis.

The following sensitivity analyses for the co-primary efficacy variables will be performed:

1. Missing data will be addressed by using MI (Markov-Chain Monte Carlo [MCMC] method for intermittent missing data, followed by monotone regression for monotone missing data) to evaluate the effect of the method for handling missing data on the analysis. The actual PASI/IGA scores will be imputed and then dichotomized to obtain the response status. The treatment differences for each imputed data set will subsequently be evaluated using the stratified CMH test as used in the primary analysis. The results from each of the imputed data sets will be combined for overall inference using Rubin's rules, which account for the uncertainty associated with the imputed values (Rubin, 1987). This will be done using SAS PROC MIANALYZE. This procedure assumes a missing at random (MAR) pattern of missingness and corresponds to an estimand of the difference in outcome improvement if all subjects tolerated or adhered to treatment (Mallinckrodt et al, 2012). This is an estimand of efficacy to evaluate the de jure hypothesis.
2. Deviations from the MAR pattern assumed above will be evaluated. A sensitivity analysis will be performed in which, as with the above analysis, intermittent missing data will be imputed using MI based on the MCMC method. However, the remaining monotone missing data will be assumed to follow a missing not at random pattern. These data will be imputed using reference-based imputation in which the imputation model is based on data from the placebo group, thereby assuming that monotone missing data follow a trajectory similar to the placebo group (Mallinckrodt et al, 2012). As specified in the previous procedure, actual PASI/IGA scores will be imputed and then dichotomized to get the response status. The treatment differences for each imputed data set will subsequently be evaluated using the stratified CMH test as used in the primary analysis. The estimand in this procedure is the difference in outcome improvement in all randomized subjects at the planned endpoint of the study attributable to the initially randomized medication (Mallinckrodt et al, 2012). This is an estimand of effectiveness to evaluate the de facto hypothesis.

3. A final sensitivity analysis will be based on observed data at Week 16. Subjects with missing data or who have prematurely discontinued IMP will be treated as missing. The same stratified CMH test as in the primary efficacy analysis will be used.

Further details on the MI procedures will be provided in the SAP.

Missing data for binary secondary variables during the Initial Treatment Period will be imputed using NRI. Missing data for continuous secondary variables will be imputed using MI. The MI procedure for continuous variables will be similar to sensitivity analysis #1 described above for the co-primary efficacy endpoints with the following differences: 1) the imputation model will use the change from Baseline (instead of actual) values by visit and no dichotomization will be necessary; and 2) the analysis model will be based on ANCOVA as opposed to the CMH test.

For the secondary endpoints evaluated at Week 52, all subjects with missing data at Week 52 or who discontinue treatment prior to Week 52 will be counted as nonresponders. Sensitivity analyses #1 and #2 will also be performed for the Week 52 secondary endpoints. A similar procedure to what is described above will be followed. Further details on this analysis will be provided in the SAP.

For other continuous efficacy variables, MI will be used to impute missing data when possible. If the imputation model cannot converge, LOCF will be used. The MI procedure will be similar to sensitivity analysis #1 described above with the following differences: 1) the imputation model will use the change from Baseline (instead of actual) values by visit and no dichotomization will be necessary; 2) instead of using the stratified CMH test, the imputed data sets will be combined and simple means and standard errors will be calculated using Rubin's rules (via SAS PROC MIANALYZE). For calculation of other descriptive statistics such as the median, min and max, Rubin's rules do not apply. Multiple imputation estimates will be computed by simply averaging the estimates from the multiple repetitions of the imputation algorithm. This is the same approach that will be used when summarizing continuous secondary efficacy variables by subgroup.

14.8 Planned interim analysis and data monitoring

After the final Week 52 visit, an interim analysis will be performed and a corresponding interim CSR may be written. A final analysis and updated final CSR will be prepared once all data (through the SFU visit) have been collected.

14.9 Determination of sample size

A total of 560 subjects will be randomly assigned in a 4:2:1 ratio to the following treatment groups:

- Bimekizumab 320mg (320 subjects)
- Ustekinumab (160 subjects)
- Placebo (80 subjects)

The primary efficacy analysis is based on the comparison of bimekizumab to placebo for the co-primary efficacy variables of PASI90 response and IGA response at Week 16. However, as described in Section 14.3, Week 16 comparisons of bimekizumab against ustekinumab for PASI90 response and IGA response will also be part of a fixed sequence testing procedure to

control for multiplicity. Therefore, this study has been powered to show statistical superiority to ustekinumab based on the co-primary endpoints.

The assumed responder rates for PASI90 at Week 16 are 75%, 58%, and 2% for bimekizumab, ustekinumab, and placebo, respectively. Additionally, the assumed responder rates for IGA are 85%, 68%, and 5% for bimekizumab, ustekinumab, and placebo, respectively. The assumed responder rates for bimekizumab are based on the Phase 2b PS0010 data. The assumptions related to the responder rates for ustekinumab are based on those observed in the CLEAR study (Thaci et al, 2015). The power to show statistical superiority of bimekizumab relative to placebo under these assumptions is >99% for the co-primary endpoints.

The power to detect a statistically significant difference between bimekizumab and ustekinumab at a 2-sided significance level of 0.05 is 95% for PASI90 response and 98% for IGA response. Because both co-primary endpoints are highly powered independently, and because PASI and IGA response tend to be highly correlated, the overall power for achieving superiority on both co-primary endpoints is not calculated here. Note that the power for the non-inferiority testing between bimekizumab and ustekimumab for both PASI90 and IGA responses is >99% based on a 1-sided significance level of 0.025 and a non-inferiority margin of 10%.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

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

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

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

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

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

The subject may withdraw his/her consent to participate in the study at any time. A subject is considered as enrolled in the study when he/she has signed the ICF. A 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 and Assent form (as applicable), 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, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other subject-related documents to be used for the study to the IRB/IEC for its review and approval.

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

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

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

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

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

15.4 Subject privacy

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

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

15.5 Protocol amendments

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

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

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

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18 APPENDICES

18.1 Protocol Amendment 1

Rationale for the amendment

The purpose of this amendment is the following:

- To remove the escape arm to allow for a 1-year comparison of bimekizumab vs ustekinumab that is not confounded by an escape arm at Week 16.
- To remove the mandatory withdrawal at Week 28 or later

The other changes in this amendment are as follows:

- Clarified the number of subjects to be screened
- Clarified that the secondary objective of the evaluation of bimekizumab compared to ustekinumab to be after 4, 12, 16, and 52 weeks of treatment
- Added assessment of the Patient Symptom Diary (daily) to the Screening and Week 16 Visits
- Clarified that the minimum time between doses should be no less than 21 days and no more than 35 days
- Removed the criterion that excluded subjects exposed to more than 3 biologic response modifiers (including no more than 1 IL-17)
- Clarified that subjects who experienced primary failure (no response within 12 weeks) to 1or more IL-17 biologic response modifiers or more than 1 biologic response modifiers other than an IL-17 should be excluded from the study
- Removed the withdrawal criterion that subjects who do not achieve a PASI50 response by Week 28 or later be withdrawn from the study
- Clarified that the same assessor should evaluate the subject at each efficacy assessment.
- Updated the assessment and management of TB and TB risk factors
- Updated the sequence testing and the analysis of the secondary efficacy variables and other efficacy variables
- Revised the List of Abbreviations

Modifications and changes

Global changes

The following changes were made throughout the protocol:

- The study design was changed to remove the escape arm.
- Mandatory withdrawal at Week 28 or later was removed.
- Minor editorial revisions were made

Specific changes

Change #1

List of abbreviations

The following abbreviations have been deleted:

~~**ESS**~~	~~**Escape Subject Set**~~
~~**MS**~~	~~**Maintenance Set**~~
~~**WK12ResS**~~	~~**Week 12 Responder Set**~~

Change #2

Section 1 Summary

Approximately 800 subjects will be screened in order to have 640 subjects randomized in the study. For each subject, the study will last a maximum of 72 weeks and will consist of 4 periods, a Screening Period (2 to 4 weeks), a double-blind, placebo- and active comparator-controlled Initial Treatment Period (16 weeks), a double-blind, active comparator-controlled Maintenance Treatment Period (36 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the last dose of IMP). After the 36-week Maintenance Treatment Period, eligible subjects will be allowed to enroll in an open-label study.

During the Treatment Period, eligible subjects will be randomized 4:3:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered sc Q4W
- Ustekinumab (45mg or 90mg, depending on subject weight) administered sc at Baseline and 4 weeks later, followed by ustekinumab sc every 12 weeks
- Placebo administered sc Q4W

Approximately 320 subjects will be randomized to bimekizumab 320mg, 240 subjects will be randomized to ustekinumab, and approximately 80 subjects will be randomized to placebo. Investigational medicinal product (IMP) will be administered in the clinic at Baseline and Q4W thereafter, until Week 16 (Initial Treatment Period). Additional nondosing study visits will occur at Week 1 and Week 2. At Week 16, subjects will enter the Maintenance Treatment Period and will be reallocated based on original treatment and response to treatment. The Maintenance Treatment Period will include dosing Q4W.

Subjects who do not achieve a PASI90 response at Week 16 of the Initial Treatment will receive bimekizumab 320mg Q4W (ie, escape treatment). At Week 52, all subjects enrolling in the open-label study will undergo the Week 52 study assessments before receiving their first treatment dose in the open-label study. All subjects not enrolling in the open-label study will have the Week 52 study assessments and will enter the SFU Period.

Has been changed to:

- Approximately **750~~800~~** subjects will be screened in order to have **560640** subjects randomized in the study. For each subject, the study will last a maximum of 72 weeks and will consist of 4 periods, a Screening Period (2 to 4 weeks), a double-blind, placebo- and active comparator-controlled Initial Treatment Period (16 weeks), a double-blind, active comparator-controlled Maintenance Treatment Period (36 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the last dose of IMP). After the 36-week Maintenance Treatment Period, eligible subjects will be allowed to enroll in an open-label study.

~~During the Treatment Period, e~~Eligible subjects will be randomized 4:**~~2~~3**:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered sc Q4W
- Ustekinumab (45mg or 90mg, depending on subject weight) administered sc at Baseline and 4 weeks later, followed by ustekinumab sc every 12 weeks
- Placebo administered sc Q4W **for 16 weeks during the Initial Treatment Period, followed by bimekizumab 320mg administered sc Q4W during the Maintenance Treatment Period**

Approximately 320 subjects will be randomized to bimekizumab 320mg, **160~~2~~40** subjects will be randomized to ustekinumab, and approximately 80 subjects will be randomized to placebo. Investigational medicinal product (IMP) will be administered in the clinic at Baseline and Q4W thereafter, until Week 16 (Initial Treatment Period). Additional nondosing study visits will occur at Week 1 and Week 2. At Week 16, subjects will enter the Maintenance Treatment Period **~~and will be reallocated based on original treatment and response to treatment~~**. The Maintenance Treatment Period will include **Q4W** dosing **~~Q4W~~ for subjects receiving bimekizumab and Q12W dosing for subjects receiving usteinumab**.

~~Subjects who do not achieve a PASI90 response at Week 16 of the Initial Treatment will receive bimekizumab 320mg Q4W (ie, escape treatment).~~ At Week 52, all subjects enrolling in the open-label study will undergo the Week 52 study assessments before receiving their first treatment dose in the open-label study. All subjects not enrolling in the open-label study will have the Week 52 study assessments and will enter the SFU Period.

Change #3

Section 2.1.2 Current treatments for psoriasis

- Brodalumab has been approved in the US for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. Brodalumab is a human monoclonal IgG2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25. Blocking IL 17RA inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines. Brodalumab has a black box warning regarding suicidal ideation and behavior.

Has been changed to:

– Brodalumab has been approved in the US for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies. **In the EU, brodalumab is indicated for the treatment of moderate to severe plaque PSO in adult patients who are candidates for systemic therapy.** Brodalumab is a human monoclonal IgG2 antibody that selectively binds to human IL-17RA and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer and IL-25. Blocking IL 17RA inhibits IL-17 cytokine-induced responses including the release of pro-inflammatory cytokines and chemokines. Brodalumab has a black box warning regarding suicidal ideation and behavior.

Change #4

Section 2.2.1.1 Completed studies

Four clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, and UP0031 in 12 healthy volunteers. Three studies (RA0123, PS0010, and PS0016) are ongoing in subjects with moderate to severe rheumatoid arthritis (RA0123) and in subjects with moderate to severe PSO (PS0010 and PS0016).

Has been changed to:

Four clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, and UP0031 in 12 healthy volunteers. ~~**Three studies (RA0123, PS0010, and PS0016) are ongoing in subjects with moderate to severe rheumatoid arthritis (RA0123) and in subjects with moderate to severe PSO (PS0010 and PS0016).**~~

Change #5

Section 2.2.1.2 Ongoing studies

Five additional studies of bimekizumab in the treatment of PSO are ongoing.

Has been changed to:

Four additional studies of bimekizumab in the treatment of PSO and 1 study in healthy volunteers are ongoing. Five additional studies of bimekizumab in the treatment of PSO are ongoing.

Change #6

Section 3.2 Secondary objectives

The secondary objectives of the study are to:

- Evaluate the efficacy of bimekizumab compared to placebo at achieving complete clearance (PASI100) after 16 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to placebo after 4 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to ustekinumab after 12 weeks, 16 weeks, and 52 weeks of treatment
- Evaluate the change in itch, pain, and scaling of bimekizumab compared to placebo after 16 weeks of treatment as reported by subjects using the Patient Symptom Diary
- Evaluate the change in psoriatic scalp disease of bimekizumab compared to placebo after 16 weeks of treatment in subjects with scalp PSO at Baseline
- Assess TEAEs, SAEs, and TEAEs leading to withdrawal adjusted by duration of subject exposure to study treatment

Has been changed to:

The secondary objectives of the study are to:

- Evaluate the efficacy of bimekizumab compared to placebo at achieving complete clearance (PASI100) after 16 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to placebo after 4 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to ustekinumab after **4 weeks,** 12 weeks, 16 weeks, and 52 weeks of treatment
- Evaluate the change in itch, pain, and scaling of bimekizumab compared to placebo after 16 weeks of treatment as reported by subjects using the Patient Symptom Diary
- Evaluate the change in psoriatic scalp disease of bimekizumab compared to placebo after 16 weeks of treatment in subjects with scalp PSO at Baseline

Change #7

Section 5.2.2 Initial Treatment Period

During the 16-week Initial Treatment Period, approximately 640 subjects will be randomized 4:3:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered sc Q4W (320 subjects)
- Ustekinumab (240 subjects):
  - For subjects weighing ≤100kg (220lbs), 45mg sc initially and 4 weeks later
  - For subjects weighing >100kg (220lbs), 90mg sc initially and 4 weeks later
- Placebo administered sc Q4W (80 subjects)

Investigational medicinal product will be administered in the clinic by sc injection at the time points specified in the schedule of assessments (Table 5-1).

Has been changed to:

During the 16-week Initial Treatment Period, approximately **560~~640~~** subjects will be randomized 4:**2~~3~~**:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered sc Q4W (320 subjects)
- Ustekinumab (**160~~240~~** subjects):
  - For subjects weighing ≤100kg (220lbs), 45mg sc initially and 4 weeks later
  - For subjects weighing >100kg (220lbs), 90mg sc initially and 4 weeks later
- Placebo administered sc Q4W (80 subjects)

Investigational medicinal product will be administered in the clinic by sc injection at the time points specified in the schedule of assessments (Table 5-1).

Change #8

Section 5.2.3 Maintenance Treatment Period

Treatment during the Maintenance Treatment Period will be based on initial treatment and response to treatment at Week 16, per the following rules:

- All subjects who do not achieve a PASI90 response at Week 16 will be allocated to the escape arm and be treated with bimekizumab 320mg Q4W.
- Subjects in the bimekizumab 320mg treatment arm who achieve a PASI90 response at Week 16 will continue to receive bimekizumab 320mg Q4W.
- Subjects in the ustekinumab treatment arm who achieve a PASI90 response at Week 16 will continue on ustekinumab (subjects weighing ≤100kg [220lbs] at Baseline will receive 45mg sc every 12 weeks; subjects weighing >100kg [220lbs] at Baseline will receive 90mg sc every 12 weeks).
- Subjects in the placebo arm who achieve a PASI90 response at Week 16 will continue on placebo.

Subjects may receive placebo injections at certain visits in order to blind the IMP (see Section 7.2).

If a subject does not achieve a PASI50 response at Week 28 or later, the subject will be withdrawn from the study after that time point.

At the end of the Maintenance Treatment Period, all subjects enrolling in the open-label study will, after signing a new ICF, undergo the Week 52 study assessments and then receive their first dose of bimekizumab in the open-label study. All subjects not enrolling in the open-label study will have the Week 52 study assessments and will enter the SFU Period.

Has been changed to:

Treatment during the Maintenance Treatment Period will be based on initial treatment ~~**and response to treatment at Week 16**~~, per the following rules:

- ~~**All subjects who do not achieve a PASI90 response at Week 16 will be allocated to the escape arm and be treated with bimekizumab 320mg Q4W.**~~

- Subjects in the bimekizumab 320mg treatment arm ~~**who achieve a PASI90 response at Week 16**~~ will continue to receive bimekizumab 320mg Q4W.
- Subjects in the ustekinumab treatment arm ~~**who achieve a PASI90 response at Week 16**~~ will continue on ustekinumab (subjects weighing ≤100kg [220lbs] at Baseline will receive 45mg sc every 12 weeks; subjects weighing >100kg [220lbs] at Baseline will receive 90mg sc every 12 weeks).
- Subjects in the placebo arm **will receive bimekizumab 320mg Q4W**~~**who achieve a PASI90 response at Week 16 will continue on placebo**~~.

Subjects may receive placebo injections at certain visits in order to blind the IMP (see Section 7.2).

~~**If a subject does not achieve a PASI50 response at Week 28 or later, the subject will be withdrawn from the study after that time point.**~~

At the end of the Maintenance Treatment Period, all subjects enrolling in the open-label study will, after signing a new ICF, undergo the Week 52 study assessments and then receive their first dose of bimekizumab in the open-label study. All subjects not enrolling in the open-label study will have the Week 52 study assessments and will enter the SFU Period.

Change #9

Table 5-1 Schedule of study assessments

Protocol activity / Visit[a]/ Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (daily)		X	X	X	X	X	X											
scalp IGA		X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X[n]			X[n]			X[n]	

[n] For bimekizumab, the minimum time between doses should be no less than 24 days and no more than 32 days.

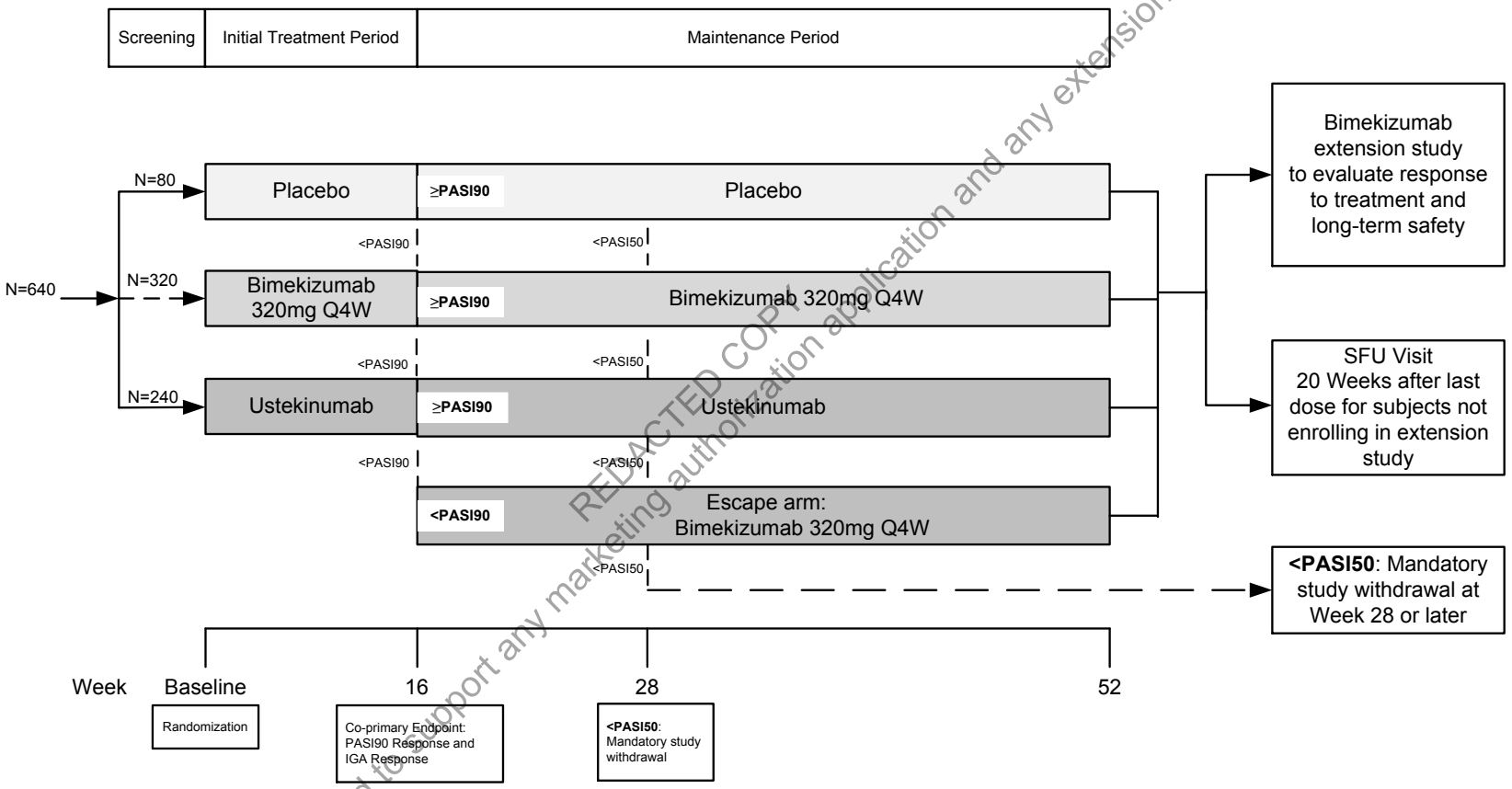
Has been changed to:

Protocol activity / Visit[a]/ Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (daily)		X	X	X	X	X	X	**X**										
scalp IGA		X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X[n]			X[n]			X[n]	

[n] For bimekizumab, the minimum time between doses should be no less than 2**14** days and no more than 3~~5~~**2** days.

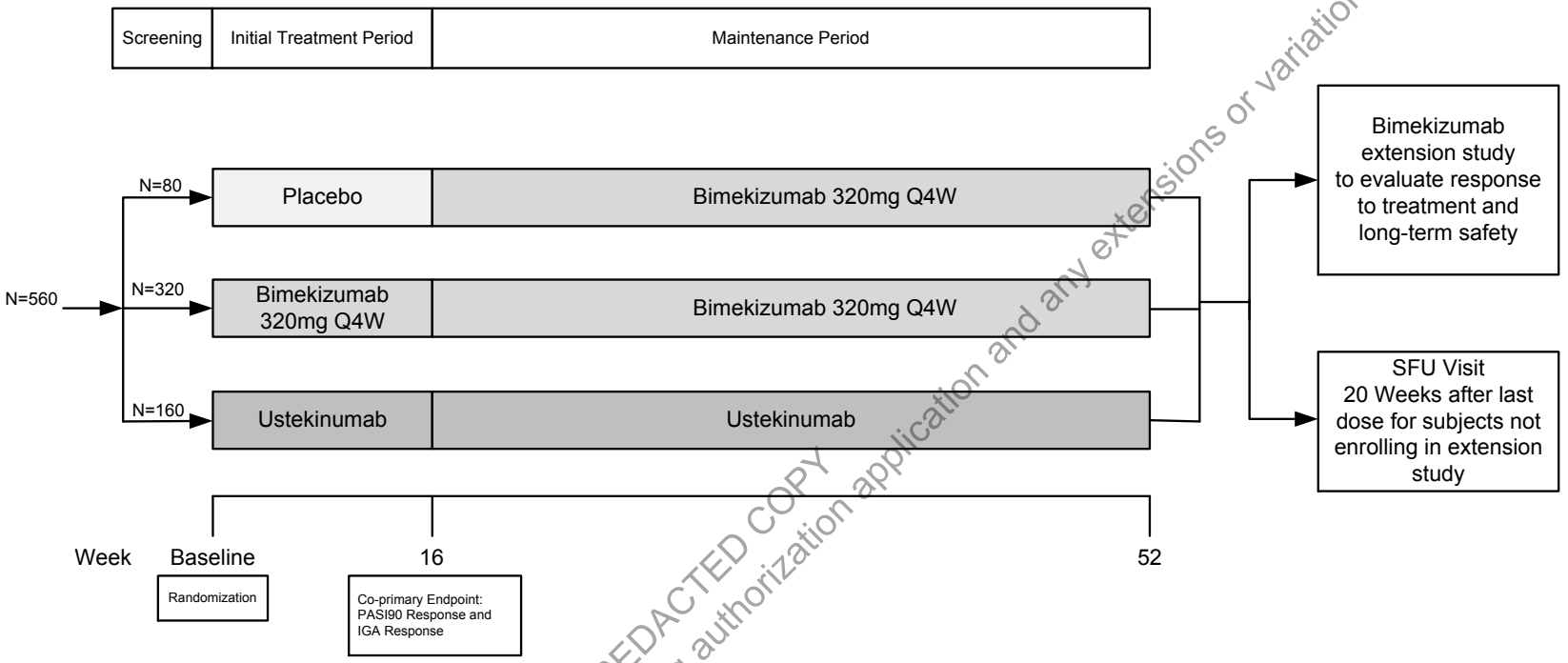
Change #10

Figure 5-1 Schematic diagram



IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks; SFU=Safety Follow-Up
Note: If a subject does not achieve a PASI50 response at Week 28 or later, the subject will be withdrawn from the study at the time point when the PASI50 response is not achieved.

Has been changed to:



IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks; SFU=Safety Follow-Up

~~**Note: If a subject does not achieve a PASI50 response at Week 28 or later, the subject will be withdrawn from the study at the time-point when the PASI50 response is not achieved.**~~

Change #11

Section 5.4 Planned number of subjects and site(s)

Approximately 860 subjects will be screened in order to have 640 subjects randomized in the study. There will be approximately 320 subjects in the bimekizumab 320mg treatment arm, 240 subjects in the ustekinumab treatment arm and 80 subjects in the placebo treatment arm. The planned number of study sites is approximately 100. Every eligible subject who signs an ICF will be randomized.

Has been changed to:

Approximately **750~~860~~** subjects will be screened in order to have **560~~640~~** subjects randomized in the study. There will be approximately 320 subjects in the bimekizumab 320mg treatment arm, **160~~240~~** subjects in the ustekinumab treatment arm and 80 subjects in the placebo treatment arm. The planned number of study sites is approximately 100. Every eligible subject who signs an ICF will be randomized.

Change #12

Section 5.8.1 Study design

The following text has been deleted:

~~The results of the Phase 2b study PS0010 indicate that approximately 80% of subjects in the bimekizumab 320mg Q4W treatment arm achieved a high level of response (PASI90). Subjects who do not achieve a PASI90 response at Week 16 are allocated to escape treatment with bimekizumab 320mg Q4W. Allocating subjects who do not achieve a PASI90 on placebo or ustekinumab to the bimekizumab 320mg Q4W escape arm provides them with the opportunity to potentially achieve a higher level of efficacy. Beyond just achieving a higher level of skin clearance, there is evidence that PASI90 is associated with higher levels of patient satisfaction (as measured by DLQI) compared with a lower PASI75 threshold (Puig et al, 2017).~~

~~If subjects are not responding to escape treatment or if they lose response over time, the mandatory withdrawal criterion for subjects who do not achieve a PASI50 response at Week 28 or later will ensure that subjects do not continue to receive prolonged exposure to study treatment that is providing a sub-optimal response, regardless of their initial randomized treatment~~.

Change #13

Section 6.2 Exclusion criterion #22

The following criterion has been deleted.

~~22. Subject has been exposed to more than 3 biological response modifiers (including no more than 1 IL-17).~~

Change #14

Section 6.2 Exclusion criterion #23

23. Subject has experienced one primary failure to an IL-17 biological response modifier (no response within 12 weeks).

Has been changed to:

23. Subject has experienced ~~**one**~~ primary failure ~~**to an IL-17 biological response modifier**~~ (no response within 12 weeks) **to 1 or more IL-17 biologic response modifier (eg, brodalumab, ixekizumab, secukinumab) OR more than 1 biologic response modifier other than an IL-17.**

Change #15

Section 6.3 Withdrawal criterion #3

The following criterion has been deleted:

~~**3. Subject does not achieve a PASI50 response at Week 28 or later.**~~

Change #16

Section 7.2 Treatment(s) to be administered

Maintenance Treatment Period dosing

Investigational medicinal product treatment during the Maintenance Treatment Period will be based on initial treatment and response to treatment at Week 16 as described in Section 5.2.3.

- Subjects who will continue to receive placebo will receive 2 placebo injections sc Q4W.
- Subjects who are to receive bimekizumab 320mg Q4W will receive 2 bimekizumab 160mg injections sc Q4W.
- Subjects randomized to receive ustekinumab will have received ustekinumab sc at Baseline and Week 4, and will continue to receive ustekinumab (based on Week 16 response) sc every 12 weeks (Weeks 16, 28, and 40). Subjects will receive placebo (2 placebo injections sc) on non-ustekinumab treatment weeks (Weeks 20, 24, 32, 36, 44, and 48). Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) will receive 1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) will receive 2 ustekinumab 45mg sc injections.

The dosing scheme is depicted in Table 7-1.

Table 7-1: Dosing Scheme

Week / Dose Assignment	Baseline (first dose)	4	8	12	16	20	24	28	32	36	40	44	48
Bimekizumab 320mg Q4W	••	••	••	••	••	••	••	••	••	••	••	••	••

Table 7-1: Dosing Scheme

Ustekinumab 45mg (subjects ≤100kg)	▲○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○
Ustekinumab 90mg (subjects >100kg)	▲▲	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○
Placebo	○○	○○	○○	○○	○○	○○	○○	○○	○○	○○	○○	○○	○○

NR=nonresponder; Q4W=every 4 weeks
Notes: A bimekizumab 160mg injection is depicted by a black circle (●). A placebo injection is depicted by a white circle (○). A ustekinumab 45mg injection is depicted by a black triangle (▲).

Note: Subjects who enter the bimekizumab 320mg Q4W escape arm will follow the Maintenance dosing scheme depicted above for the bimekizumab 320mg Q4W/Q4W group.

Has been changed to:

Maintenance Treatment Period dosing

Investigational medicinal product treatment during the Maintenance Treatment Period will be based on initial treatment ~~**and response to treatment at Week 16**~~ as described in Section 5.2.3.

- ~~**Subjects who will continue to receive placebo will receive 2 placebo injections sc Q4W.**~~
- Subjects who ~~**are to receive bimekizumab 320mg Q4W**~~ **received bimekizumab or placebo in the Initial Treatment Period will** receive 2 bimekizumab 160mg injections sc Q4W.
- Subjects randomized to receive ustekinumab will have received ustekinumab sc at Baseline and Week 4, and will continue to receive ustekinumab sc every 12 weeks (Weeks 16, 28, and 40). Subjects will receive placebo (2 placebo injections sc) on non-ustekinumab treatment weeks (Weeks 20, 24, 32, 36, 44, and 48). Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) will receive 1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) will receive 2 ustekinumab 45mg sc injections.

The dosing scheme is depicted in Table 7-1.

Table 7-1: Dosing Scheme

Week **Dose Assignment**	**Baseline (first dose)**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Bimekizumab 320mg Q4W	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●
Ustekinumab 45mg (subjects ≤100kg)	▲○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○
Ustekinumab 90mg (subjects >100kg)	▲▲	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○
Placebo	○○	○○	○○	○○	●●	●●	●●	●●	●●	●●	●●	●●	●●

NR=nonresponder; Q4W=every 4 weeks

Notes: A bimekizumab 160mg injection is depicted by a black circle (●). A placebo injection is depicted by a white circle (○). A ustekinumab 45mg injection is depicted by a black triangle (▲).
~~**Note: Subjects who enter the bimekizumab 320mg Q4W escape arm will follow the Maintenance dosing scheme depicted above for the bimekizumab 320mg Q4W/Q4W group.**~~

Change #17

Table 7-2 Prohibited psoriasis medications

Anti-IL-17 therapy	3 months (bimekizumab is excluded per exclusion criteria)

Has been changed to:

Anti-IL-17 therapy secukinumab ixekizumab brodalumab	3 months (bimekizumab is excluded per exclusion criteria)

Change #18

Section 7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subject treatment assignment will be stratified by region and prior biologic exposure (yes/no). The IRT 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.

Has been changed to:

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subject treatment assignment will be stratified by region and prior biologic exposure (yes/no). ~~**The IRT 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.

Change #19

Section 8.1 Screening Visit (2 to 4 Weeks)

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

- eC-SSRS
- Concomitant medication

Has been changed to:

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

- eC-SSRS
- **Patient Symptom Diary (daily)**
- Concomitant medication

Change #20

Section 8.2.2 Week 1 Visit (±3 days relative to Baseline)

The bullet for PHQ-9 has been deleted.

Change #21

Section 8.2.6 Week 12 Visit (±3 days relative to Baseline)

The bullet for WPAI-SHP V2.0 has been deleted.

Change #22

Section 8.2.7 Week 16 Visit (±3 days relative to Baseline)

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

- eC-SSRS
- scalp IGA for subjects with scalp involvement at Baseline

Has been changed to:

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

- eC-SSRS
- **Patient Symptom Diary (daily)**
- scalp IGA for subjects with scalp involvement at Baseline

Change #23

Section 9 Assessment of Efficacy

The following text has been added:

The PASI, IGA, scalp IGA, mNAPSI, and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each assessment.

Change #24

Section 9.1 Psoriasis Area and Severity Index

The percent area of involvement (BSA%) is estimated across 4 body areas; head, upper extremities, trunk, and lower extremities. Assessors will enter the degree of involvement for a given region as a percentage (0-100%) which will then be mapped into a grade on a scale of 0-6 (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) (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 extremities	Left, right, upper lower, flexor surface, extensor surface	20%	0 to 6
Trunk	Front, back, groin	30%	0 to 6
Lower extremities	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, respectively.

The total BSA affected by PSO will be derived based on the regional BSA values provided when assessing the PASI score.

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

Has been changed to:

The percent area of involvement (BSA%) is estimated across 4 body areas; head, upper extremities, trunk, and lower extremities. Assessors will enter the degree of involvement for a

given region ~~as a percentage (0-100%) which will then be mapped into a grade~~ on a scale of 0 **to** 6 (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) (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 extremities	Left, right, upper lower, flexor surface, extensor surface	20%	0 to 6
Trunk	Front, back, groin	30%	0 to 6
Lower extremities	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, respectively.

The total BSA affected by PSO will be **entered as a percentage from 0 to 100**~~derived based on the regional BSA values provided when assessing the PASI score~~.

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

Change #25

Section 9.11 Patient Symptom Diary responses

UCB developed a new PRO measure that will be used to assess key symptoms relevant to patients with moderate to severe chronic plaque PSO. PS0010 used 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 BaselineVisit, following which the device will be dispensed to the subject for home use until the Week 16 Visit. The ePRO diary will be administered on a daily basis from Baseline to the Week 16 Visit.

Has been changed to:

UCB developed a new PRO measure that will be used to assess key symptoms relevant to patients with moderate to severe chronic plaque PSO. PS0010 used 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~~Baseline~~** Visit, following which the device will be dispensed to the subject for home use until the Week 16 Visit. The ePRO diary will be administered on a daily basis from **Screening~~Baseline~~** to the Week 16 Visit.

Change #26

Section 12.1.1.4 Other safety topics of interest

The following paragraph was deleted:

~~The following safety topics are prespecified as being of interest for this study, based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines belonging to the same class of drugs. There are no specific AE reporting requirements for these topics, however special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB), are in place.~~

Change #27

Section 12.2 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 #9, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12-2.

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

The following laboratory parameters will be measured:

Table 12-2: Laboratory measurements

Hematology	**Chemistry**	**Urinalysis dipstick**[a]
Basophils	Calcium	pH
Eosinophils	Chloride	Albumin (protein)
Lymphocytes	Magnesium	Glucose
Atypical lymphocytes	Potassium	Blood
Monocytes	Sodium	Leukocyte esterase
Neutrophils	Glucose	Nitrite
Hematocrit	BUN	Urine dipstick for pregnancy testing[b]

Table 12-2: Laboratory measurements

Hematology	Chemistry	Urinalysis dipstick[a]
Hemoglobin	Creatinine	
MCH	ALP	
MCHC	AST	
MCV	ALT	
Platelet count	GGT	
RBC count	Total bilirubin	
WBC count	LDH	
	Serum pregnancy testing[c]	

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

[a] A urine microscopic examination will be performed if the result for albumin (protein), leukocyte esterase, blood or nitrite is abnormal. A urine microscopic examination will include: WBC, RBC, epithelial cells (squamous, transitional and renal tubular), hyaline casts, WBC casts, RBC casts, waxy casts, granular casts, calcium oxalate crystals, uric acid crystals, triphosphate crystals, yeast, bacteria, amorphous urates, and amorphous phosphates.

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

Has been changed to:

Clinical laboratory assessments consist of serum chemistry, hematology, urinalysis, and urine drug screen. 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 #9, Section 6.2) will be performed at Screening in addition to those measurements listed in Table 12-2.

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

The following laboratory parameters will be measured:

Table 12-2: Laboratory measurements

Hematology	Chemistry	Urinalysis dipstick[a]
Basophils	Calcium	pH
Eosinophils	Chloride	Albumin (protein)
Lymphocytes	Magnesium	Glucose
Atypical lymphocytes	Potassium	Blood
Monocytes	Sodium	Leukocyte esterase
Neutrophils	Glucose	Nitrite

Table 12-2: Laboratory measurements

Hematology	**Chemistry**	**Urinalysis dipstick**[a]
Hematocrit	BUN	Urine dipstick for pregnancy testing[b]
Hemoglobin	Creatinine	**Urine drug screen**[c]
MCH	ALP	
MCHC	AST	
MCV	ALT	
Platelet count	GGT	
RBC count	Total bilirubin	
WBC count	LDH	
	Serum pregnancy testing[c]	

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; ; GGT=gamma glutamyltransferase; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; **PEOT=Premature End of Treatment;** RBC=red blood cell; WBC=white blood cell

[a] A urine microscopic examination will be performed if the result for albumin (protein), leukocyte esterase, blood or nitrite is abnormal. A urine microscopic examination will include: WBC, RBC, epithelial cells (squamous, transitional and renal tubular), hyaline casts, WBC casts, RBC casts, waxy casts, granular casts, calcium oxalate crystals, uric acid crystals, triphosphate crystals, yeast, bacteria, amorphous urates, and amorphous phosphates.

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

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

Change #28

Section 12.3.1 Assessment and management of TB and TB risk factors, Item d

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

Has been changed to:

d. **NTMB infection is defined as a clinical infection caused by mycobacterial species other than those belonging to the Mycobacterium tuberculosis complex~~Current or history of NTMB infection despite prior or current therapy~~**.

Change #29

Section 12.3.1.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD is recommended) will be performed as described in Table 5-1 for all subjects. The test results will be reported as positive, negative, or indeterminate. Positive TB test results must be reported as an adverse event and appropriately updated once the final diagnosis is known (e.g. active TB, latent TB, or false positive TB test). UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is

identified, subject must undergo appropriate study-specified withdrawal procedures. The retest during Screening must be done during the protocol-defined Screening window.

Has been changed to:

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

Change #30

Section 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 that received at least 1 dose of the IMP.

The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the IMP and have a valid measurement of the co-primary efficacy variables at Baseline.

The Escape Subject Set (ESS) will consist of all subjects who receive at least 1 dose of escape bimekizumab treatment at Week 16 or later.

The Week 16 Responder Set (WK16ResS) will consist of all subjects who achieve a PASI90 response at Week 16 and receive at least 1 dose of blinded maintenance treatment at Week 16 or later.

The Maintenance Set (MS) will consist of all subjects who have a PASI score at Week 16 to evaluate response and who receive at least 1 dose of maintenance treatment at Week 16 or later. Note that the MS combines the ESS and the WK16ResS.

The Active Medication Set (AMS) will consist of all subjects who have received at least 1 dose of active IMP (bimekizumab or ustekinumab). The AMS will be used for summaries of safety that include all data from Baseline (Week 0) to Week 52.

The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding of the data.

Has been changed to:

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 that received at least 1 dose of the IMP.

The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the IMP and have a valid measurement of the co-primary efficacy variables at Baseline.

~~**The Escape Subject Set (ESS) will consist of all subjects who receive at least 1 dose of escape bimekizumab treatment at Week 16 or later.**~~

~~**The Week 16 Responder Set (WK16ResS) will consist of all subjects who achieve a PASI90 response at Week 16 and receive at least 1 dose of blinded maintenance treatment at Week 16 or later.**~~

~~**The Maintenance Set (MS) will consist of all subjects who have a PASI score at Week 16 to evaluate response and who receive at least 1 dose of maintenance treatment at Week 16 or later. Note that the MS combines the ESS and the WK16ResS.**~~

The Active Medication Set (AMS) will consist of all subjects who have received at least 1 dose of active IMP (bimekizumab or ustekinumab). The AMS will be used for summaries of safety that include all data **from Initial Treatment Period and/or Maintenance Treatment Period**~~**from Baseline (Week 0) to Week 52**~~.

The Per-Protocol Set (PPS) will consist of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variable. Important protocol deviations will be predefined and subjects with important protocol deviations will be evaluated during ongoing data cleaning meetings prior to unblinding of the data.

Change #31

Section 14.2 General statistical considerations

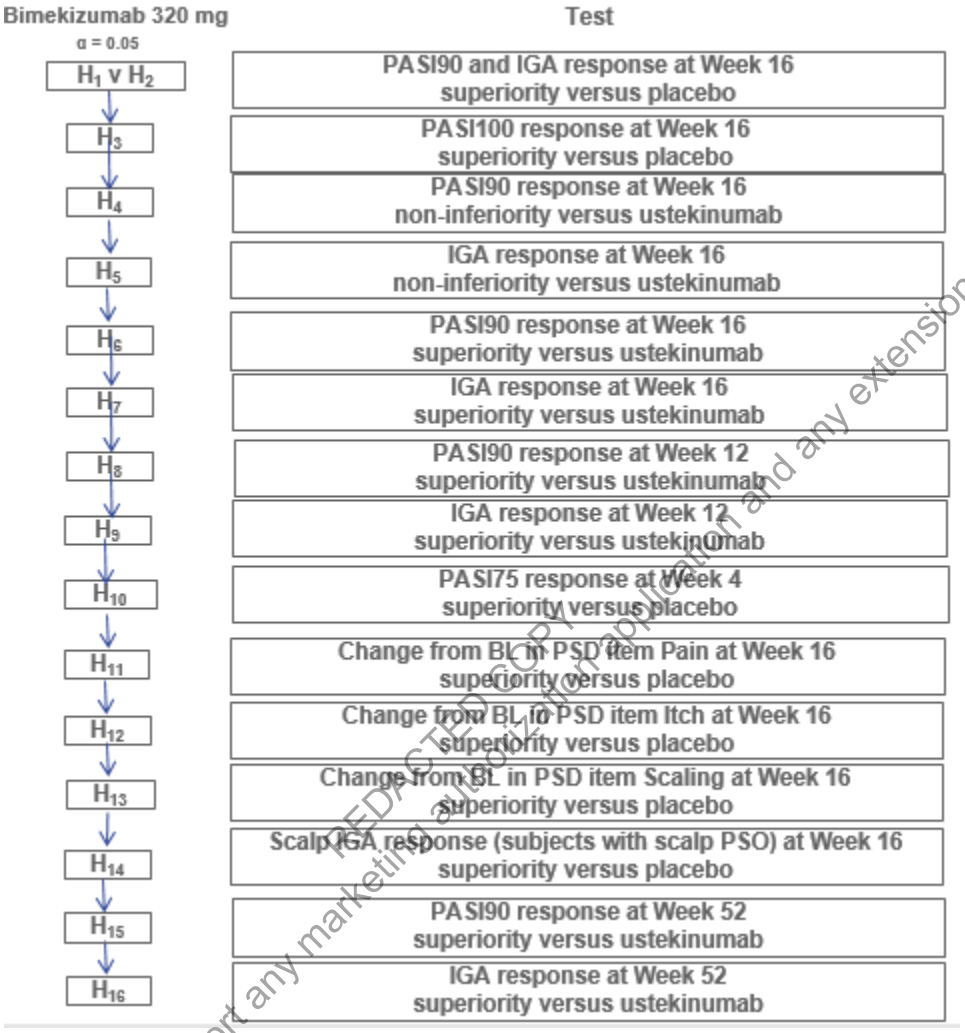
The hypotheses (H_1, H_2, H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{10}, H_{11}, H_{12}, H_{13}, H_{14}, H_{15}, and H_{16}) comparing bimekizumab vs. placebo or bimekizumab vs. ustekinumab will be tested at a 2-sided alpha level of 0.05.

Has been changed to:

The hypotheses (H_1, H_2, H_3, H_4, H_5, H_6, H_7, H_8, H_9, H_{10}, H_{11}, H_{12}, H_{13}, H_{14}, H_{15}, ~~**and**~~ H_{16}, **and** H_{17}) comparing bimekizumab vs. placebo or bimekizumab vs. ustekinumab will be tested at a 2-sided alpha level of 0.05.

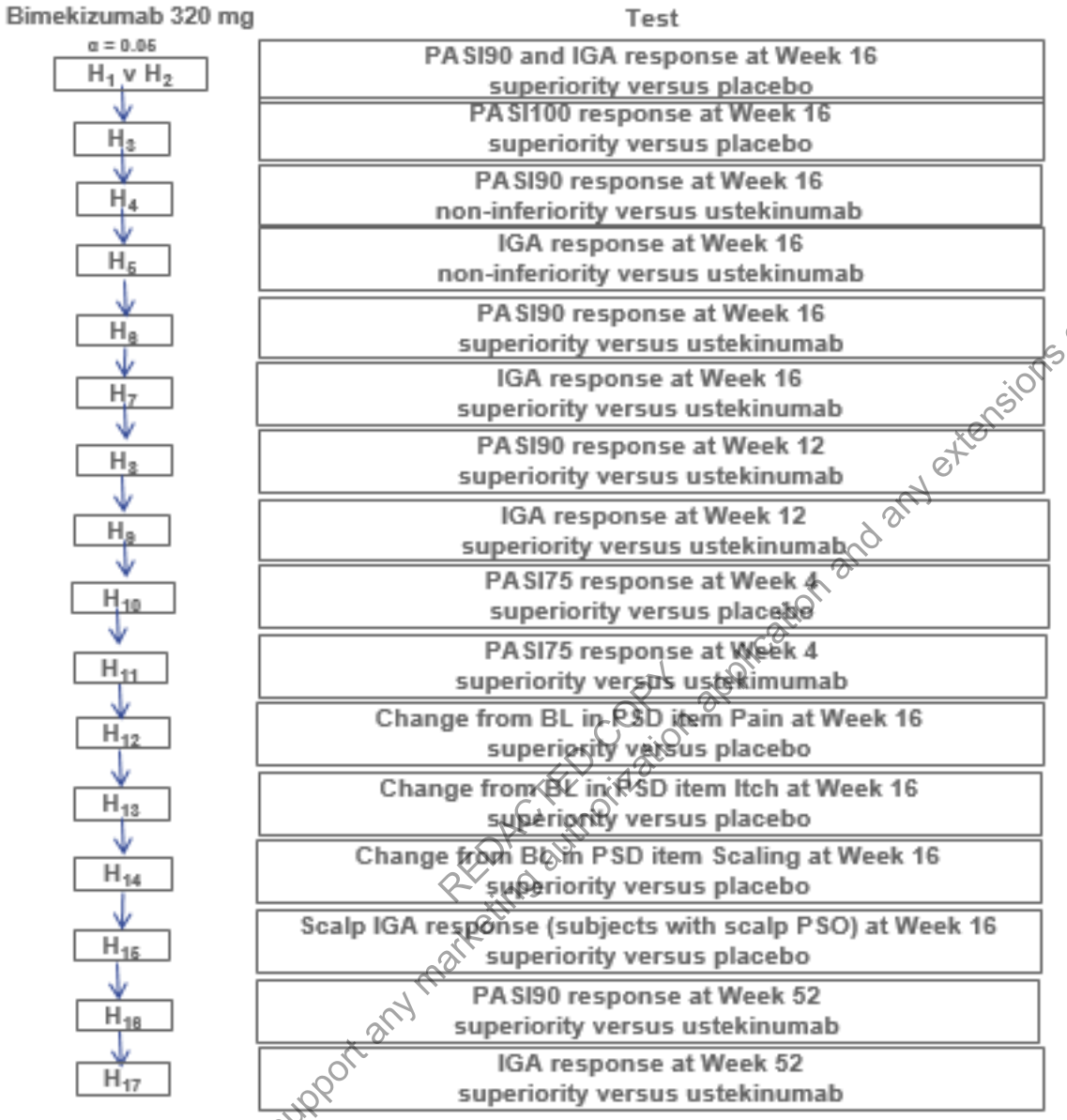
Change #32

Figure 14-1 Sequence of testing



BL=Baseline; Chg=change; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; PSD=Patient Symptom Diary; PSO=psoriasis

Has been changed to:



BL=Baseline; ~~Chg=change; DLQI=Dermatology Life Quality Index;~~ IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; PSD=Patient Symptom Diary; PSO=psoriasis

Change #33

Section 14.3.1.1 Sensitivity analyses

As a sensitivity analysis to the primary analysis method, logistic regression based on the RS will be used. The odds ratio of the responder rates at Week 16 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and prior biologic exposure (yes/no). The odds ratio, associated CI, and p-value based on the Wald test will be presented. If the logistic regression model is unable to converge, then prior biologic exposure may be dropped from the model to facilitate convergence. If the model is still unable to

converge, then region may be removed from the model as well. As with the primary analysis, missing data will be handled using NRI.

The center-by-treatment interaction will be tested by replacing region with center in the logistic regression model described above and adding a center-by-treatment interaction term. In the model, center will be based on the original centers prior to pooling. However, if the model is unable to converge due to a low number of subjects at a given center, a pooling (to be described in the SAP) will be applied in order to allow the model to converge.

In order to obtain reasonable estimates of variability for a treatment arm at a given center, a minimum of 24 subjects will be considered acceptable for a center to be included in the model without pooling. Given the 4:3:1 randomization allocation scheme, this should provide a minimum of about 12 subjects in the bimekizumab arm, 9 subjects in the ustekinumab arm, and 3 subjects in the placebo arm. Centers with fewer than 24 subjects will be eligible for pooling.

The following center pooling algorithm will be used for each geographic region:

- If a center has 24 or more subjects, then no pooling will be done for that center.
- Centers with fewer than 24 subjects will be ordered from largest to smallest with pooling proceeding in the following manner:
  - Two or more centers will be combined until the cumulative subject total is at least 24.
  - Once a pooled center has at least 24 subjects, the process will continue in an iterative fashion for the subsequent centers in the ordered list, where a new pooled center begins each time at least 24 subjects has been reached in the previous pool.
  - If this iterative process reaches the end of the ordered list of centers where the final pooled center has fewer than 24 subjects, then the subjects from the centers in that pool will be combined with the pooled center formed in the previous iteration.

This procedure is only to be performed within a geographic region – there will be no pooling of centers across regions.

Has been changed to:

As a sensitivity analysis to the primary analysis method, logistic regression based on the RS will be used. The odds ratio of the responder rates at Week 16 will be estimated and tested between treatment groups using a logistic regression model with factors of treatment group, region, and prior biologic exposure (yes/no). The odds ratio, associated CI, and p-value based on the Wald test will be presented. If the logistic regression model is unable to converge, then prior biologic exposure may be dropped from the model to facilitate convergence. If the model is still unable to converge, then region may be removed from the model as well. **In addition, if the logistic regression model cannot converge due to lack of any placebo responders, then Fisher's exact test will be used for inferential comparisons to placebo.** As with the primary analysis, missing data will be handled using NRI.

The center-by-treatment interaction will be tested by replacing region with center in the logistic regression model described above and adding a center-by-treatment interaction term. In the model, center will be based on the original centers prior to pooling. However, if the model is

unable to converge due to a low number of subjects at a given center, a pooling (to be described in the SAP) will be applied in order to allow the model to converge.

In order to obtain reasonable estimates of variability for a treatment arm at a given center, a minimum of **21~~24~~** subjects will be considered acceptable for a center to be included in the model without pooling. Given the 4:**~~2~~3**:1 randomization allocation scheme, this should provide a minimum of about 12 subjects in the bimekizumab arm, **~~6~~9** subjects in the ustekinumab arm, and 3 subjects in the placebo arm. Centers with fewer than **21~~24 s~~**ubjects will be eligible for pooling.

The following center pooling algorithm will be used for each geographic region:

- If a center has **21~~24~~** or more subjects, then no pooling will be done for that center.
- Centers with fewer than **21~~24~~** subjects will be ordered from largest to smallest with pooling proceeding in the following manner:
  - Two or more centers will be combined until the cumulative subject total is at least **21~~24~~**.
  - Once a pooled center has at least **21~~24~~** subjects, the process will continue in an iterative fashion for the subsequent centers in the ordered list, where a new pooled center begins each time at least **21~~24~~** subjects has been reached in the previous pool.
  - If this iterative process reaches the end of the ordered list of centers where the final pooled center has fewer than **21~~24~~** subjects, then the subjects from the centers in that pool will be combined with the pooled center formed in the previous iteration.

This procedure is only to be performed within a geographic region – there will be no pooling of centers across regions.

Change #34

Section 14.3.2.1.2 Maintenance Treatment Period

Because it is anticipated that most placebo subjects will escape to bimekizumab treatment at Week 16, statistical comparisons against placebo after Week 16 will not be performed. However, bimekizumab will be compared to ustekinumab at Week 52 for the RS. The analysis of PASI90 and IGA at Week 52 will be based on a stratified CMH test where region and prior biologic exposure will be used as stratification variables. Pairwise treatment comparisons will be made based on the p-value for the general association.

Missing data will be imputed using NRI. Subjects who do not achieve a PASI90 response at Week 16 and are therefore eligible for escape will be treated as PASI90 and IGA nonresponders at Week 52. All other subjects with missing data at Week 52 or who discontinue study treatment prior to Week 52 will also be treated as non-responders for this secondary efficacy analysis. Furthermore, since subjects who do not achieve a PASI50 response at Week 28 or beyond are to be removed from the study, all such subjects will also be treated as non-responders at Week 52, whether or not they were actually removed from the study.

Has been changed to:

Because **~~it is anticipated that most~~all** placebo subjects will **~~escape to~~receive** bimekizumab treatment **starting** at Week 16, statistical comparisons against placebo after Week 16 will not be

performed. However, bimekizumab will be compared to ustekinumab at Week 52 for the RS. The analysis of PASI90 and IGA at Week 52 will be based on a stratified CMH test where region and prior biologic exposure will be used as stratification variables. Pairwise treatment comparisons will be made based on the p-value for the general association.

Missing data will be imputed using NRI. ~~**Subjects who do not achieve a PASI90 response at Week 16 and are therefore eligible for escape will be treated as PASI90 and IGA nonresponders at Week 52.**~~ All ~~**other**~~ subjects with missing data at Week 52 or who discontinue study treatment prior to Week 52 will also be treated as non-responders for this secondary efficacy analysis. ~~**Furthermore, since subjects who do not achieve a PASI50 response at Week 28 or beyond are to be removed from the study, all such subjects will also be treated as non-responders at Week 52, whether or not they were actually removed from the study.**~~

Change #35

Section 14.3.2.2 Analysis of the other efficacy variables

The other efficacy variables in the Initial Treatment Period will be analyzed for all subjects in the RS. For the Maintenance Period, summaries will primarily be based on the MS (or split between the ESS and Wk16ResS as appropriate).

Binary (responder) variables will be summarized using frequency tables by treatment group for each visit.

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

…

For other efficacy variables during the Maintenance Treatment Period, summaries will include the bimekizumab and ustekinumab treatment groups. Placebo will not be included in these summaries as few placebo subjects are expected to continue on placebo during the Maintenance Treatment Period. Details of these summaries will be described further in the SAP, but there will be 3 key approaches for understanding the data in the Maintenance Treatment Period:

1. Summary of data for the RS through Week 52 based on randomized treatment group. Subjects who escape at Week 16 will be treated as non-responders during Maintenance (for responder variables) or have their Week 16 values carried forward (for continuous variables).
2. Summary of Maintenance Treatment Period data among responders only (ie, WK16ResS).
3. Summary of Maintenance Treatment Period data for subjects who escape at Week 16 (ie, ESS) by treatment group at randomization.

Has been changed to:

The other efficacy variables in the Initial Treatment Period will be analyzed for all subjects in the RS. For the Maintenance **Treatment** Period, summaries ~~**will primarily**~~ be based on the ~~**MS (or split between the ESS**~~ **RS** ~~**and Wk16ResS as appropriate)**~~. **Full details will be specified in the SAP.**

Binary (responder) variables will be summarized using frequency tables by treatment group for each visit.

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

…

For other efficacy variables during the Maintenance Treatment Period, summaries will include the bimekizumab and ustekinumab treatment groups. ~~**Placebo will not be included in these summaries as few placebo subjects are expected to continue on placebo during the Maintenance Treatment Period.**~~ Details of these summaries will be described further in the SAP, but there will be ~~**32**~~ key approaches for understanding the data in the Maintenance Treatment Period:

1. Summary of data for the RS through Week 52 based on randomized treatment group. ~~**Subjects who escape at Week 16 will be treated as non-responders during Maintenance (for responder variables) or have their Week 16 values carried forward (for continuous variables).**~~
2. Summary of Maintenance Treatment Period data among responders only (ie, WK16ResS).
3. ~~**Summary of Maintenance Treatment Period data for subjects who escape at Week 16 (ie, ESS) by treatment group at randomization.**~~

Change #36

Section 14.5.1 Safety analyses

Safety variables will be analyzed for all subjects in the SS. The AMS will be used for summaries of safety that include all data from Baseline (Week 0) to Week 52.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized descriptively by treatment group, primary system organ class, High Level Term (HLT), and preferred term. Additional tables will summarize AEs by intensity and relationship to IMP, AEs leading to withdrawal from the study, SAEs, and deaths. Adverse Events of Special Monitoring will be summarized and will be described in greater detail in the SAP.

Has been changed to:

Safety variables will be analyzed for ~~**all**~~ subjects in the SS. The AMS will be used for summaries of safety that include data from ~~**Baseline (Week 0) to Week 52**~~**the Initial Treatment Period and/or Maintenance Treatment Period**.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized descriptively by treatment group, primary system organ class, High Level Term (HLT), and preferred term. Additional tables will summarize AEs by intensity and relationship to IMP, AEs leading to withdrawal from the study, SAEs, and deaths. ~~**Adverse Events of Special Monitoring**~~**Specific safety topics of interest** will be summarized and will be described in greater detail in the SAP.

Change #37

Section 14.7 Handling of dropouts or missing data

For the secondary endpoints evaluated at Week 52, subjects who meet the criterion for escape at Week 16 (ie, do not achieve a PASI90 response) will be imputed as nonresponders for PASI90 and IGA at Week 52. All other subjects with missing data at Week 52 or who discontinue randomized treatment prior to Week 52 will also be counted as nonresponders. Furthermore, since subjects who do not achieve a PASI50 response at Week 28 or beyond are to be removed from the study, all such subjects will also be treated as non-responders at Week 52, whether or not they were actually removed from the study.

Sensitivity analyses #1 and #2 will also be performed for the Week 52 secondary endpoints. A similar procedure to what is described above will be followed with the exception that subjects who meet the criterion for escape at Week 16 (ie, do not achieve a PASI90 response) and those who meet the criterion for mandatory withdrawal (ie, do not achieve a PASI50 response at Week 28 or later) will be considered nonresponders at Week 52 and will be handled outside of the MI procedure. Further details on this analysis will be provided in the SAP.

Has been changed to:

For the secondary endpoints evaluated at Week 52, **all** subjects **~~who meet the criterion for escape at Week 16 (ie, do not achieve a PASI90 response) will be imputed as nonresponders for PASI90 and IGA at Week 52. All other subjects~~** with missing data at Week 52 or who discontinue randomized treatment prior to Week 52 will **~~also~~** be counted as nonresponders. **~~Furthermore, since subjects who do not achieve a PASI50 response at Week 28 or beyond are to be removed from the study, all such subjects will also be treated as non-responders at Week 52, whether or not they were actually removed from the study.~~**

Sensitivity analyses #1 and #2 will also be performed for the Week 52 secondary endpoints. A similar procedure to what is described above will be followed **~~with the exception that subjects who meet the criterion for escape at Week 16 (ie, do not achieve a PASI90 response) and those who meet the criterion for mandatory withdrawal (ie, do not achieve a PASI50 response at Week 28 or later) will be considered nonresponders at Week 52 and will be handled outside of the MI procedure~~**. Further details on this analysis will be provided in the SAP.

Change #38

Section 14.9 Determination of sample size

A total of 640 subjects will be randomly assigned in a 4:3:1 ratio to the following treatment groups:

- Bimekizumab 320mg (320 subjects)
- Ustekinumab (240 subjects)
- Placebo (80 subjects)

Has been changed to:

A total of **560~~640~~** subjects will be randomly assigned in a 4:**2~~3~~**:1 ratio to the following treatment groups:

- Bimekizumab 320mg (320 subjects)
- Ustekinumab (**160~~240~~** subjects)
- Placebo (80 subjects)

Change #39

Section 14.9 Determination of sample size

The power to detect a statistically significant difference between bimekizumab and ustekinumab at a 2-sided significance level of 0.05 is 98% for PASI90 response and >99% for IGA response. Because both co-primary endpoints are highly powered independently, and because PASI and IGA response tend to be highly correlated, the overall power for achieving superiority on both co-primary endpoints is not calculated here as it is similar to the lower of the individual tests. Note that the power for the non-inferiority testing between bimekizumab and ustekimumab for both PASI90 and IGA responses is >99% based on a 1-sided significance level of 0.025 and a non-inferiority margin of 10%.

Has been changed to:

The power to detect a statistically significant difference between bimekizumab and ustekinumab at a 2-sided significance level of 0.05 is 9**58**% for PASI90 response and ~~>~~9**89**% for IGA response. Because both co-primary endpoints are highly powered independently, and because PASI and IGA response tend to be highly correlated, the overall power for achieving superiority on both co-primary endpoints is not calculated here as it is similar to the lower of the individual tests. Note that the power for the non-inferiority testing between bimekizumab and ustekimumab for both PASI90 and IGA responses is >99% based on a 1-sided significance level of 0.025 and a non-inferiority margin of 10%.

18.2 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment was the following:

- Correct the information regarding the number of ongoing studies
- Add a new other efficacy variable (absolute and percent change from Baseline in the product of IGA and BSA [IGAxBSA])
- Correct the Exclusion Criterion cross-reference in Section 5.1 Study description
- Clarify the dosing window
- Add percentage of BSA as an assessment at all visits
- Correct all text throughout the protocol to clarify that PGADA and HAQ-DI will be performed on all subjects at Baseline
- Remove the pp-IGA assessment at Week 1 and Week 2

- Add a PGADA assessment at Week 4
- Remove the IGRA Tuberculosis test at Week 44
- Clarify that the Maintenance Treatment Period will begin with the administration of bimekizumab, ustekinumab, or placebo at Week 16
- Remove the 30% enrollment limit for subjects with prior biologic exposure
- Delete the erroneous statements that at Week 16 subjects will be reallocated to a new treatment group based on the PASI response
- Correct discrepancies between Section 8 Study procedures by visit and Table 5-1 Schedule of study assessments
- Clarify in footnote c of Table 12-2 Laboratory measurements the visits in which the urine drug screen will be performed
- Revised text throughout document to consistently use the term Maintenance Treatment Period
- Revise the section regarding the determination of sample size

In addition, minor spelling, editorial, and formatting changes were made, and the List of abbreviations was updated.

Specific changes

Change #1

Section 2.2.1.2 Ongoing studies

Four additional studies of bimekizumab in the treatment of PSO and 1 study in healthy volunteers are ongoing. Five additional studies of bimekizumab in the treatment of PSO are ongoing.

Has been changed to:

Four additional studies of bimekizumab in the treatment of PSO and 1 study in healthy volunteers are ongoing. **~~Five additional studies of bimekizumab in the treatment of PSO are ongoing.~~**

Change #2

Section 4.3.1 Other efficacy variable(s)

The following was added to the bulleted list of other efficacy variables:

- Absolute and percent change from Baseline in the product of IGA and BSA (IGAxBSA)

Change #3

Section 5.1 Study description

PS0009 is a randomized, double-blind, placebo- and active comparator-controlled study to evaluate the efficacy and safety of bimekizumab administered sc to subjects with PSO. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe plaque PSO (PASI ≥12 and BSA ≥10% and IGA score ≥3 [on a 5-point scale]) who are a candidate for ustekinumab, or for systemic PSO therapy and/or phototherapy and/or photochemotherapy. Subjects may have been previously exposed to a biologic therapy (see Exclusion Criteria #22 and #23).

Has been changed to:

PS0009 is a randomized, double-blind, placebo- and active comparator-controlled study to evaluate the efficacy and safety of bimekizumab administered sc to subjects with PSO. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe plaque PSO (PASI ≥12 and BSA ≥10% and IGA score ≥3 [on a 5-point scale]) who are a candidate for ustekinumab, or for systemic PSO therapy and/or phototherapy and/or photochemotherapy. Subjects may have been previously exposed to a biologic therapy (see Exclusion Criteri**ona #22 and** ~~**#22 and**~~ #23).

Change #4

Table 5-1 Schedule of study assessments

Table 5-1: Schedule of study assessments

Visit[a] / Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Informed consent[c]	X															X[d]		
Inclusion/exclusion	X	X																
Urine drug screen	X																X	
Demographic data	X																	
Psoriasis history	X																	
Significant past medical history and concomitant diseases	X	X[e]																
Physical exam[f, g]	X							X		X			X				X	X
Height		X																
Body weight		X						X		X			X				X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Urinalysis	X	X						X		X		X		X		X	X	X
ECG	X							X				X					X	
Pregnancy testing[i]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing[k]	X																	
HIV testing[k]	X																	
Chest x-ray[l]	X																	
IGRA Tuberculosis test	X														X	X		

Table 5-1: Schedule of study assessments

Visit[a] / Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Tuberculosis questionnaire	X	X						X		X			X			X	X	X
Blood sample for bimekizumab plasma concentrations[m]		X	X	X	X	X	X	X			X			X			X	X
Blood sample for anti-bimekizumab antibodiesm		X			X	X	X	X			X			X			X	X
For participating centers: Blood sample for immunophenotyping[c,m]		X	X			X	X	X									X	
Blood sample genomic, proteomic, metabolomics, and candidate biomarker analyses[c,m]		X	X			X	X	X									X	
Blood sample genetic/epigenetic analysis[c,m]		X															X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X			X			X			X	
PHQ-9	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (daily)	X	X	X	X	X	X	X	X										
scalp IGA		X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X[n]			X[n]			X[n]	
mNAPSI		X			X[o]	X[o]	X[o]	X[o]			X[o]			X[o]			X[o]	

Table 5-1: Schedule of study assessments

Visit[a] / Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
pp-IGA		X	X[p]	X[p]	X[p]	X[p]	X[p]	X[p]			X[p]			X[p]			X[p]	
EQ-5D-3L		X			X	X	X	X			X			X			X	
SF-36		X			X	X	X	X			X			X			X	
Patient Global Assessment of psoriasis[q]											X			X			X	
PASE		X															X	
PGADA[r]		X					X	X			X			X			X	
HAQ-DI[r]		X			X	X	X	X			X			X			X	
WPAI-SHP V2.0		X						X		X				X			X	
Photographs of skin and nails (subset of sites)		X	X	X	X	X	X	X		X			X				X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT[s,t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bimekizumab, ustekinumab, or placebo administration[s,t]		X			X	X	X	X[u]	X	X	X	X	X	X	X	X		

Table 5-1: Schedule of study assessments

Protocol activity / Visit[a] / Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	

DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; eCRF=electronic Case Report Form; EQ-5D-3L=Euro-Quality of Life 5-Dimensions 3-level; HAQ-DI=Health Assessment Questionnaire-Disability Index; HIV=human immunodeficiency virus; ICF=Informed Consent Form; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; PASE= Psoriatic Arthritis Screening and Evaluation; PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area Severity Index; PEOT=Premature End of Treatment; PGADA=Patient's Global Assessment of Disease Activity; PHQ-9=Patient Health Questionnaire 9; SF-36=Short Form 36-item Health Survey; SFU=Safety Follow-Up; scalp IGA=scalp-specific Investigator's Global Assessment; TB=tuberculosis; WPAI-SHP=Work Productivity and Activity Impairment Questionnaire-specific health problem

[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 ICF will be required for subjects who decide to participate in the genomics, genetics, and proteomics substudy. The ICF must be signed prior to collecting any samples for the substudy. Samples for immunophenotyping will be analyzed immediately. All PD samples and genomic, proteomic, and metabolomics samples will be stored at -80°C at the central biorepository for up to 20 years.

[d] A separate ICF is required to be completed for the open-label study.

[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] The physical examination will include examination of the following systems: eyes, hair, and skin; respiratory; CV; and GI.

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

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

[j] Subjects who have evidence of or test positive for hepatitis B by any of the following criteria: 1) positive for hepatitis B surface antigen (HBsAg+); 2) positive for anti-hepatitis B core antibody (HBcAb+) 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.

[k] The HIV test results will not be recorded in the eCRF.

[l] Screening chest x-ray must occur within 3 months prior to Screening Visit.

[m] All blood samples taken prior to dosing, except at Visit 2 (at which no dose administration occurs).

[n] The scalp IGA will only be assessed for those subjects with scalp involvement (scalp IGA score >0) at Baseline.

[o] The mNAPSI will be assessed only in subjects with nail involvement (mNAPSI score >0) at Baseline.

[p] The pp-IGA will only be assessed in subjects with palmoplantar involvement (pp-IGA score >0) at Baseline.

[q] The Patient Global Assessment of psoriasis will be performed as part of the patient symptoms diary on a weekly basis from baseline through the initial treatment period with a +3 day completion window. During the maintenance period this assessment will be completed at each clinic visit specified with a ±3 day completion window.
[r] The PGADA and HAQ-DI are assessed only for subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47).
[s] IMP administration is based on randomization.
[t] For bimekizumab, the minimum time between doses should be no less than 21 days and no more than 35 days.
[u] At Week 16 subjects will be re-allocated based on original treatment and response to treatment and will receive their first Maintenance Treatment Period dose.

Has been changed to:

Table 5-1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Informed consent[c]	X															X[d]		
Inclusion/exclusion	X	X																
Urine drug screen	X																X	
Demographic data	X																	
Psoriasis history	X																	
Significant past medical history and concomitant diseases	X	X[s]																
Physical exam[f,g]	X							X		X			X				X	X
Height		X																
Body weight		X						X		X			X				X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X	X	X	X	X	X	X	X		X		X		X		X	X	X

Table 5-1: Schedule of study assessments

Protocol activity \ Visit[a]/ Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Urinalysis	X	X						X		X		X		X		X	X	X
ECG	X							X				X					X	
Pregnancy testing[i]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing[j]	X																	
HIV testing[k]	X																	
Chest x-ray[l]	X																	
IGRA Tuberculosis test	X														~~X~~	X		
Tuberculosis questionnaire	X	X						X		X			X			X	X	X
Blood sample for bimekizumab plasma concentrations[m]		X	X	X	X	X	X	X			X			X			X	X
Blood sample for anti-bimekizumab antibodies[m]		X			X	X	X	X			X			X			X	X
For participating centers: Blood sample for immunophenotyping[c,m]		X	X			X	X	X									X	
Blood sample genomic, proteomic, metabolomics, and candidate biomarker analyses[c,m]		X	X			X	X	X									X	
Blood sample genetic/epigenetic analysis[c,m]		X															X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 5-1: Schedule of study assessments

Protocol activity \ Visit[a]/ Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Percentage of BSA	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**
DLQI		X	X	X	X	X	X	X			X			X			X	
PHQ-9	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (daily)	X	X	X	X	X	X	X	X										
scalp IGA		X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X[n]			X[n]			X[n]	
mNAPSI		X			X[o]	X[o]	X[o]	X[o]			X[o]			X[o]			X[o]	
pp-IGA		X	**X**[p]	X[n]	X[p]	X[p]	X[p]	X[p]			X[p]			X[p]			X[p]	
EQ-5D-3L		X			X	X	X	X			X			X			X	
SF-36		X			X	X	X	X			X			X			X	
Patient Global Assessment of psoriasis[q]											X			X			X	
PASE		X															X	
PGADA[r]		X			**X**		X	X			X			X			X	
HAQ-DI[r]		X			X	X	X	X			X			X			X	
WPAI-SHP V2.0		X						X		X				X			X	
Photographs of skin and nails (subset of sites)		X	X	X	X	X	X	X		X			X				X	

Table 5-1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Period (weeks after first dose)									SFU[b]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT[s,t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bimekizumab, ustekinumab, or placebo administration[s,t]		X			X	X	X	X[u]	X	X	X	X	X	X	X	X		

BSA=body surface area; CV=cardiovascular; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; eCRF=electronic Case Report Form; EQ-5D-3L=Euro-Quality of Life 5-Dimensions 3-level; **GI=gastrointestinal;** HAQ-DI=Health Assessment Questionnaire-Disability Index; **HCV=hepatitis C virus;** HIV=human immunodeficiency virus; ICF=Informed Consent Form; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; **mNAPSI=Modified Nail Psoriasis Severity Index Score; ~~PASE= Psoriatic Arthritis Screening and Evaluation;~~** PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area Severity Index; **PD=pharmacodynamics;** PEOT=Premature End of Treatment; PGADA=Patient's Global Assessment of Disease Activity; PHQ-9=Patient Health Questionnaire 9; **pp-IGA=palmoplantar Investigator's Global Assessment; PsA=psoriatic arthritis;** SF-36=Short Form 36-item Health Survey; SFU=Safety Follow-Up; scalp IGA=scalp-specific Investigator's Global Assessment; TB=tuberculosis; WPAI-SHP=Work Productivity and Activity Impairment Questionnaire-specific health problem

[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 **for subjects who do not enroll in the open-label study**.

[c] A separate ICF will be required for subjects who decide to participate in the genomics, genetics, and proteomics substudy. The ICF must be signed prior to collecting any samples for the substudy. Samples for immunophenotyping will be analyzed immediately. All PD samples and genomic, proteomic, and metabolomics samples will be stored at -80°C at the central biorepository for up to 20 years.

[d] A separate ICF is required to be completed for the open-label study.

[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] The physical examination will include examination of the following systems: eyes, hair, and skin; respiratory; CV; and GI.

[h] Vital signs **sitting systolic and diastolic** blood pressure, pulse rate, and **body** temperature) are to be measured prior to blood sampling, and prior to dosing, where applicable.

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

[j] Subjects who have evidence of or test positive for hepatitis B by any of the following criteria: 1) positive for hepatitis B surface antigen (HBsAg+); 2) positive for anti-hepatitis B core antibody (HBcAb+) 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.

[k] The HIV test results will not be recorded in the eCRF.

[l] Screening chest x-ray must occur within 3 months prior to Screening Visit.

[m] All blood samples taken prior to dosing, except at **Visit 1 and** Visit 2 (at which no dose administration occurs).

[n] The scalp IGA will only be assessed for those subjects with scalp involvement (scalp IGA score >0) at Baseline.

[o] The mNAPSI will be assessed only in subjects with nail involvement (mNAPSI score >0) at Baseline.

[p] The pp-IGA will only be assessed in subjects with palmoplantar involvement (pp-IGA score >0) at Baseline.

[q] The Patient Global Assessment of psoriasis will be performed as part of the patient symptoms diary on a weekly basis from baseline through the initial treatment period with a +3 day completion window. During the ~~m~~**Maintenance Treatment** ~~p~~**Period** this assessment will be completed at each clinic visit specified with a ±3 day completion window.

[r] The PGADA and HAQ-DI are assessed **for all subjects at Baseline. At all subsequent visits, the PGADA and HAQ-DI are assessed** only for subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47).

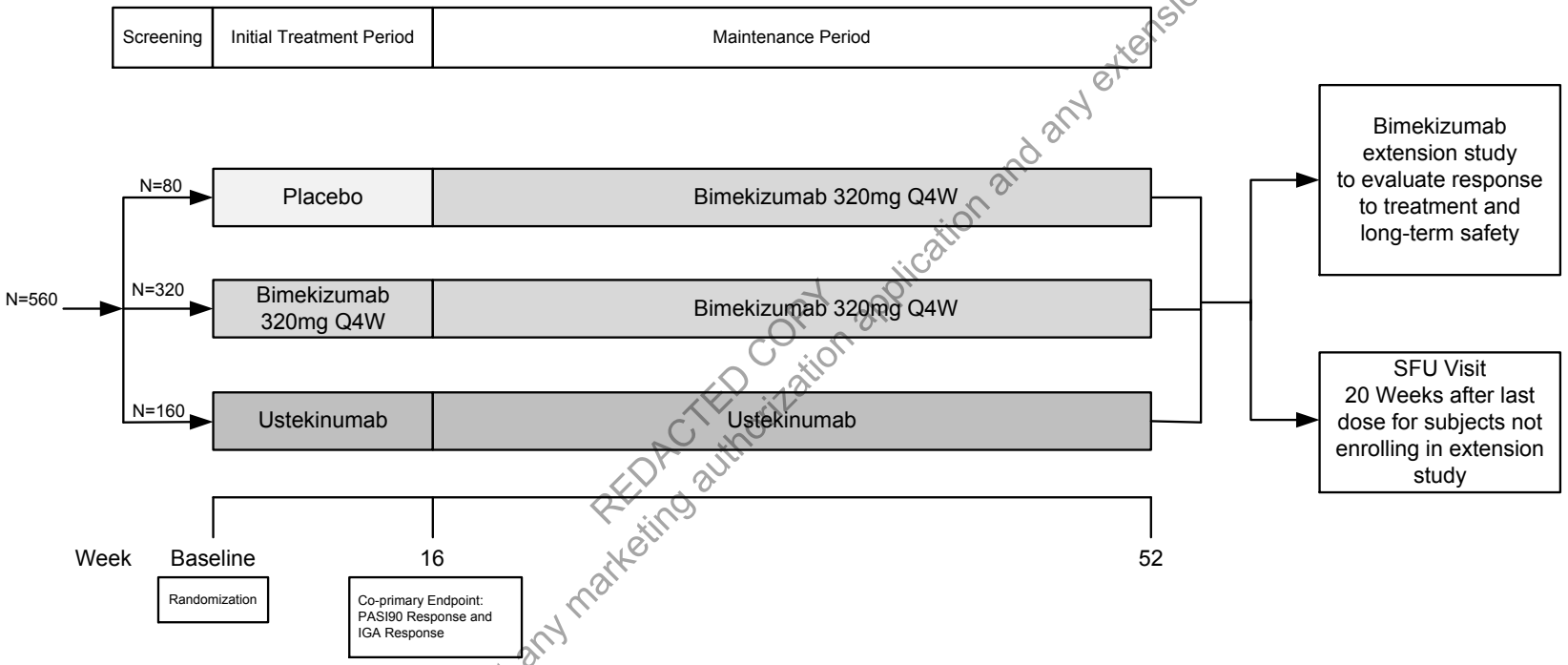
[s] IMP administration is based on randomization.

[t] **The dosing window is ±7 days relative to the scheduled dosing visit**~~**For bimekizumab, the minimum time between doses should be no less than 21 days and no more than 35 days**~~.

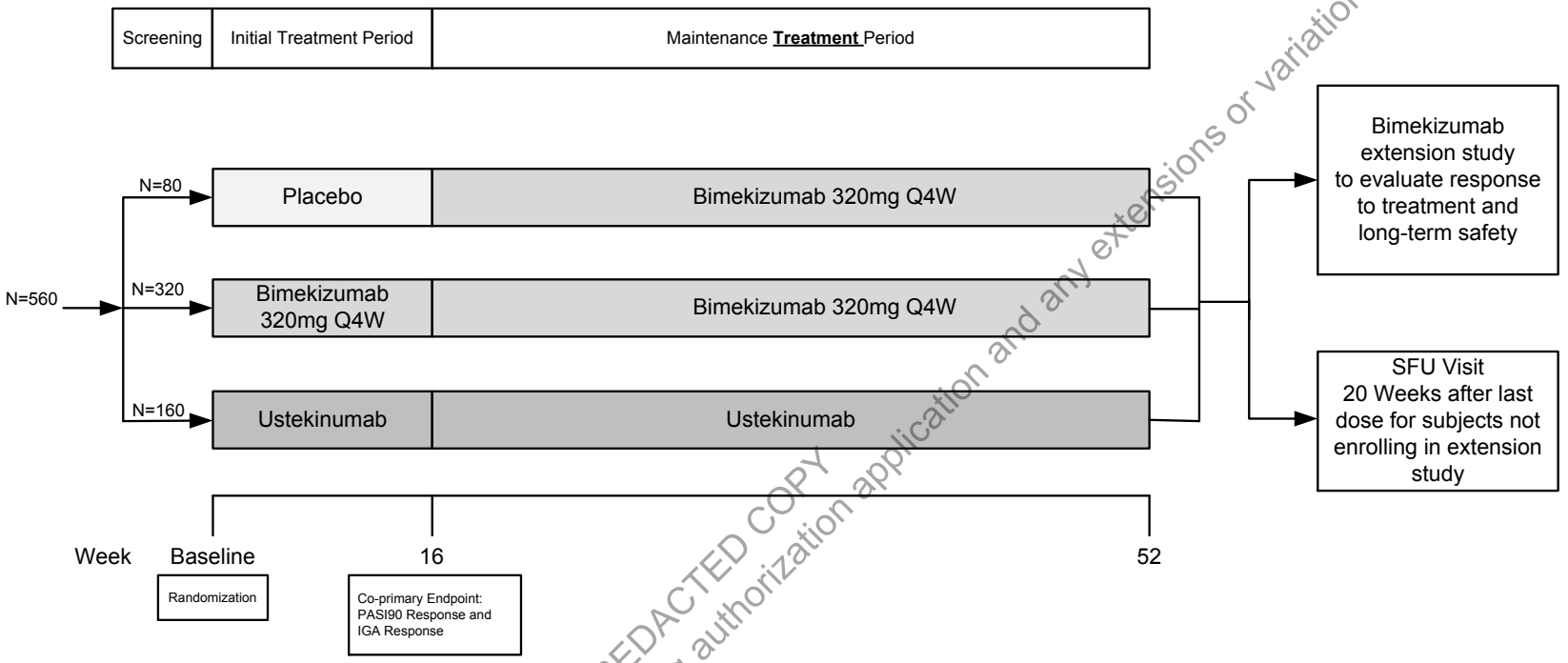
~~[u] **At Week 16 subjects will be re-allocated based on original treatment and response to treatment and will receive their first Maintenance Treatment Period dose.**~~

Change #5

Figure 5-1 Schematic diagram



Has been changed to:



Change #6

Section 6.2 Exclusion criterion #27

27. Subject has presence of severe depression, indicated by a score ≥15 using the screening PHQ-9. Medication used to treat depression should be stable for 4 weeks prior to baseline.

Has been changed to:

27. Subject has presence of severe depression, indicated by a score **≥of** 15 **to 19** using the screening PHQ-9. Medication used to treat depression should be stable for 4 weeks prior to baseline.

Change #7

Section 6.3 Withdrawal criterion #2

2. Moderately severe depression as indicated by a PHQ-9 score ≥15 if this represents an increase of 3 points compared to last visit.

Has been changed to:

2. Moderately severe depression as indicated by a PHQ-9 score **≥of**15 **to 19** if this represents an increase of 3 points compared to last visit.

Change #8

Section 7.8.1 Permitted concomitant treatments (medications and therapies)

The following was deleted:

The following concomitant medications are permitted during the study.

Change #9

Section 7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subject treatment assignment will be stratified by region and prior biologic exposure (yes/no). 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 IRT regarding a particular subject.

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

At Week 16, subjects may be reallocated to a new treatment group based on their PASI response.

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

Has been changed to:

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subject treatment assignment will be stratified by region and prior biologic exposure (yes/no). **~~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 IRT regarding a particular subject.

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

~~At Week 16, subjects may be reallocated to a new treatment group based on their PASI response.~~

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

Change #10

Section 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 21 days and no more than 35 days.
- For the SFU Visit (20 weeks after the last dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

Has been changed to:

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 dosing window is ±7 days relative to the scheduled dosing visit~~The minimum of time between doses should be no less than 21 days and no more than 35 days~~**.
- For the SFU Visit (20 weeks after the last dose), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

Change #11

Section 8.1 Screening Visit (2 to 4 Weeks), Section 8.2.1 Baseline Visit, Section 8.2.2 Week 1 Visit (±3 days relative to Baseline), Section 8.2.3 Week 2 Visit (±3 days relative to Baseline), Section 8.2.4 Week 4 Visit (±3 days relative to Baseline), Section 8.2.5 Week 8 Visit (±3 days relative to Baseline), Section 8.2.6 Week 12 Visit (±3 days relative to Baseline), Section 8.2.7 Week 16 Visit (±3 days relative to Baseline), Section 8.3.1 Week 20 Visit (±3 days relative to Baseline), Section 8.3.2 Week 24 Visit (±3 days relative to Baseline), Section 8.3.3 Week 28 Visit (±3 days relative to Baseline), Section 8.3.4 Week 32 Visit (±3 days relative to Baseline), Section 8.3.5 Week 36 Visit (±3 days relative to Baseline), Section 8.3.6 Week 40 Visit (±3 days relative to Baseline), Section 8.3.7 Week 44 Visit (±3 days relative to Baseline), Section 8.3.8 Week 48 Visit (±3 days relative to Baseline), Section 8.3.9 Week 52 Visit (±3 days relative to Baseline), and **Section 8.5 Safety Follow-Up Visit (20 weeks after last dose, -3 days/+7 days)**

The following was added to the bulleted lists:

- Percentage of BSA

Change #12

Section 8.2.1 Baseline Visit

The following items in the bulleted list:

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses
  - Genetic/epigenetic analysis
- PGADA (only for subjects with PsA)

- HAQ-DI (only for subjects with PsA)

Have been changed to:

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses **(participating subjects only)**
  - Genetic/epigenetic analysis **(participating subjects only)**
- PGADA ~~**(only for subjects with PsA)**~~
- HAQ-DI ~~**(only for subjects with PsA)**~~

Change #13

Section 8.2.2 Week 1 Visit (±3 days relative to Baseline)

The following was deleted from the bulleted list:

- pp-IGA

Change #14

Section 8.2.3 Week 2 Visit (±3 days relative to Baseline)

The following was added to the bulleted list:

- DLQI

Change #15

Section 8.2.3 Week 2 Visit (±3 days relative to Baseline)

The following was deleted from the bulleted list:

- pp-IGA

Change #16

Section 8.2.4 Week 4 Visit (±3 days relative to Baseline)

The following was added to the bulleted list:

- PGADA (only for subjects with PsA)

Change #17

Section 8.2.6 Week 4 Visit (±3 days relative to Baseline) and Section 8.2.7 Week 16 Visit (±3 days relative to Baseline)

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses

Has been changed to:

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses **(participating subjects only)**

Change #18

Section 8.2.7 Week 16 Visit (±3 days relative to Baseline)

After completion of the above-mentioned procedures, administration of bimekizumab, ustekinumab, or placebo will occur.

Has been changed to:

After completion of the above-mentioned procedures, **the Maintenance Treatment Period will begin with** administration of bimekizumab, ustekinumab, or placebo ~~**will occur**~~.

Change #19

Section 8.2.7 Week 16 Visit (±3 days relative to Baseline) and Section 8.3.7 Week 44 Visit (±3 days relative to Baseline)

The following was deleted from the bulleted lists:

- IGRA Tuberculosis test

Change #20

Section 8.3.5 Week 36 Visit (±3 days relative to Baseline)

The following was deleted from the bulleted list:

- Bimekizumab plasma concentrations
- Anti-bimekizumab antibodies

Change #21

Section 8.3.9 Week 52 Visit (±3 days relative to Baseline)

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses
  - Immunophenotyping (participating centers only)
  - Genetic/epigenetic analysis

Has been changed to:

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Genomic, proteomic, metabolomics, and candidate biomarker analyses **(participating subjects only)**
  - Immunophenotyping (participating centers only)
  - Genetic/epigenetic analysis **(participating subjects only)**

Change #22

Section 9 Assessment of efficacy

The PASI, IGA, scalp IGA, mNAPSI, and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each assessment.

Has been changed to:

The PASI, **BSA,** IGA, scalp IGA, mNAPSI, and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably the same assessor should evaluate the subject at each assessment.

Change #23

Section 9.4 Patient Health Questionnaire 9

A score of 15 to 19 is considered to indicate moderately severe major depression, and a score >20 is considered to be severe major depression.

Has been changed to:

A score of 15 to 19 is considered to indicate moderately severe major depression, and a score ~~>~~≥20 is considered to be severe major depression.

Change #24

Section 9.10 Patient Global Assessment of psoriasis

During the maintenance period, this assessment will be completed within a ±3-day completion window at the visits specified in Table 5-1.

Has been changed to:

During the ~~**m**~~**Maintenance Treatment ~~p~~Period**, this assessment will be completed within a ±3-day completion window at the visits specified in Table 5-1.

Change #25

Section 9.14 HAQ-DI score

Subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47) will complete the HAQ-DI at the visits specified in Table 5-1.

Has been changed to:

All subjects will complete the HAQ-DI at Baseline. Subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47) will complete the HAQ-DI at the visits specified in Table 5-1.

Change #26

Section 9.16 Photographs

At certain clinical sites, representative photographs of the changes in skin and nail appearance will be captured. Subjects will have full body (anterior and posterior views, below neck) and nail photographs taken. Photographs will be anonymized.

Has been changed to:

At certain clinical sites, representative photographs of the changes in skin and nail appearance will be captured. Subjects will have full body (anterior and posterior views~~**, below neck**~~) and nail photographs taken. Photographs will be anonymized.

Change #27

Table 12-2 Laboratory measurements, footnote c

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

Has been changed to:

[c] Urine drug screen will be performed at Screening Visit**,** and **Week 52 or** PEOT Visit

Change #28

Section 14.9 Determination of sample size

The power to detect a statistically significant difference between bimekizumab and ustekinumab at a 2-sided significance level of 0.05 is 95% for PASI90 response and 98% for IGA response. Because both co-primary endpoints are highly powered independently, and because PASI and IGA response tend to be highly correlated, the overall power for achieving superiority on both co-primary endpoints is not calculated here as it is similar to the lower of the individual tests. Note that the power for the non-inferiority testing between bimekizumab and ustekimumab for both PASI90 and IGA responses is >99% based on a 1-sided significance level of 0.025 and a non-inferiority margin of 10%.

Has been changed to:

The power to detect a statistically significant difference between bimekizumab and ustekinumab at a 2-sided significance level of 0.05 is 95% for PASI90 response and 98% for IGA response. Because both co-primary endpoints are highly powered independently, and because PASI and IGA response tend to be highly correlated, the overall power for achieving superiority on both co-primary endpoints is not calculated here ~~**as it is similar to the lower of the individual tests**~~. Note that the power for the non-inferiority testing between bimekizumab and ustekimumab for both PASI90 and IGA responses is >99% based on a 1-sided significance level of 0.025 and a non-inferiority margin of 10%.

Change #29

Section 17 REFERENCES

The following references were deleted from the list:

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

Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, Hsu MC, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in

patients with moderate-to-severe psoriasis: Results from a randomized, doubleblind, placebo-controlled phase III trial. J Am Acad Dermatol. 2010;63(3):457-65.

Puig L, Thom H, Mollon P, Tian H, Ramakrishna GS. Clear or almost clear skin improves the quality of life in patients with moderate-to-severe psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2017;31(2):213-220.

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

Sozu T, Sugimoto T, Hamasaki T. Sample size determination in clinical trials with multiple co-primary binary endpoints. Statistics in Medicine. 2010;29:2169-79.

Sozu T, Sugimoto T, Hamasaki T. Sample size determination in clinical trials with multiple co-primary endpoints including mixed continuous and binary variables. Biometrical Journal. 2012;5:716-29.

18.3 Protocol Amendment 3

Rationale for the amendment

The purpose of this amendment was the following:

- Update name and contact information for Sponsor study physician
- Extend the duration of the Screening Period, and therefore the overall study duration, by 1 week
- Update list of current treatment for PSO to reflect changes in labeling and approved countries
- Update list of completed and ongoing bimekizumab studies to reflect completion of study UP0042
- Clarify calculation of PASI responder rates
- Remove references to PD assessments as they will not be conducted in this study
- Update Schedule of study assessments to include a hematology and biochemistry sample at Week 20, to modify the visits at which the TB questionnaire, body weight, physical examination, and ECG are assessed, and to modify the visits at which photographs are taken
- Clarify that all visits from first dose to Week 24 would have a ±3 day visit window, while all visits from Week 28 to end of study would have a ±7 day window
- Clarify the dosing window
- Modify exclusion criterion to clarify exclusion of subjects who have participated in other studies of bimekizumab, other medications (systemic or topical), or devices
- Modify exclusion criteria pertaining to history of malignancy, systemic disease, and major depression
- Add new withdrawal criteria for nonresponders and for subjects with newly diagnosed IBD
- Clarify withdrawal criteria for subjects with depression or suicidal ideation or behavior
- Clarify that for subjects receiving ustekinumab, dosing is based on weight at Baseline

- Update prohibited concomitant medications to include tildrakizumab and risankizumab
- Corrected discrepancies between Section 8 Study procedures by visit and Table 5-1 Schedule of study assessments
- Revise PASE questionnaire scoring
- Remove immunophenotyping assessments
- Clarify photography requirements
- Clarify definition of abortion
- Updated laboratory measurements to be performed
- Provide additional details for requirements for IMP rechallenge in the event of PDILI
- Defined a Maintenance Set as an analysis population
- Update the definition of the FAS Set
- Clarify regions for analyses
- Update the sequence testing

In addition, minor spelling, editorial, and formatting changes were made, and the List of abbreviations was updated.

Change #1

Study Contact Information

Sponsor Study Physician

Name:	[redacted], MD
Address:	UCB Biosciences, 8010 Arco Corporation Drive, Raleigh, NC 27617
Phone:	[redacted]
Fax:	[redacted]

Sponsor Study Physician

Name:	[redacted], **MD, PhD**
Address:	UCB Biosciences, 8010 Arco Corporation Drive, Raleigh, NC 27617
Phone:	[redacted]
Fax:	[redacted]

Change #2

Section 1 Summary, second and third paragraphs

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

Approximately 750 subjects will be screened in order to have 560 subjects randomized in the study. For each subject, the study will last a maximum of 72 weeks and will consist of 4 periods, a Screening Period (2 to 4 weeks), a double-blind, placebo- and active comparator-controlled Initial Treatment Period (16 weeks), a double-blind, active comparator-controlled Maintenance Treatment Period (36 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the last dose of investigational medicinal product (IMP).

Has been changed to:

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

Approximately 750 subjects will be screened in order to have 560 subjects randomized in the study. For each subject, the study will last a maximum of ~~**72**~~ **73** weeks and will consist of 4 periods, a Screening Period (2 to ~~**4**~~ **5** weeks), a double-blind, placebo- and active comparator-controlled Initial Treatment Period (16 weeks), a double-blind, active comparator-controlled Maintenance Treatment Period (36 weeks), and a Safety Follow-Up (SFU) Period (20 weeks after the ~~**last**~~ **final** dose of investigational medicinal product (IMP).

Change #3

Section 1 Summary, second to last paragraph

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

Has been changed to:

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

Change #4

Section 2.1.2 Current treatments for psoriasis, first paragraph

Therapy for patients with PSO 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,

cyclosporine, the oral phosphodiesterase 4 (PDE4) inhibitor apremilast, or biologic agents, such as tumor necrosis factor (TNF) antagonists, interleukin (IL) 12/23 inhibitors, IL-23p19 inhibitors and IL-17A inhibitors. The effectiveness of TNF inhibitors in the treatment of PSO 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 PSO. Interleukin inhibitors approved for this indication include the IL-12/23 antagonist ustekinumab, the IL-23p19 antagonist guselkumab (in the US only), the IL-17A inhibitors secukinumab and ixekizumab, and the IL-17 receptor antagonist brodalumab.

Has been changed to:

Therapy for patients with PSO 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**~~ **phototherapy**, methotrexate, cyclosporine, the oral phosphodiesterase 4 (PDE4) inhibitor apremilast, or biologic agents, such as tumor necrosis factor (TNF) antagonists, interleukin (IL) 12/23 inhibitors, IL-23p19 inhibitors and IL-17A inhibitors. The effectiveness of TNF inhibitors in the treatment of PSO 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 PSO. Interleukin inhibitors approved for this indication include the IL-12/23 antagonist ustekinumab, the IL-23p19 antagonist guselkumab ~~**(in the US only)**~~, the IL-17A inhibitors secukinumab and ixekizumab, and the IL-17 receptor antagonist brodalumab.

Change #5

Section 2.1.2 Current treatments for psoriasis, third bullet

- 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.

Has been changed to:

- ~~**Chemophototherapy**~~ **Phototherapy** 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.

Change #6

Section 2.1.2 Current treatments for psoriasis, last bullet, second and fourth sub-bullets

  - Ustekinumab has been approved in the US and the EU for the treatment of adult patients with moderate to severe plaque PSO who are candidates for phototherapy or systemic therapy. Ustekinumab is a human immunoglobulin (Ig) G1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines, naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation.

– Guselkumab has been approved in the US for the treatment of adult patients with moderate to severe plaque PSO who are candidates for systemic therapy or phototherapy. It is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

Has been changed to:

– Ustekinumab has been approved in the US and the EU for the treatment of ~~**adult**~~ patients with moderate to severe plaque PSO who are candidates for phototherapy or systemic therapy. Ustekinumab is a human immunoglobulin (Ig) G1κ monoclonal antibody that binds with specificity to the p40 protein subunit used by both the IL-12 and IL-23 cytokines, naturally occurring cytokines that are involved in inflammatory and immune responses, such as natural killer cell activation and CD4+ T-cell differentiation and activation.

– Guselkumab has been approved in the US **and the EU** for the treatment of adult patients with moderate to severe plaque PSO who are candidates for systemic therapy or phototherapy. It is a human monoclonal IgG1λ antibody that selectively binds to the p19 subunit of interleukin 23 (IL-23) and inhibits its interaction with the IL-23 receptor. IL-23 is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Guselkumab inhibits the release of proinflammatory cytokines and chemokines.

Change #7

Section 2.2.1.1 Completed studies

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

Hs been changed to:

~~**Four**~~ **Five** clinical studies of bimekizumab have been completed: UP0008 in 39 subjects with mild to moderate plaque PSO, RA0124 in 30 healthy volunteers, PA0007 in 53 subjects with PsA, ~~**and**~~ UP0031 in 12 healthy volunteers**, and UP0042 in 48 healthy volunteers**.

And the following paragraph has been added:

UP0042 was a randomized double-blind, placebo-controlled, single-dose, parallel-group study to evaluate the safety, tolerability, and pharmacokinetics of bimekizumab administered as subcutaneous injection to Japanese and Caucasian healthy subjects. This study demonstrated that the PK profiles following single administration of 80mg, 160mg, and 320mg with sc injection were dose proportional with a linear elimination in both Japanese and Caucasian subjects and that the PK profiles of Japanese and Caucasian subjects were considered to be generally similar. A single dose of bimekizumab (80mg, 160mg, or 320mg) administered as sc injection was generally safe and well tolerated in

healthy Japanese and Caucasian subjects and no major differences in safety findings were observed between Japanese and Caucasian subjects.

Change #8

Section 2.2.1.1 Ongoing studies

Four additional studies of bimekizumab in the treatment of PSO and 1 study in healthy volunteers are ongoing.

- PS0010 is a Phase 2b, double-blind, placebo-controlled, dose ranging study to evaluate the safety, efficacy, PK, and pharmacodynamics (PD) of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PS0011 is a long-term extension study for subjects who completed PS0010 to assess the long-term safety, tolerability, and efficacy of bimekizumab.
- PS0016 is a Phase 2a, subject-blind, Investigator-blind study to evaluate the time course of PD response, safety, and PK of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PS0018 is a long-term extension study for eligible subjects from PS0016 to assess the safety, tolerability, and efficacy of bimekizumab.
- UP0042 is a Phase 1 study designed to evaluate the safety, tolerability, and PK of bimekizumab administered as an sc injection of 80mg, 160mg, or 320mg to Japanese and Caucasian healthy subjects.

Has been changed to:

Four additional studies of bimekizumab in the treatment of PSO ~~**and 1 study in healthy volunteers**~~ are ongoing.

- PS0010 is a Phase 2b, double-blind, placebo-controlled, dose ranging study to evaluate the safety, efficacy, PK, and pharmacodynamics (PD) of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PS0011 is a long-term extension study for subjects who completed PS0010 to assess the long-term safety, tolerability, and efficacy of bimekizumab.
- PS0016 is a Phase 2a, subject-blind, Investigator-blind study to evaluate the time course of PD response, safety, and PK of bimekizumab in adult subjects with moderate to severe chronic plaque PSO.
- PS0018 is a long-term extension study for eligible subjects from PS0016 to assess the safety, tolerability, and efficacy of bimekizumab.
- ~~**UP0042 is a Phase 1 study designed to evaluate the safety, tolerability, and PK of bimekizumab administered as an sc injection of 80mg, 160mg, or 320mg to Japanese and Caucasian healthy subjects.**~~

Change #9

Section 3.3 Other objectives, 12th bullet

- Assess the PK and PD of bimekizumab

Has been changed to:

- Assess the PK ~~**and PD**~~ of bimekizumab

Change #10

Section 4.3 Other variables

The following text has been added:

The other variables are listed below and will be evaluated according to the planned assessments Table 5-1.

Change #11

Section 4.3.1 Other efficacy variables, last sentence in third paragraph

Note that PASI responder rates will always be calculated relative to the Baseline (first dose) Visit.

Has been changed to:

~~**Note that**~~ Unless otherwise stated PASI responder rates will ~~**always**~~ be calculated relative to the Baseline Visit (first dose).

Change #12

Section 4.4 Pharmacokinetic and pharmacodynamic variable(s)

Section 4.4.1.1 Pharmacokinetic and pharmacodynamic variables

The PK variable is the plasma concentration of bimekizumab.

For subjects enrolled in participating centers, immunophenotyping by flow cytometry on whole blood will be performed.

Has been changed to:

Section 4.3.3 Pharmacokinetic ~~and pharmacodynamic~~ variable~~(s)~~

~~**Section 4.4.1.1 Pharmacokinetic and pharmacodynamic variables**~~

The PK variable is the plasma concentration of bimekizumab.

~~**For subjects enrolled in participating centers, immunophenotyping by flow cytometry on whole blood will be performed.**~~

Change #13

Section 4.5 Pharmacogenomic variables

Section 4.6 Immunological variable

Have been changed to:

Section 4.3.4 Pharmacogenomic variables

Section 4.3.5 Immunological variable

Change #14

Section 5.1 Study description

PS0009 is a randomized, double-blind, placebo- and active comparator-controlled study to evaluate the efficacy and safety of bimekizumab administered sc to subjects with PSO. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe plaque PSO (PASI ≥12 and BSA ≥10% and IGA score ≥3 [on a 5-point scale]) who are a candidate for ustekinumab, or for systemic PSO therapy and/or phototherapy and/or photochemotherapy. Subjects may have been previously exposed to a biologic therapy (see Exclusion Criterion #23).

Has been changed to:

PS0009 is a randomized, double-blind, placebo- and active comparator-controlled study to evaluate the efficacy and safety of bimekizumab administered sc to subjects with PSO. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe plaque PSO (PASI ≥12 and BSA ≥10% and IGA score ≥3 [on a 5-point scale]) who are a candidate for ustekinumab, or for systemic PSO therapy and/or phototherapy ~~**and/or photochemotherapy**~~. Subjects may have been previously exposed to a biologic therapy (see Exclusion Criterion #23).

Change #15

Section 5.2 Study periods

This study will include 4 periods, a Screening Period (2 to 4 weeks), an Initial Treatment Period (16 weeks), a Maintenance Treatment Period (36 weeks), and a SFU Period (20 weeks after the last dose of IMP). After completion of the Maintenance Treatment Period, eligible subjects will be allowed to enroll in an open-label study. Subjects enrolling into the open-label study will not have the PS0009 SFU Visit.

Has been changed to:

This study will include 4 periods, a Screening Period (2 to ~~**4**~~**5** weeks), an Initial Treatment Period (16 weeks), a Maintenance Treatment Period (36 weeks), and a SFU Period (20 weeks after the ~~**last**~~ **final** dose of IMP). After completion of the Maintenance Treatment Period, eligible subjects will be allowed to enroll in an open-label study. Subjects enrolling into the open-label study will not have the PS0009 SFU Visit.

Change #16

Section 5.2.1 Screening Period

The Screening Period will last 2 weeks, but can be extended up to a total of 4 weeks.

Has been changed to:

The Screening Period will last 2 weeks, but can be extended up to a total of **~~4~~ 5** weeks **in cases where a laboratory assessment needs to be repeated or to allow washout of prohibited medications**.

Change #17

Section 5.2.2 Initial Treatment Period

- Ustekinumab (160 subjects):
  - For subjects weighing ≤100kg (220lbs), 45mg sc initially and 4 weeks later
  - For subjects weighing >100kg (220lbs), 90mg sc initially and 4 weeks later

Has been changed to:

- Ustekinumab (160 subjects):
  - For subjects weighing ≤100kg (220lbs) **at Baseline**, 45mg sc initially and 4 weeks later
  - For subjects weighing >100kg (220lbs) **at Baseline**, 90mg sc initially and 4 weeks later

Change #18

Section 5.3 Study duration per subject

For each subject, the study will last a maximum of up to 72 weeks, as follows:

- Screening Period: 2 to 4 weeks

Has been changed to:

For each subject, the study will last a maximum of up to **~~72~~ 73** weeks, as follows:

- Screening Period: 2 to **~~4~~ 5** weeks

Change #19

Section 5.5 Anticipated regions and countries

- The regions planned for study conduct are Europe, Canada, and the US, with possible extension to other regions and countries.

Has been changed to:

The regions planned for study conduct are **North America, Western** Europe, ~~**Canada, and the US**~~ **Central/Eastern Europe, and Asia/Australia**, with possible extension to other regions and countries.

Change #20

Section 5.6 Schedule of study assessments

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

Has been changed to:

The schedule of study assessments is presented in Table 5-1. **At each visit, all study assessments should be performed prior to administration of IMP.**

Table 5--1 Schedule of study assessments

Protocol activity \ Visit[a]/ Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[bb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Informed consent[c]	X															X[d]		
Inclusion/exclusion	X	X																
Urine drug screen	X																X	
Demographic data	X																	
Psoriasis history	X																	
Significant past medical history and concomitant diseases	X	X[e]																
Physical exam[f, g]	X							X		X			X				X	X
Height		X																
Body weight		X						X		X			X				X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X	X	X	X	X	X	X	X		X		X		X		X	X	X
Urinalysis	X	X						X		X		X		X		X	X	X
ECG	X							X				X					X	
Pregnancy testing[i]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing[j]	X																	
HIV testing[k]	X																	
Chest x-ray[l]	X																	
IGRA Tuberculosis test	X															X		

Table 5--1 Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[bb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Tuberculosis questionnaire	X	X						X		X			X			X	X	X
Blood sample for bimekizumab plasma concentrations[m]		X	X	X	X	X	X	X			X			X			X	X
Blood sample for anti-bimekizumab antibodies[m]		X			X	X	X	X			X			X			X	X
For participating centers: Blood sample for immunophenotyping[c,m]		X	X			X	X	X									X	
Blood sample genomic, proteomic, metabolomics, and candidate biomarker analyses[c,m]		X	X			X	X	X									X	
Blood sample genetic/epigenetic analysis[c,m]		X															X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Percentage of BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X			X			X			X	
PHQ-9	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (daily)	X	X	X	X	X	X	X	X										
scalp IGA		X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X[n]			X[n]			X[n]	
mNAPSI		X			X[o]	X[o]	X[o]	X[o]			X[o]			X[o]			X[o]	

Table 5--1 Schedule of study assessments

Protocol activity \ Visit[a]/ Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[bb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
pp-IGA		X			X[p]	X[p]	X[p]	X[p]			X[p]			X[p]			X[p]	
EQ-5D-3L		X			X	X	X	X			X			X			X	
SF-36		X			X	X	X	X			X			X			X	
Patient Global Assessment of psoriasis[q]											X			X			X	
PASE		X															X	
PGADA[r]		X			X		X	X			X			X			X	
HAQ-DI[r]		X			X	X	X	X			X			X			X	
WPAI-SHP V2.0		X						X		X				X			X	
Photographs of skin and nails (subset of sites)		X	X	X	X	X	X	X		X			X				X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT[s,t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bimekizumab, ustekinumab, or placebo administration[s,t]		X			X	X	X	X	X	X	X	X	X	X	X	X		

BSA=body surface area; CV=cardiovascular; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; eCRF=electronic Case Report Form; EQ-5D-3L=Euro-Quality of Life 5-Dimensions 3-level; GI=gastrointestinal; HAQ-DI=Health Assessment Questionnaire-Disability Index; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=Informed Consent Form; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; mNAPSI=Modified Nail Psoriasis Severity Index Score; PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area Severity Index; PD=pharmacodynamics; PEOT=Premature End of Treatment; PGADA=Patient's Global Assessment of Disease Activity; PHQ-9=Patient Health

Table 5--1 Schedule of study assessments

Protocol activity \ Visit[a]/ Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[bb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	

Questionnaire 9; pp-IGA=palmoplantar Investigator's Global Assessment; PsA=psoriatic arthritis; SF-36=Short Form 36-item Health Survey; SFU=Safety Follow-Up; scalp IGA=scalp-specific Investigator's Global Assessment; TB=tuberculosis; WPAI-SHP=Work Productivity and Activity Impairment Questionnaire-specific health problem

[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 for subjects who do not enroll in the open-label study.

[c] A separate ICF will be required for subjects who decide to participate in the genomics, genetics, and proteomics substudy. The ICF must be signed prior to collecting any samples for the substudy. Samples for immunophenotyping will be analyzed immediately. All PD samples and genomic, proteomic, and metabolomics samples will be stored at -80°C at the central biorepository for up to 20 years.

[d] A separate ICF is required to be completed for the open-label study.

[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] The physical examination will include examination of the following systems: eyes, hair, and skin; respiratory; CV; and GI.

[h] Vital signs (sitting systolic and diastolic blood pressure, pulse rate, and body temperature) are to be measured prior to blood sampling, and prior to dosing, where applicable.

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

[j] Subjects who have evidence of or test positive for hepatitis B by any of the following criteria: 1) positive for hepatitis B surface antigen (HBsAg+); 2) positive for anti-hepatitis B core antibody (HBcAb+) 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.

[k] The HIV test results will not be recorded in the eCRF.

[l] Screening chest x-ray must occur within 3 months prior to Screening Visit.

[m] All blood samples taken prior to dosing.

[n] The scalp IGA will only be assessed for those subjects with scalp involvement (scalp IGA score >0) at Baseline.

[o] The mNAPSI will be assessed only in subjects with nail involvement (mNAPSI score >0) at Baseline.

[p] The pp-IGA will only be assessed in subjects with palmoplantar involvement (pp-IGA score >0) at Baseline.

[q] The Patient Global Assessment of psoriasis will be performed as part of the patient symptoms diary on a weekly basis from baseline through the initial treatment period with a +3 day completion window. During the Maintenance Treatment Period this assessment will be completed at each clinic visit specified with a ±3 day completion window.

[r] The PGADA and HAQ-DI are assessed for all subjects at Baseline. At all subsequent visits, the PGADA and HAQ-DI are assessed only for subjects with PsA

Table 5--1 Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[bb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	

at Baseline (defined as a past medical history of PsA or PASE ≥47).

[s] IMP administration is based on randomization.

[t] The dosing window is ±7 days relative to the scheduled dosing visit.

Has been changed to:

Table 5-1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[cb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Informed consent[c]	X															X[d]		
Inclusion/exclusion	X	X																
Urine drug screen	X																X	
Demographic data	X																	
Psoriasis history	X																	
Significant past medical history and concomitant diseases	X	X[e]																
Physical exam[f, g]	X	**X**					**X**	~~**X**~~		X			X				X	X

Table 5-1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[cb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Height		X																
Body weight		X					**X**	~~**X**~~		X			X				X	
Vital signs[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology and biochemistry	X	X	X	X	X	X	X	X	**X**	X		X		X		X	X	X
Urinalysis	X	X					X			X		X		X		X	X	X
ECG	X						**X**	~~**X**~~				X					X	
Pregnancy testing[i]	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hepatitis B and C testing[j]	X																	
HIV testing[k]	X																	
Chest x-ray[l]	X																	
IGRA Tuberculosis test	X															X		
Tuberculosis questionnaire	X	X					**X**	~~**X**~~		X			X			~~**X**~~	X	X
Blood sample for bimekizumab plasma concentrations[m]		X	X	X	X	X	X	X			X			X			X	X
Blood sample for anti-bimekizumab antibodies[m]		X			X	X	X	X			X			X			X	X
~~**For participating centers: Blood sample for immunophenotyping[c,m]**~~		~~**X**~~	~~**X**~~			~~**X**~~	~~**X**~~	~~**X**~~									~~**X**~~	

Table 5-1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[cb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
Blood sample genomic, proteomic, metabolomics, and candidate biomarker analyses[c,m]		X	X			X	X	X									X	
Blood sample genetic/epigenetic analysis[c,m]		X															X	
PASI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Percentage of BSA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLQI		X	X	X	X	X	X	X			X			X			X	
PHQ-9	X	X			X	X	X	X	X	X	X	X	X	X	X	X	X	
eC-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient Symptom Diary (daily)	X	X	X	X	X	X	X	X										
scalp IGA		X	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]			X[n]			X[n]			X[n]	
mNAPSI		X			X[o]	X[o]	X[o]	X[o]			X[o]			X[o]			X[o]	
pp-IGA		X			X[p]	X[p]	X[p]	X[p]			X[p]			X[p]			X[p]	
EQ-5D-3L		X			X	X	X	X			X			X			X	
SF-36		X			X	X	X	X			X			X			X	
Patient Global Assessment of psoriasis[q]											X			X			X	
PASE		X															X	

Table 5-1: Schedule of study assessments

Visit[a]/ Week / Protocol activity	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[cb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	
PGADA[r]		X			X		X	X			X			X			X	
HAQ-DI[r]		X			X	X	X	X			X			X			X	
WPAI-SHP V2.0		X						X		X				X			X	
Photographs of skin and nails (subset of sites)		X	**X**	**X**	X	X	X	X		~~**X**~~	**X**		~~**X**~~	**X**			X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
IRT[s,t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Bimekizumab, ustekinumab, or placebo administration[s,t]		X			X	X	X	X	X	X	X	X	X	X	X	X		

BSA=body surface area; CV=cardiovascular; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; eCRF=electronic Case Report Form; EQ-5D-3L=Euro-Quality of Life 5-Dimensions 3-level; GI=gastrointestinal; HAQ-DI=Health Assessment Questionnaire-Disability Index; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ICF=Informed Consent Form; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; mNAPSI=Modified Nail Psoriasis Severity Index Score; PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area Severity Index; PD=pharmacodynamics; PEOT=Premature End of Treatment; PGADA=Patient's Global Assessment of Disease Activity; PHQ-9=Patient Health Questionnaire 9; pp-IGA=palmoplantar Investigator's Global Assessment; PsA=psoriatic arthritis; SF-36=Short Form 36-item Health Survey; SFU=Safety Follow-Up; scalp IGA=scalp-specific Investigator's Global Assessment; TB=tuberculosis; WPAI-SHP=Work Productivity and Activity Impairment Questionnaire-specific health problem

[a] Visit windows of ~~+/- 3~~ **±3** days from the first dose **to the Week 24 visit. Visit windows of ±7 days from the Week 28 visit to the Week 52 visit. The** SFU Visit window is **±7 days ~~-3 and +7 days~~** from ~~**last**~~ **final** dose.

[b] The SFU Visit will occur 20 weeks after the ~~**last**~~ **final** dose for subjects who do not enroll in the open-label study.

[c] ~~**A separate ICF will be required for subjects who decide to participate in the genomics, genetics, and proteomics substudy. The ICF must be signed prior to collecting any samples for the substudy. Samples for immunophenotyping will be analyzed immediately.**~~ All ~~**PD samples and**~~ genomic, proteomic, and metabolomics samples will be stored at -80°C at the central biorepository for up to 20 years.

Table 5-1: Schedule of study assessments

Protocol activity / Visit[a] / Week	Screening	Initial Treatment Period (weeks after first dose)							Maintenance Treatment Peri (weeks after first dose)									SFU[cb]
		Baseline (first dose)	1	2	4	8	12	16	20	24	28	32	36	40	44	48	52/ PEOT	

[d] A separate ICF is required to be completed for the open-label study.
[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] The physical examination will ~~**include examination of the following systems: eyes, hair, and skin; respiratory; CV; and GI**~~ **be performed as per Section 12.3.5**.
[h] Vital signs (sitting systolic and diastolic blood pressure, pulse rate, and body temperature) are to be measured prior to blood sampling, and prior to dosing, where applicable.
[i] Pregnancy testing will consist of serum testing at the Screening. The pregnancy test will be urine at all other visits.
[j] Subjects who have evidence of or test positive for hepatitis B by any of the following criteria: 1) positive for hepatitis B surface antigen (HBsAg+); 2) positive for anti-hepatitis B core antibody (HBcAb+) 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.
[k] The HIV test results will not be recorded in the eCRF.
[l] Screening chest x-ray must occur within 3 months prior to Screening Visit.
[m] All blood samples taken prior to dosing ~~**except at Visit 1 and Visit 2 (at which no dose administration occurs)**~~.
[n] The scalp IGA will only be assessed for those subjects with scalp involvement (scalp IGA score >0) at Baseline.
[o] The mNAPSI will be assessed only in subjects with nail involvement (mNAPSI score >0) at Baseline.
[p] The pp-IGA will only be assessed in subjects with palmoplantar involvement (pp-IGA score >0) at Baseline.
[q] The Patient Global Assessment of psoriasis will be performed as part of the patient symptoms diary on a weekly basis from baseline through the initial treatment period ~~**with a +3 day completion window**~~. During the Maintenance Treatment Period this assessment will be completed at ~~**each clinic visit specified with a ±3 day completion window**~~ **the specified clinic visits**.
[r] The PGADA and HAQ-DI are assessed for all subjects at Baseline. At all subsequent visits, the PGADA and HAQ-DI are assessed only for subjects with PsA at Baseline (defined as a past medical history of PsA or PASE ≥47).
[s] IMP administration is based on randomization.
[t] The dosing window is ~~**±7**~~ **±3** days relative to the scheduled dosing visit **through Week 24. The dosing window is ±7 days from Week 28 through the end of the study**.

Change #21

Section 5.7 Schematic diagram

The following footnote was added after Figure 5-1 Schematic diagram:

Note: At Week 24 and all following visits, subjects on continuous treatment with the same IMP for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period are defined as nonresponders and should discontinue IMP.

Change #22

Section 6.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met at Screening and be reconfirmed at the Baseline Visit:

6. Subject is a candidate for systemic PSO therapy and/or phototherapy and/or photochemotherapy.

Have been changed to:

To be eligible to participate in this study, all of the following criteria must be met at Screening and ~~**be reconfirmed**~~ at the Baseline Visit:

6. Subject is a candidate for systemic PSO therapy and/or phototherapy ~~**and/or photochemotherapy**~~.

Change #23

Section 6.2 Exclusion criteria

3. Subject previously participated in another study of a medication (systemic) under investigation within the 12 weeks or at least 5 half-lives prior to the Screening Visit, whichever is greater, or is currently participating in another study of a medication (systemic) under investigation.
4. Subject previously participated in another study of a topical medication under investigation within the 4 weeks prior to the Screening Visit, or is currently participating in another study of a topical medication under investigation.
5. Subject previously participated in another study of a medical device under investigation within the 4 weeks prior to the Screening Visit, or is currently participating in another study of a medical device under investigation.

14. Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer, or ductal carcinoma in situ of the breast.
17. Subject has any systemic disease (eg, renal failure, heart failure, hypertension, liver disease, diabetes) considered by the Investigator to be uncontrolled, unstable, or likely to progress to a clinically significant degree during the course of the study.

27. Subject has presence of severe depression, indicated by a score of 15 to 19 using the screening PHQ-9. Medication used to treat depression should be stable for 4 weeks prior to Baseline.

Have been changed to:

3a. Subject ~~**previously participated in another study of a medication (systemic) under investigation within the 12 weeks or at least 5 half-lives prior to the Screening Visit, whichever is greater, or**~~ is currently participating in another study of a medication (systemic) under investigation. **Subject must be washed out of the medication for 12 weeks or at least 5 half-lives prior to the Baseline Visit, whichever is greater.**

4a. Subject ~~**previously participated in another study of a topical medication under investigation within the 4 weeks prior to the Screening Visit**~~, or is currently participating in another study of a topical medication under investigation. **Subject must be washed out of the medication for 4 weeks prior to the Baseline Visit.**

5a. Subject ~~**previously participated in another study of a medical device under investigation within the 4 weeks prior to the Screening Visit, or**~~ is currently, **or was within the 4 weeks prior to the Baseline** Visit, participating in another study of a medical device under investigation.

14a. Subject has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer, ~~**or ductal carcinoma in situ of the breast.**~~

17a. Subject has any systemic disease ~~**(eg, renal failure, heart failure, hypertension, liver disease, diabetes**~~ **ie, cardiovascular, neurological, renal, liver, metabolic, gastrointestinal, hematological, immunological, etc.)** considered by the Investigator to be uncontrolled, unstable, or likely to progress to a clinically significant degree during the course of the study.

27a. Subject has presence of **moderately severe major depression or** severe **major** depression, indicated by a score of **15 to 19 ≥15** using the screening PHQ-9. Medication used to treat depression should be stable for **4-8** weeks prior to Baseline.

Change #24

Section 6.2 Exclusion criteria

The following text has been added:

30. Subject is taking or has taken prohibited psoriasis medications without meeting the mandatory washout period relative to the Baseline Visit (Table 7-2).

Change #25

Section 6.3 Withdrawal criteria

The following withdrawal criteria have been added, modified, and/or renumbered:

8. **At Week 24 and all following visits, subjects on continuous treatment for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period are defined as nonresponders and should discontinue study product.**
9. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test (see Section 12.1.4 for more information regarding pregnancies).
10. A subject considered as having either a suspected new LTB infection or who develops active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by IGRA or other diagnostic means) must be immediately discontinued from IMP and a PEOT Visit must be scheduled as soon as possible, but not later than the next regular visit.

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

    Confirmed active TB is an SAE and must be captured 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 is provided in Section 12.3.1.
11. **Subjects with newly diagnosed inflammatory bowel disease (IBD) or with IBD flares during the study must:**

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

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

12. Subjects **must be referred** immediately to a mental health care professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk ~~**for either of the following:**~~

- Active suicidal ideation as indicated by a positive response ("Yes") to Question~~s~~ 4 ~~**or 5 or to the suicidal behavior questions**~~ of the "Since Last Visit" version of the eC-SSRS.
- Moderately severe **major** depression as indicated by a PHQ-9 score of 15 to 19 if this represents an increase of 3 points compared to last visit.

13. Subjects **must be referred immediately to a mental healthcare professional and** must be withdrawn in case of:

- **Active suicidal ideation as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the eC-SSRS**
- Any suicidal behavior since last visit.
- Severe **major** depression as indicated by a PHQ-9 score ≥20.

The mental health consultation ~~**will be documented**~~ **must be recorded** in source documentation.

Change #26

Section 7.2 Treatment(s) to be administered

Double-blind Initial Treatment Period dosing

- Subjects randomized to receive ustekinumab will receive ustekinumab sc at Baseline and Week 4, followed by placebo (2 placebo injections sc) at Week 8 and Week 12. Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) will receive 1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) will receive 2 ustekinumab 45mg sc injections.

Maintenance Treatment Period dosing

- Subjects randomized to receive ustekinumab will have received ustekinumab sc at Baseline and Week 4, and will continue to receive ustekinumab sc every 12 weeks (Weeks 16, 28, and 40). Subjects will receive placebo (2 placebo injections sc) on non-ustekinumab treatment weeks (Weeks 20, 24, 32, 36, 44, and 48). Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) will receive 1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) will receive 2 ustekinumab 45mg sc injections.

Has been changed to:

Double-blind Initial Treatment Period dosing

- Subjects randomized to receive ustekinumab will receive ustekinumab sc at Baseline and Week 4, followed by placebo (2 placebo injections sc) at Week 8 and Week 12. Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) **at Baseline** will receive 1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) **at Baseline** will receive 2 ustekinumab 45mg sc injections.

Maintenance Treatment Period dosing

- Subjects randomized to receive ustekinumab will have received ustekinumab sc at Baseline and Week 4, and will continue to receive ustekinumab sc every 12 weeks (Weeks 16, 28, and 40). Subjects will receive placebo (2 placebo injections sc) on non-ustekinumab treatment weeks (Weeks 20, 24, 32, 36, 44, and 48). Because ustekinumab dosing is based on weight, on ustekinumab treatment weeks subjects ≤100kg (220lbs) **at Baseline** will receive

1 ustekinumab 45mg sc injection and 1 placebo injection and subjects >100kg (220lbs) **at Baseline** will receive 2 ustekinumab 45mg sc injections.

Change #27

Section 7.2 Treatment(s) to be administered

Table 7-1: Dosing scheme

Week **Dose Assignment**	**Baseline (first dose)**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Bimekizumab 320mg Q4W	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●
Ustekinumab 45mg (subjects ≤100kg)	▲○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○
Ustekinumab 90mg (subjects >100kg)	▲▲	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○
Placebo	○○	○○	○○	○○	●●	●●	●●	●●	●●	●●	●●	●●	●●

Q4W=every 4 weeks

Has been changed to:

Table 7-1: Dosing scheme

Week **Dose Assignment**	**Baseline (first dose)**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
Bimekizumab 320mg Q4W	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●	●●
Ustekinumab 45mg (subjects ≤100kg)	▲○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○	▲○	○○	○○
Ustekinumab 90mg (subjects >100kg)	▲▲	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○	▲▲	○○	○○
Placebo/ **bimekizumab 320mg Q4W**	○○	○○	○○	○○	●●	●●	●●	●●	●●	●●	●●	●●	●●

Q4W=every 4 weeks

Change #28

Section 7.6 Drug Accountability

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 study material, including recording the administration information on source documents.

Has been changed to:

Unblinded study staff will be delegated the responsibility to receive, inventory and destroy the used kits. The packaging identifies each kit by a unique number, but due to the commercial packaging of the comparator, the unblinded study staff will be responsible in order to maintain the blind. 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 study material, including recording the administration information on source documents.

Change #29

Section 7.8.2 Prohibited concomitant treatments (medications and therapies)

Table 7-2: Prohibited psoriasis medications

Drug	Washout period relative to Baseline Visit
Topicals except for those permitted (Section 7.8.1.1)	2 weeks
Systemic retinoids	3 months
Systemic treatment (nonbiological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) fumaric acid esters specifically used for the treatment of PSO systemic corticosteroids phototherapy or photochemotherapy	1 month
Anti-TNFs: adalimumab (including biosimilar) etanercept (including biosimilar) infliximab (including biosimilar), golimumab, certolizumab pegol	 Any exposure to adalimumab 1 month for etanercept 3 months for infliximab (including biosimilar), golimumab, certolizumab pegol
Other biologics and other systemic therapies, eg: apremilast, tofacitinib alefacept, efalizumab, guselkumab ustekinumab, briakinumab rituximab	 2 weeks for apremilast and tofacitinib 3 months for alefacept, efalizumab, and guselkumab 6 months for ustekinumab and briakinumab 12 months for rituximab
Anti-IL-17 therapy: brodalumab ixekizumab secukinumab	3 months (bimekizumab is excluded per exclusion criteria)
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)	3 months or 5 half-lives, whichever is greater

Table 7-2: Prohibited psoriasis medications

Drug	Washout period relative to Baseline Visit
Any other antipsoriatic agent (topical) under investigation	1 month

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

Has been changed to:

Table 7-2: Prohibited psoriasis medications

Drug	Washout period relative to Baseline Visit
Topicals except for those permitted (Section 7.8.1.1)	2 weeks
Systemic retinoids	3 months
Systemic treatment (nonbiological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) fumaric acid esters specifically used for the treatment of PSO systemic corticosteroids phototherapy ~~**or photochemotherapy**~~	1 month
Anti-TNFs: adalimumab (including biosimilar) etanercept (including biosimilar) infliximab (including biosimilar), golimumab, certolizumab pegol	 Any exposure to adalimumab 1 month for etanercept 3 months for infliximab (including biosimilar), golimumab, certolizumab pegol
Other biologics and other systemic therapies, eg: apremilast, tofacitinib alefacept, efalizumab, guselkumab **tildrakizumab, risankizumab** ustekinumab, briakinumab rituximab	 2 weeks for apremilast and tofacitinib 3 months for alefacept, efalizumab, and guselkumab **5 months for tildrakizumab and risankizumab** 6 months for ustekinumab and briakinumab 12 months for rituximab
Anti-IL-17 therapy: brodalumab ixekizumab secukinumab	3 months (bimekizumab is excluded per exclusion criteria)
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)	3 months or 5 half-lives, whichever is greater
Any other antipsoriatic agent (topical) under investigation	1 month

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

Change #30

Section 7.10 Randomization and numbering of subjects, first paragraph

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subject treatment assignment will be stratified by region and prior biologic exposure (yes/no). The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

Has been changed to:

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or designee). The randomization schedule will be produced by the IRT vendor. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule. Subject treatment assignment will be stratified by region **(North America, Western Europe, Central/Eastern Europe, and Asia/Australia)** and prior biologic exposure (yes/no). The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

Change #31

Section 8 STUDY PROCEDURES BY VISIT, first bullet

- 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 dosing window is ±7 days relative to the scheduled dosing visit.
- For the SFU Visit (20 weeks after the last dose), the visit window should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

Has been changed to:

- **From the Week1 visit to the Week 24 visit, ~~Visit~~ 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.~~ From the Week 28 visit to the Week 52 visit, visit windows are ±7 days.** Changes to the dosing schedule outside of the visit window must be discussed with the Medical Monitor.
- **The dosing window is ±3 days relative to the scheduled dosing visit through Week 24.** The dosing window is ±7 days relative to the scheduled dosing visit **from Week 28 through the end of the study.**
- For the SFU Visit (20 weeks after the **~~last~~ final** dose), the visit window **~~should occur no more than 3 days prior to the scheduled visit date and within 7 days after~~** is ±7 days relative to the scheduled visit date **~~(-3 days/+7 days)~~**.

Change #32

Section 8.1 Screening Visit (2 to 4 weeks)

Has been changed to:

Section 8.1 Screening Visit (2 to 4~~-~~5 weeks)

Change #33

Sections 8.2.1 Baseline Visit

The following has been added from the bulleted list:

- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB

Change #34

Sections 8.2.1 Baseline Visit, 8.2.2 Week 1 Visit (±3 days relative to Baseline), 8.2.5 Week 8 Visit (±3 days relative to Baseline), 8.2.6 Week 12 Visit (±3 days relative to Baseline), 8.3.9 Week 52 (~~±3~~ ±7 days),

The following has been deleted from the bulleted list:

- Immunophenotyping (participating centers only)

Change #35

Section 8.2.6 Week 12 Visit (±3 days relative to Baseline)

The following have been added to the bulleted list:

- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Body weight
- TB questionnaire
- Record 12-lead ECG

Change #36

Section 8.2.7 Week 16 Visit (±3 days relative to Baseline)

The following have been deleted from the bulleted list:

- Physical exam including evaluation of signs and symptoms of active TB and risk for exposure to TB
- Body weight

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Immunophenotyping (participating centers only)
- Record 12-lead ECG
- TB questionnaire

Change #37

Section 8.3.1 Week 20 Visit (±3 days relative to Baseline)

The following have been added to the bulleted list:

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Hematology and biochemistry

Change #38

Section 8.3.2 Week 24 Visit (±3 days relative to Baseline)

The following have been deleted from the bulleted list:

- Collection of blood and urine samples for the following clinical laboratory tests should be obtained prior to dosing:
  - Urinalysis ~~**and electrolytes**~~
- Photographs of skin and nails (participating centers only)

Change #39

Sections 8.3.3 Week 28 Visit (±3 days relative to Baseline) and 8.3.6 Week 40 Visit (±3 days relative to Baseline)

The following has been added to the bulleted list:

- Photographs of skin and nails (participating centers only)

Change #40

Sections 8.3.3 Week 28 (±3 days), 8.3.4 Week 32 (±3 days), 8.3.5 Week 36 (±3 days), 8.3.6 Week 40 (±3 days), 8.3.7 Week 44 (±3 days), 8.3.8 Week 48 (±3 days), and 8.3.9 Week 52 (±3 days)

Has been changed to:

Sections 8.3.3 Week 28 (~~±3~~ ±7 days), 8.3.4 Week 32 (~~±3~~ ±7 days), 8.3.5 Week 36 (~~±3~~ ±7 days), 8.3.6 Week 40 (~~±3~~±7 days), 8.3.7 Week 44 (~~±3~~ ±7 days), 8.3.8 Week 48 (~~±3~~ ±7 days), and 8.3.9 Week 52 (~~±3~~ ±7 days)

Change #41

Section 8.3.5 Week 36 Visit (±3 days relative to Baseline)

The following has been deleted from the bulleted list:

- Photographs of skin and nails (participating centers only)

Change #42

Section 8.3.8 Week 48 Visit (±7 days relative to Baseline)

The following has been deleted from the bulleted list:

- TB questionnaire

Change #43

Section 8.5 Safety Follow-Up Visit (20 weeks after last dose, -3 days/+7 days)

Has been changed to:

Section 8.5 Safety Follow-Up Visit (20 weeks after ~~last~~ <u>final</u> dose, ~~-3 days/+7 days~~ <u>±7 days</u>)

Change #44

Section 9 ASSESSMENT OF EFFICACY

The PASI, BSA, IGA, scalp IGA, mNAPSI, and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Preferably, the same assessor should evaluate the subject at each assessment.

Has been changed to:

The PASI, BSA, IGA, scalp IGA, mNAPSI, and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. **~~Preferably, the~~ The** same assessor should evaluate the subject at each assessment.

Change #45

Section 9.10 Patient Global Assessment of psoriasis, second and third paragraphs

The Patient Global Assessment of PSO will be performed as part of the patient symptoms diary from baseline through the Initial Treatment Period; the assessment is to completed within a +3 day completion window at each of the visits specified in Table 5-1.

During the double-blind Maintenance Treatment Period, this assessment will be completed within a +3 day completion window at the visits specified in Table 5-1.

Has been changed to:

The Patient Global Assessment of PSO will be performed as part of the patient symptoms diary from **~~baseline~~ Screening** through the Initial Treatment Period**~~; the assessment is to completed within a +3 day completion window at each of the visits specified in Table 5-1~~**.

During the double-blind Maintenance Treatment Period, this assessment will be completed **~~within a +3 day completion window~~** at the visits specified in Table 5-1.

Change #46

Section 9.11 Patient Symptom Diary responses, second paragraph

The ePRO diary will also administer the patient global assessment of PSO as noted above appropriate anchor items 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 diaryeach 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.

Has been changed to:

The ePRO diary will also administer the patient global assessment of PSO as noted above appropriate anchor items 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.

Change #47

Section 9.12 PASE questionnaire

The PASE questionnaire is a self-administered tool to screen for active PsA in patients with PSO (Husni et al, 2014). The questionnaire consists of 15 items that are divided into a 7-item symptoms subscale and an 8-item functions subscale. Standardized responses are based on 5 categories relating to agreement (strongly agree [1], agree [2], no idea [3], disagree [4], and strongly disagree [5]).

Has been changed to:

The PASE questionnaire is a self-administered tool to screen for active PsA in patients with PSO (Husni et al, 2014). The questionnaire consists of 15 items that are divided into a 7-item symptoms subscale and an 8-item functions subscale. Standardized responses are based on 5

categories relating to agreement (**strongly agree [~~1~~5], agree [~~2~~4],** no idea [3], **disagree [42], and strongly disagree [~~5~~1]**).

Change #48

Section 9.16 Photographs

At certain clinical sites, representative photographs of the changes in skin and nail appearance will be captured. Subjects will have full body (anterior and posterior views) and nail photographs taken. Photographs will be anonymized.

Has been changed to:

At certain clinical sites, representative photographs of the changes in skin and nail appearance will be captured. Subjects will have full body (anterior and posterior views) **~~and nail~~** photographs taken. **Only those subjects with nail disease at Baseline will have nail photographs taken. Only those subjects with palmoplantar disease at Baseline will have photographs of their palms or soles of their feet taken. Only those subjects scalp disease at Baseline will have scalp photographs taken.** Photographs will be anonymized.

Change #49

Section 10 Assessment Of Pharmacokinetic/ Pharmacodynamic/ And Pharmacogenomic Variable(s)

Section 10.1 Pharmacokinetic and pharmacodynamic variables

Blood samples for measurement of PK assessments (Section 4.4) 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.

Pharmacokinetic samples from subjects receiving ustekinumab will not be analyzed, but stored for potential future PK analysis and anti-drug antibody determination.

At participating centers, immunophenotyping will be assessed by flow cytometry using fluorescent-activated cell sorting on whole blood of T-cells, B-cells, natural killer cells, and T-helper subsets.

Has been changed to:

Section 10 Assessment Of Pharmacokinetic And Pharmacogenomic Variable(s)

Section 10.1 Pharmacokinetic variables

Blood samples for measurement of PK assessments (Section 4.4) 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.

Pharmacokinetic samples from subjects receiving ustekinumab will not be analyzed, but stored for potential future PK analysis and anti-drug antibody determination.

~~**At participating centers, immunophenotyping will be assessed by flow cytometry using fluorescent-activated cell sorting on whole blood of T-cells, B-cells, natural killer cells, and T-helper subsets.**~~

Change #50

Section 12.1.4 Pregnancy

- The subject should immediately stop the intake of the IMP or be down-titrated as instructed at the PEOT visit.

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

Have been changed to:

- The subject should immediately stop the intake of the IMP ~~**or be down-titrated as instructed at the PEOT visit**~~.

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

Change #51

Section 12.2 Laboratory measurements

Table 12-2: Laboratory measurements

Hematology	Chemistry	Urinalysis dipstick[a]
Basophils	Calcium	pH
Eosinophils	Chloride	Albumin (protein)

Table 12-2: Laboratory measurements

Hematology	Chemistry	Urinalysis dipstick[a]
Lymphocytes	Magnesium	Glucose
Atypical lymphocytes	Potassium	Blood
Monocytes	Sodium	Leukocyte esterase
Neutrophils	Glucose	Nitrite
Hematocrit	BUN	Urine dipstick for pregnancy testing[b]
Hemoglobin	Creatinine	Urine drug screen[d]
MCH	ALP	
MCHC	AST	
MCV	ALT	
Platelet count	GGT	
RBC count	Total bilirubin	
WBC count	LDH	
	Serum pregnancy testing[b]	

Has been changed to:

Table 12-2: Laboratory measurements

Hematology	Chemistry	Urinalysis dipstick[a]
Basophils	Calcium	pH
Eosinophils	Chloride	Albumin (protein)
Lymphocytes	Magnesium	Glucose
~~**Atypical lymphocytes**~~	Potassium	Blood
Monocytes	Sodium	Leukocyte esterase
Neutrophils	Glucose	Nitrite
Hematocrit	BUN	Urine dipstick for pregnancy testing[b]
Hemoglobin	Creatinine	Urine drug screen[d]
MCH	ALP	
MCHC	AST	
MCV	ALT	
Platelet count	GGT	
RBC count	Total bilirubin	
WBC count	~~**LDH**~~	

Table 12-2: Laboratory measurements

Hematology	Chemistry	Urinalysis dipstick[a]
	Serum pregnancy testing[b]	

Change #52

Section 12.2.1 Evaluation of PDILI

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

Has been changed to:

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

Change #53

Section 12.2.1.2.1 IMP restart/rechallenge (if applicable)

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

Has been changed to:

Section 12.2.1.2.1 IMP restart/rechallenge ~~(if applicable)~~

~~**Rechallenge with a substance potentially causing drug-induced liver injury is dangerous, may be fatal, and must not occur.**~~ **Rechallenge with IMP can occur only if ALL of the following requirements are met:**

- **The results of additional testing and monitoring described in Section 12.2.1.3 and Section 12.2.1.4 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).**
- **The subject has shown clear therapeutic benefit from the IMP.**
- **Subject's ALT or AST elevations do not exceed ≥5xULN.**
- **Subject's total bilirubin is <2xULN.**
- **Subject has no signs or symptoms of hypersensitivity or hepatitis.**
- **The rechallenge is approved by the UCB responsible physician, DMC, and a hepatologist. The hepatologist must be external to UCB but may be a member of the DMC. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the subject.**
- **Subject agrees to the Investigator-recommended monitoring plan.**

Change #54

Section 12.3.1 Assessment and management of TB and TB risk factors

b. High risk of acquiring TB infection:

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

Has been changed to:

b. High risk of acquiring TB infection:

- Known **close** exposure to another person with active TB infection within the 3 months prior to Screening.

Change #55

Section 12.3.1.1 Tuberculosis assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD is recommended) will be performed as described in Table 5-1 for all subjects.

Has been changed to:

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB ~~**GOLD**~~ **test** is recommended) will be performed as described in Table 5-1 for all subjects.

Change #56

Section 12.3.1.3 Tuberculosis questionnaire, last paragraph

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

Has been deleted:

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

Change #57

Section 12.3.1.4 Tuberculosis management, second paragraph

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

Has been changed to:

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

Change #58

Section 12.3.2 Pregnancy testing

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 IMP 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.

Has been changed to:

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 IMP **~~and at all subsequent post-dosing visits~~ at the visits specified in Table 5-1**. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

Change #59

Section 13.3.1.1 Electronic Health Record extraction pilot

It is anticipated that a selection of data points (Demography, Medical History, Concomitant Medications, and potentially Vital Signs) will be collected via the subjects' Electronic Healthcare Record (EHR) at specific sites as part of a small EHR Pilot. Retrieve Form for Data Capture (RFD) will be used to extract the selected data points from the EHR and imported into the EDC system. An archive of selected data points, at the time of extraction, will be stored at the sites.

Has been deleted:

~~Section 13.3.1.1 Electronic Health Record extraction pilot~~

~~It is anticipated that a selection of data points (Demography, Medical History, Concomitant Medications, and potentially Vital Signs) will be collected via the subjects' Electronic Healthcare Record (EHR) at specific sites as part of a small EHR Pilot. Retrieve Form for Data Capture (RFD) will be used to extract the selected data points from the EHR and~~

~~**imported into the EDC system. An archive of selected data points, at the time of extraction, will be stored at the sites.**~~

Change #60

Section 14.1 Definition of analysis sets

The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the IMP and have a valid measurement of the co-primary efficacy variables at Baseline.

Has been changed to:

The Maintenance Set will consist of all subjects who have received at least 1 dose of active IMP (bimekizumab or ustekinumab) in the Maintenance Treatment Period.

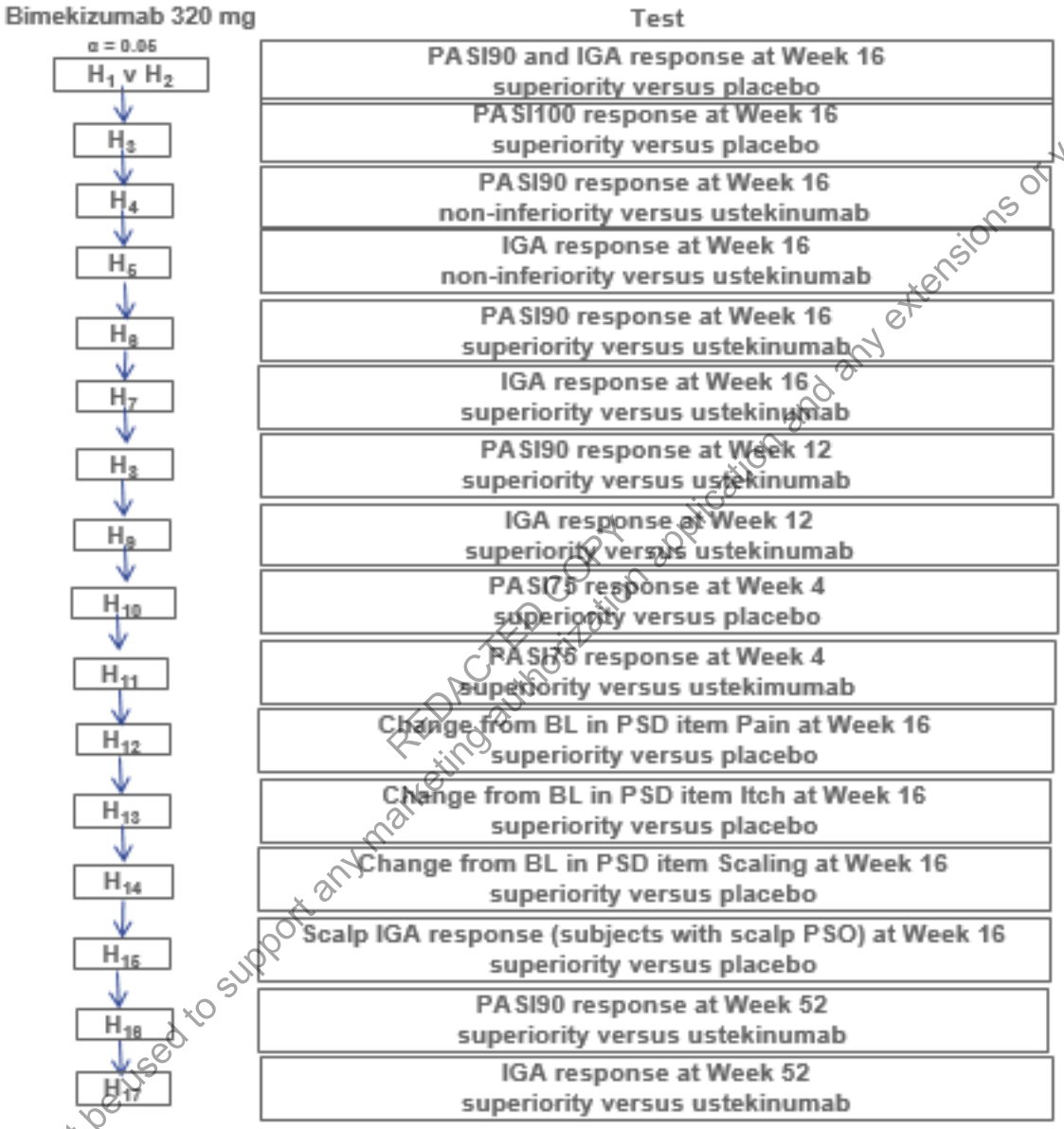
The Full Analysis Set (FAS) will consist of all randomized subjects that received at least 1 dose of the IMP and have a valid measurement **for each** of the co-primary efficacy variables at Baseline.

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

Change #61

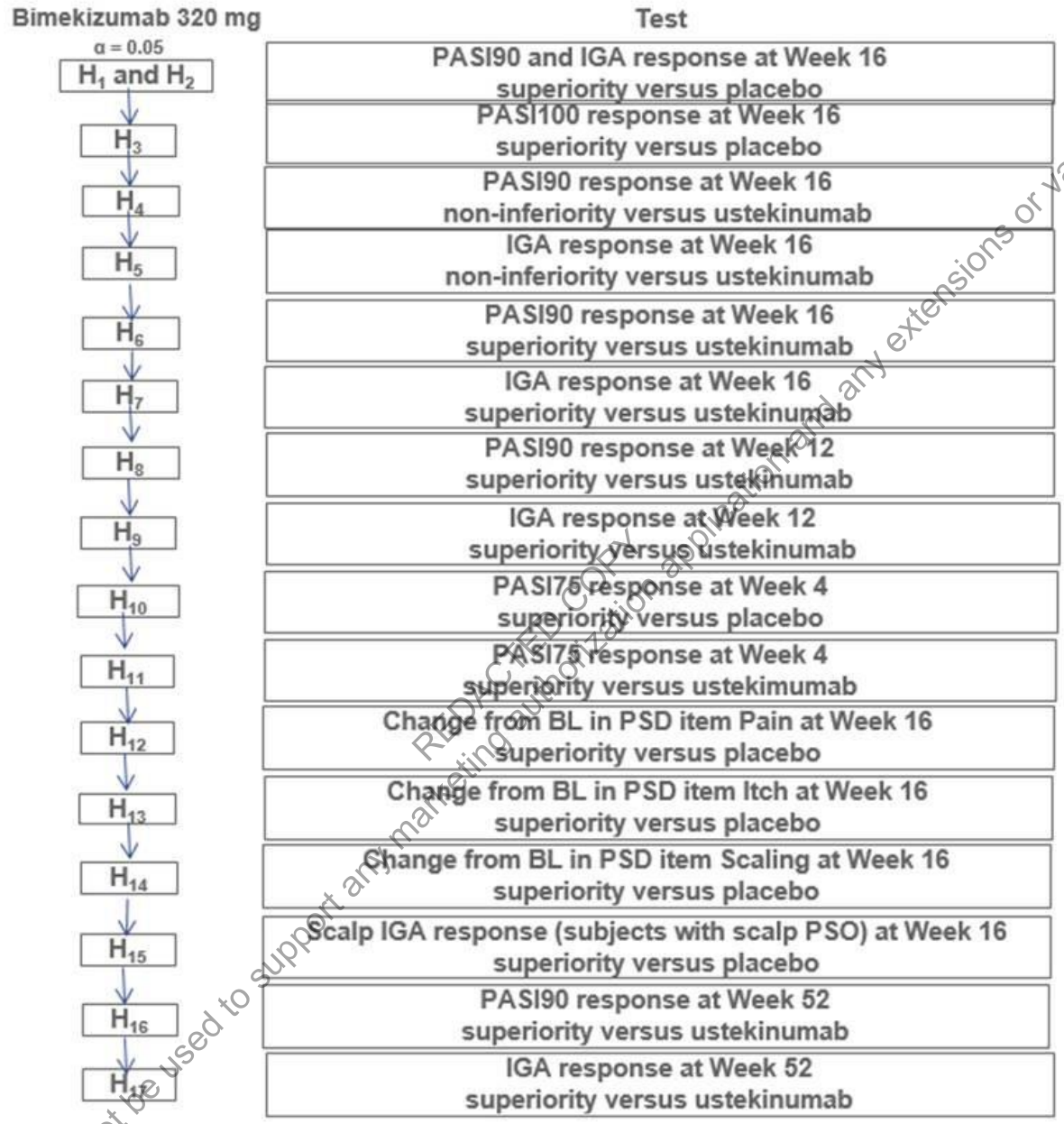
Section 14.2 General statistical considerations

Figure 14-1: Sequence of testing



.**Has been changed to:**

Figure 14-1: Sequence of testing



Change #62

Section 14.4 Subgroup analyses

Subgroup analyses will be performed on the primary and secondary efficacy variables that are part of the fixed sequence testing procedure described in Section 14.3. The following variables for subgroup analyses will be defined: age, gender, disease duration, region, weight, body mass index (BMI), prior systemic chemotherapy or photochemotherapy, prior biologic exposure, prior

systemic therapy of any kind, Baseline disease severity, 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 that are part of the fixed sequence testing procedure described in Section 14.3. The following variables for subgroup analyses will be defined: age, gender, disease duration, region, weight, body mass index **~~(BMI)~~**, prior systemic chemotherapy or **~~photochemotherapy~~ phototherapy**, prior biologic exposure, prior systemic therapy of any kind, Baseline disease severity, and antibody positivity. These summaries will be based on imputed data (NRI) and will include descriptive statistics only.

Change #63

Section 14.5.2 Pharmacokinetic/pharmacodynamic analyses

The relationship between efficacy response (PASI/IGA) and bimekizumab plasma concentration will be explored via graphical and a model based (PK-PD) approach quantify the time course of dose/exposure response. In addition, the relationship between safety and exposure will also be explored. The data will be combined with that from other bimekizumab trials in psoriasis for a pooled, cross trial analysis. The details of this analysis will be described in a data analysis plan, and the analysis itself will be reported separately from the Clinical Study Report (CSR). Candidate biomarkers may include, but are not limited to: IL-17A/IL-17F pathway signaling and PSO biology (eg, IL-17A, IL-17F, IL-23, IL-6, TNF, DC-STAMP, and circulating osteoclast precursors). The details of the model and the approach will be specified in a data analysis plan.

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

Has been changed to:

Section 14.5.2 Pharmacokinetic~~/pharmacodynamic~~ analyses

~~The relationship between efficacy response (PASI/IGA) and bimekizumab plasma concentration will be explored via graphical and a model-based (PK-PD) approach to quantify the time course of dose/exposure response. In addition, the relationship between safety and exposure will also be explored. The data will be combined with that from other bimekizumab trials in psoriasis for a pooled, cross trial analysis. The details of this analysis will be described in a data analysis plan, and the analysis itself will be reported separately from the Clinical Study Report (CSR). Candidate biomarkers may include, but are not limited to: IL-17A/IL-17F pathway signaling and PSO biology (eg, IL-17A, IL-17F, IL-23, IL-6, TNF, DC-STAMP, and circulating osteoclast precursors) (not applicable in Japan). The details of the model and the approach will be specified in a data analysis plan.~~

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

Change #64

Section 14.6 Handling of protocol deviations

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

Has been changed to:

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.

Change #65

Section 17 References

The following reference has been deleted:

~~Bretz F, Maurer W, Brannath W, Posch M. A graphical approach to sequentially rejective multiple test procedure. Statistics in Medicine. 2009;28:586-604.~~

18.4 Protocol Amendment 4

Rationale for the amendment

The purpose of this amendment was to update the secondary and "other" efficacy variables to be consistent with the wording in the statistical analysis plan (SAP). The secondary and "other" efficacy variables for the scalp IGA response, and the "other" efficacy variable for the IGA response were updated to clarify that the response required "at least a 2-category improvement from Baseline," as it is described in the SAP.

For the Patient Symptom Diary, the secondary and "other" efficacy variables were updated from "change from Baseline" to "response" on the items of itch, pain, and scaling in order to align the protocol with the planned responder analyses described in the SAP which define clinically meaningful thresholds of change for defining treatment response, rather than change from Baseline. The hierarchy figure (Figure 14.1) was also updated to reflect this change. There is no change to the frequency of diary assessments or how the diary assessments are performed.

The name and contact information of the Clinical Project Manager was also changed.

Change #1

Clinical Project Manager

Name:	[redacted]
Address:	UCB Biosciences, 8010 Arco Corporation Drive, Raleigh, NC 27617
Phone:	[redacted]
Fax:	[redacted]

Has been changed to:

Name:	[redacted]
Address:	UCB Biosciences, 8010 Arco Corporation Drive, Raleigh, NC 27617
Phone:	[redacted]
Fax:	[redacted]

Change #2

Section 4.2.1 Secondary efficacy variables

The following bullets:

- Change from Baseline in the Patient Symptom Diary responses for itch, pain, and scaling at Week 16
- Scalp IGA response (Clear or Almost Clear) at Week 16 for subjects with scalp PSO at Baseline

Have been changed to:

- ~~Change from Baseline in the~~ Patient Symptom Diary responses for itch, pain, and scaling at Week 16
- Scalp IGA response (Clear or Almost Clear **with at least a 2-category improvement from Baseline**) at Week 16 for subjects with scalp PSO at Baseline

Change #3

Section 4.3.1 Other efficacy variable(s)

The following bullets:

- IGA response (Clear)
- Change from Baseline in the Patient Symptom Diary responses
- Scalp-specific Investigator's Global Assessment (scalp IGA) response (Clear or Almost Clear) for subjects with scalp PSO at Baseline

Has been changed to:

- IGA response (Clear **with at least a 2-category improvement from Baseline**)
- ~~Change from Baseline in the~~ Patient Symptom Diary responses
- Scalp-specific Investigator's Global Assessment (scalp IGA) response (Clear or Almost Clear **with at least a 2-category improvement from Baseline**) for subjects with scalp PSO at Baseline

Change #4

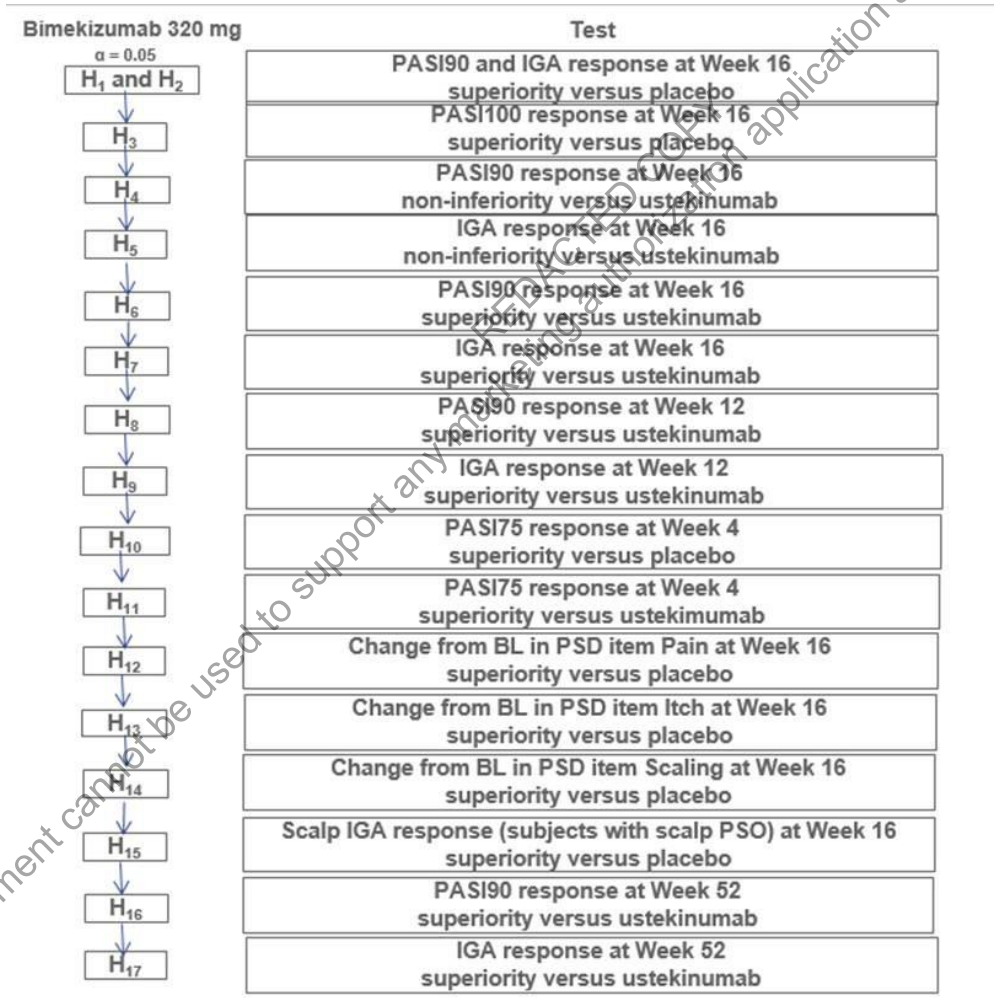
Section 9.11 Patient Symptom Diary responses

A third paragraph has been added:

The Patient Symptom Diary responses for itch, pain, and scaling at Week 16 will be computed based on the responder definition as well as the absolute and percent change from Baseline. Each of the Patient Symptom Diary response scores included in the statistical testing procedure (itch, pain, and scaling) will be characterized in terms of the cumulative percent of subjects demonstrating a pre-specified point improvement at Week16. The threshold for the Patient Symptom Diary response score of itch, pain, and scaling is 2.39, 1.98, and 2.86, respectively. The responder analysis will be limited to the subjects with a Baseline Patient Symptom Diary response score at or above the applicable threshold score (ie, at least 2.39, 1.98, and 2.86 for itch, pain, and scaling, respectively).

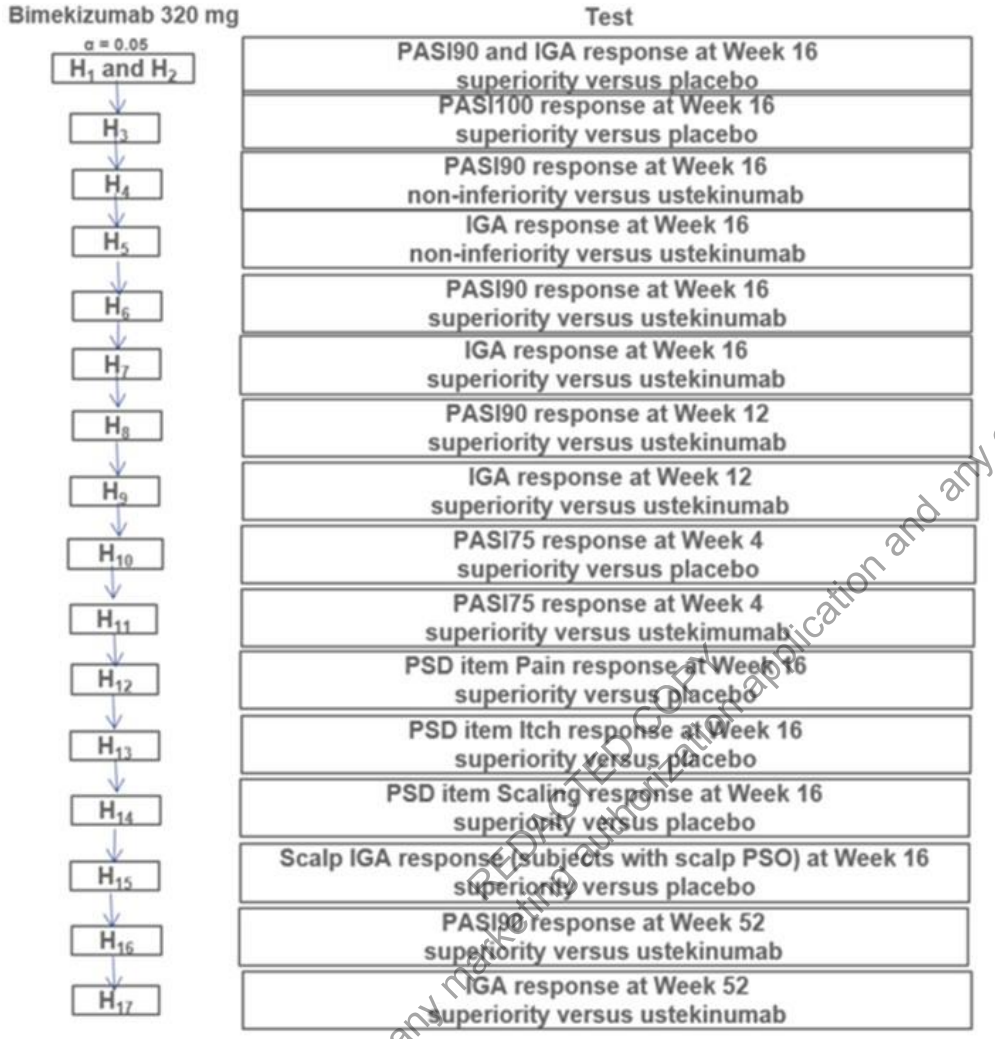
Change #5

Figure 14 1: Sequence of testing



BL=Baseline; IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; PSD=Patient Symptom Diary; PSO=psoriasis

Has been changed to:



~~BL=Baseline;~~ IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; PSD=Patient Symptom Diary; PSO=psoriasis

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.

Approval Signatures

Name: ps0009-protocol-amend-4

Version: 1.0

Document Number: CLIN-000134866

Title: PS0009 Protocol Amendment 4

Approved Date: 23 May 2019

Document Approvals	
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 22-May-2019 19:51:04 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 22-May-2019 19:54:05 GMT+0000
Approval Verdict: Approved	Name: [redacted] Capacity: Clinical Date of Signature: 23-May-2019 05:35:09 GMT+0000