PROTOCOL PS0018 AMENDMENT 3

A MULTICENTER, 48-WEEK, OPEN-LABEL EXTENSION STUDY TO ASSESS THE LONG-TERM SAFETY, TOLERABILITY, AND EFFICACY OF BIMEKIZUMAB IN ADULT SUBJECTS WITH MODERATE TO SEVERE CHRONIC PLAQUE PSORIASIS

PHASE 2

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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LIST OF ABBREVIATIONS

AE	adverse event
AESM	adverse event for special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area (affected by psoriasis)
cAMP	cyclic adenosine monophosphate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
EAER	exposure adjusted event rate
EAIR	exposure adjusted incidence rate
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale-Anxiety
HADS-D	Hospital Anxiety and Depression Scale-Depression
HLT	high level term
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator's Global Assessment
IGRA	interferon gamma release assay

IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
iv	intravenous
IXRS	interactive voice or web response system
LTB	latent tuberculosis
mAb	monoclonal antibody
NSAID	nonsteroidal anti-inflammatory drug
NTMB	nontuberculous mycobacterium
PASI	Psoriasis Area and Severity Index
PDE4	phosphodiesterase 4
PDILI	potential drug-induced liver injury
PK	pharmacokinetics
PK-PPS	Pharmacokinetics Per-Protocol Set
PS	Patient Safety
PT	preferred term
Q4W	every 4 weeks
QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous(ly)
SFU	Safety Follow-Up
SOC	system organ class
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

1 SUMMARY

PS0018 is a multicenter, 48-week, open-label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult subjects with moderate to severe chronic plaque psoriasis who participated in PS0016.

During the Open-Label Treatment Period, subjects will attend study visits at the site every 4 weeks (Q4W) for study assessments and administration of bimekizumab (if applicable) by study site staff through Week 48. Following completion or early withdrawal from the 48-week Open-Label Treatment Period, subjects will return for a Safety Follow-Up (SFU) Visit at 20 weeks after their last dose of bimekizumab. Subjects withdrawing early from the study will undergo the Early Withdrawal Visit assessments and will enter the SFU Period.

Bimekizumab will initially be administered at a dose of 160mg Q4W subcutaneously (sc) during the 48-week Open-Label Treatment Period. There will be an option to increase the dose to 320mg Q4W at the discretion of the Investigator if the subject's Psoriasis Area and Severity Index (PASI) response is ≥50% to <75% reduction from the Baseline of PS0016 at Week 12 or later. If the subject's disease is adequately controlled on the 320mg Q4W dose, they may return to 160mg Q4W at the discretion of the Investigator. The decision to return to 160mg Q4W dosing should be based upon treatment response, tolerability, and Investigator discretion, with the aim to use the dosing regimen that achieves the optimal benefit-risk for each subject. If a subject does not achieve a PASI50 at Week 12 or later then they will be withdrawn from the study.

Up to 45 subjects are anticipated to enroll in PS0018 at approximately 15 sites in Europe and North America, with possible extension to other regions and countries as required in PS0016.

The primary objective of the study is to assess the long-term safety and tolerability of bimekizumab. Secondary objectives of the study are to assess the safety and tolerability of increasing the dose of bimekizumab from 160mg Q4W to 320mg Q4W; to assess the pharmacokinetics (PK) of bimekizumab; to assess the immunogenicity of bimekizumab; and to assess the efficacy of open-label bimekizumab 160mg Q4W administered over 48 weeks.

The primary safety variable is the incidence of treatment-emergent adverse events (TEAEs) adjusted by duration of subject exposure to treatment. The secondary safety variables are severity and frequency of TEAEs and change from Baseline of PS0016 in clinical laboratory values (chemistry, hematology, and urinalysis), vital signs, physical examination, and 12-lead electrocardiogram (ECG) results.

Pharmacokinetic variables are plasma concentrations of bimekizumab. The immunological variable is anti-bimekizumab antibody levels prior to and following study treatment. The efficacy assessments are PASI, Investigator's Global Assessment (IGA), body surface area (BSA) affected by psoriasis, and the Hospital Anxiety and Depression Scale (HADS); a detailed list of efficacy variables is presented in Section 4.4.

2 INTRODUCTION

2.1 Psoriasis

Psoriasis is a common, chronic inflammatory disease characterized by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and

infiltration of T lymphocytes, neutrophils, and other types of leukocytes in affected skin. Though the pathophysiology of psoriasis is not fully understood, the importance of T-cells and inflammatory cytokines has been demonstrated by the clinical benefit provided by therapies directed at these targets (Kreuger and Ellis, 2005).

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

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

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

2.1.1 Global epidemiology of psoriasis

Psoriasis affects approximately 3% of the adult US population (Rachakonda et al, 2014; Kurd and Gelfand, 2009) and its onset can begin at any age (Augustin et al, 2010; Icen et al, 2009). The reported worldwide incidence and prevalence of psoriasis varies greatly depending on age, gender, ethnicity, and geography primarily due to genetic and environmental factors. Estimates of incidence and prevalence include all types of psoriasis. Plaque psoriasis is the most common form of psoriasis therefore reported estimates of the magnitude of this condition are likely weighted heavily by this subtype. Both the incidence and prevalence of psoriasis are higher among Caucasians and those living in higher latitudes. Psoriasis affects approximately 2% to 4% of the population of western countries. Geographical differences are also influenced by case definition, study design, and the definition of prevalence (Parisi et al, 2013; Langley et al, 2005; Raychaudhuri and Gross, 2000).

2.1.2 Current treatments for psoriasis

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

- Topical steroids (eg, triamcinolone, mometasone, clobetasol, betamethasone, hydrocortisone) are generally used as first-line treatment of psoriasis. High-strength steroids are typically reserved for use on the arms and legs. Areas such as the face and skin folds (axillary, inguinal regions, etc) are usually treated with a low potency steroid. Chronic use of topical steroids can lead to corticosteroid-related side effects and is generally discouraged.
- Vitamin D analogs (eg, calcipotriol and tacalcitol) are commonly used to treat mild to moderate psoriasis, and work best within the mild patients. They are safe but lack efficacy for many moderate to severe patients.
- Chemophototherapy is a frequent option for moderate to severe patients, but the inconvenience of multiple treatment visits and varying efficacy limits its use in the market.
- Methotrexate is a systemic immunosuppressant and is used in moderate to severe patients. Toxicity concerns, particularly in older patients, are a major drawback.
- Apremilast is an oral small-molecule inhibitor of PDE4 that is also approved for treatment of adults with moderate to severe plaque psoriasis. Phosphodiesterase 4 inhibitors work intracellularly to modulate a network of pro-inflammatory 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), and IL-17A inhibitors are the treatment options of choice for patients with moderate to severe plaques psoriasis who are candidates for systemic therapy or phototherapy. These products are injected sc or delivered via intravenous (iv) infusion and while effective, TNFα inhibitors come with boxed warnings including the risk of serious infections and reports of lymphoma and malignancy in children and adolescent patients. The efficacy of TNFα inhibitors in treating psoriasis has been attributed to their inhibition of Th17-T cells. Different from the traditional systemic drugs that impact the entire immune system, biologics target specific parts of the immune system and offer reduced multi-organ toxicity and adverse effects associated with traditional treatments.

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

2.2 Bimekizumab

Bimekizumab (also known as UCB4940) is an engineered, humanized, full-length immunoglobulin G1 mAb with high affinity for human IL-17A and IL-17F, important proinflammatory cytokines of the IL-17 family believed to play important roles in autoimmune and inflammatory diseases. Interleukin-17A has been shown to have a role in pathogenesis of several autoimmune disorders and IL-17F has been increasingly recognized to contribute to the

pathogenesis of a number of inflammatory diseases, including psoriasis, ulcerative colitis, asthma, ankylosing spondylitis, psoriatic arthritis, and rheumatoid arthritis. While anti-IL-17A antibodies have demonstrated efficacy in patients with psoriasis, psoriatic arthritis, and ankylosing spondylitis, as yet, no therapeutic approach is available that fully inhibits the activity of IL-17F. Bimekizumab selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro. Therefore, it permits an evaluation of the potential for additional efficacy, that may be conferred by dual inhibition of both cytokines, in patients suffering from diseases in which both cytokines are active.

2.2.1 Clinical

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

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

RA0124 was a Phase 1, open-label, parallel-group, single-dose study in healthy subjects. The primary objective of this study was to determine the absolute bioavailability of single sc doses of bimekizumab (80mg and 160mg). The secondary objectives were to evaluate the dose proportionality of bimekizumab 80mg and 160mg sc, and to evaluate the safety and tolerability of these sc doses and 160mg given by iv infusion. In RA0124, the absolute bioavailability was similar for the 2 doses tested (0.656 and 0.631 for the bimekizumab 80mg and 160mg sc doses, respectively). The PK of bimekizumab was linear in the tested dose range and the median $t_{1/2}$ following sc administration was similar to that following iv administration (27.81 days and 28.25 days for bimekizumab 160mg sc and 160mg iv, respectively).

Bimekizumab has also been investigated in a Phase 1b, proof of concept, randomized, placebo-controlled, multiple dose study (PA0007). The primary objective of PA0007 was to assess the safety and PK of multiple dose administration of iv bimekizumab in subjects with psoriatic arthritis. Four active doses and a placebo were tested. Drug was administered as a loading dose at Week 0, and 2 additional doses were administered at Week 3 and Week 6. In each treatment group, subjects received a total of 3 doses of bimekizumab, administered every 3 weeks as shown below:

- 80mg loading dose followed by 40mg at Weeks 3 and 6
- 160mg loading dose followed by 80mg at Weeks 3 and 6
- 240mg loading dose followed by 160 mg at Weeks 3 and 6
- 560mg loading dose followed by 320mg at Weeks 3 and 6

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

Infections (mostly nasopharyngitis) were the most commonly reported events in both the active treatment and the placebo group. None of the infections were considered serious or required treatment with antibiotics. Two subjects in the active treatment group experienced 1 local candida infection each (oropharhyngitis and vulvovaginitis, respectively) that were nonserious and resolved with topical therapy. There was a reduction in mean neutrophil count in the active treatment group, although this drop was not clinically relevant and a clear relationship with dose or time was not evident. Some increases in liver function tests were reported, but none had a convincing relationship to exposure to study medication. The exploratory analysis showed clinically relevant improvement in activity of psoriatic arthritis and in skin involvement in those subjects with concomitant active psoriatic lesions.

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

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

The current study, PS0018, is a 48-week open-label extension study for eligible subjects who participated in PS0016 (including subjects who relapse at Week 16 through 28 in PS0016), a Phase 2a, randomized, subject-blind, Investigator-blind study in adult subjects with moderate to severe chronic plaque psoriasis. In PS0016, subjects will be randomized 2:1 to receive the following study treatment regimens:

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

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 observed 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 OBJECTIVES

3.1 Primary objective

The primary objective of the study is to assess the long-term safety and tolerability of bimekizumab.

3.2 Secondary objectives

Secondary objectives of the study are:

- To assess the safety and tolerability of increasing the dose of bimekizumab from 160mg Q4W to 320mg Q4W for subjects with an inadequate response at Week 12
- To assess PK of bimekizumab
- To assess the immunogenicity of bimekizumab
- To assess the efficacy of open-label bimekizumab 160mg Q4W administered over 48 weeks

4 STUDY VARIABLES

4.1 Safety variables

4.1.1 Primary safety variable

The primary safety variable is the incidence of TEAEs adjusted by duration of subject exposure to treatment.

4.1.2 Other safety variables

Change from Baseline variables will be defined relative to the Baseline measurement from PS0016.

The other safety variables are:

- Severity and frequency of TEAEs
- Change from Baseline in clinical laboratory values (chemistry, hematology, and urinalysis)
- Change from Baseline in vital signs
- Change from Baseline in physical examination
- Change from Baseline in 12-lead ECG results

4.2 Pharmacokinetic variables

The PK variables are:

- Plasma concentrations of bimekizumab

4.3 Immunological variables

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

4.4 Efficacy variables

Change from Baseline variables will be defined relative to the Baseline measurement from PS0016.

The efficacy variables are listed below and will be evaluated at all scheduled visits in accordance with the schedule of assessments in Table 5–1.

- PASI50, PASI75, PASI90, and PASI100 response
- IGA response (Clear or Almost Clear with at least a 2 category improvement from Baseline on a 5-point scale)
- Absolute and percent change from Baseline in PASI score
- Shift from Baseline in IGA score
- Absolute and percent change from Baseline in the BSA affected by psoriasis
- Change from Baseline in the HADS Anxiety (HADS-A) and Depression (HADS-D) scores
- Percentage of subjects with scores below 8 in HADS-A and HADS-D (subjects with normal scores)

5 STUDY DESIGN

5.1 Study description

PS0018 is a multicenter, 48-week, open-label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult subjects with moderate to severe chronic plaque psoriasis who participated in PS0016.

During the Open-Label Treatment Period, subjects will attend study visits at the site Q4W for study assessments and administration of bimekizumab by study site staff through Week 48. Following completion or early withdrawal from the 48-week Open-Label Treatment Period, subjects will return for a SFU Visit 20 weeks after their last dose of bimekizumab. Subjects withdrawing early from the study will undergo the Early Withdrawal Visit assessments and will enter the SFU Period.

Bimekizumab will initially be administered at a dose of 160mg Q4W subcutaneously (sc) during the 48 week Open Label Treatment Period. There will be an option to increase the dose to 320mg Q4W at the discretion of the Investigator if the subject's PASI response is ≥50% to <75% reduction from the Baseline of PS0016 at Week 12 or later. If the subject's disease is adequately controlled on the 320mg Q4W dose, they may return to 160mg Q4W at the discretion of the Investigator. The decision to return to 160mg Q4W dosing should be based upon treatment response, tolerability, and Investigator discretion, with the aim to use the dosing regimen that achieves the optimal benefit-risk for each subject. If a subject does not achieve a PASI50 at Week 12 or later then they will be withdrawn from the study.

A schedule of study assessments in presented in Table 5–1.

A study schematic diagram of PS0018 is presented in Figure 5–1.

5.1.1 Study duration per subject

The study duration for each subject is estimated to be up to a maximum of 64 weeks:

- Open-Label Treatment Period: up to 48 weeks
- SFU Visit: 20 weeks after the last dose of bimekizumab

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

5.1.2 Planned number of subjects and sites

Up to 45 subjects are anticipated to enroll in PS0018 at approximately 15 sites.

5.1.3 Anticipated regions and countries

The regions planned for study conduct are Europe and North America, with possible extension to other regions and countries as required in PS0016.

5.2 Schedule of study assessments

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

Table 5–1: Schedule of study assessments

Visit Week [a] / Protocol activity	PS0018 Baseline	Open-Label Treatment Period												
		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48/ WD	SFU [b]
Informed consent	X [c]													
Inclusion/exclusion	X [d]													
Physical exam [e]	X [f]												X	X
Body weight	X [f]												X	X
Vital signs [g]	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology/biochemistry/urinalysis [h]	X [f]		X		X		X		X		X		X	X
12-lead ECG	X [f]						X						X	X
Pregnancy testing [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
IGRA TB test [j]	X [f]												X	X
TB questionnaire	X [f]			X			X			X			X	
Blood sample for bimekizumab plasma concentrations [k]	X [f]	X	X	X	X			X			X		X	X
Blood sample for anti-bimekizumab antibodies [k]	X [f]	X	X	X	X			X			X		X	X
PASI	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
IGA	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	X
BSA	X [f]	X	X	X	X	X	X	X	X	X	X	X	X	
HADS	X [f]			X			X			X			X	
Concomitant medications	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 [l]
IXRS	X	X	X	X	X	X	X	X	X	X	X	X		
Bimekizumab administration [m, n]	X	X	X	X [m]	X [m]	X [m]	X [m]	X [m]	X [m]	X [m]	X [m]	X [m]		

Table 5–1: Schedule of study assessments

Visit Week [a] / Protocol activity	PS0018 Baseline	Open-Label Treatment Period												
		Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48/ WD	SFU [b]

BSA=body surface area; C-SSRS=Columbia-Suicide Severity Rating Scale;ECG=electrocardiogram; HADS=Hospital Anxiety and Depression Scale; IGA=Investigator's Global Assessment; IGRA=interferon gamma release assay; IXRS=interactive voice or web response system; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; SFU=Safety Follow-Up; TB=tuberculosis; WD= withdrawal; Wk=week

[a] Visit windows of ±3 days from the first dose (Baseline) at all visits except SFU, which has a window of -3 and +7 days from scheduled visit date.

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

[c] Ensure that the informed consent for PS0018 was completed by the subject (must be done before any study assessments are performed for PS0018).

[d] To be performed prior to the first dose of open-label bimekizumab.

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

[f] The noted PS0018 Baseline assessments will be obtained at the final visit of PS0016 and do not need to be recorded on the case report form for this study.

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

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

[i] Pregnancy testing will be urine testing at all visits except SFU, which will be a serum test.

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

[k] All blood samples are to be taken prior to dosing.

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

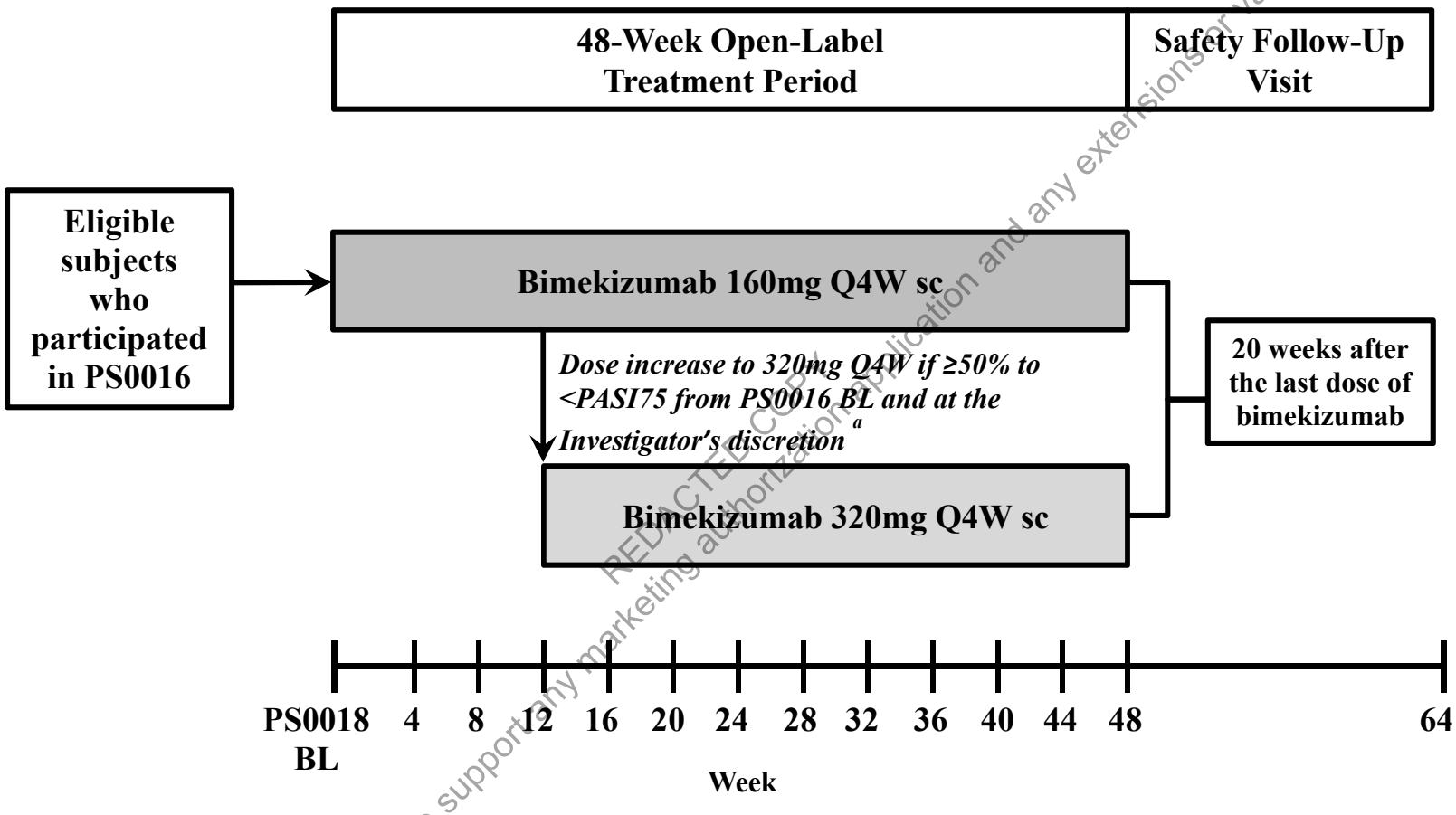
[m] Bimekizumab will initially be administered at a dose of 160mg Q4W subcutaneously (sc) during the 48 week Open Label Treatment Period. There will be an option to increase the dose to 320mg Q4W at the discretion of the Investigator if the subject's PASI response is ≥50% to <75% reduction from the Baseline of PS0016 at Week 12 or later. If the subject's disease is adequately controlled on the 320mg Q4W dose, they may return to 160mg Q4W at the discretion of the Investigator. The decision to return to 160mg Q4W dosing should be based upon treatment response, tolerability, and Investigator discretion, with the aim to use the dosing regimen that achieves the optimal benefit-risk for each subject. If a subject does not achieve a PASI50 at Week 12 or later then they will be withdrawn from the study.

[n] Subjects should not receive their first dose in PS0018 until at least 4 weeks (+/-3 days) after their last dose in PS0016.

5.3 Schematic diagram

A study schematic diagram of PS0018 is presented in Figure 5–1.

Figure 5–1: Schematic diagram



BL=Baseline; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; sc=subcutaneously

[a] Bimekizumab will initially be administered at a dose of 160mg Q4W subcutaneously (sc) during the 48 week Open Label Treatment Period. There will be an option to increase the dose to 320mg Q4W at the discretion of the Investigator if the subject's PASI response is ≥50% to <75% reduction from the Baseline of PS0016 at Week 12 or later. If the subject's disease is adequately controlled on the 320mg Q4W dose, they may return to 160mg Q4W at the discretion of the Investigator. The decision to return to 160mg Q4W dosing should be based upon treatment response, tolerability, and Investigator discretion, with the aim to use the dosing regimen that achieves the optimal benefit-risk for each subject. If a subject does not achieve a PASI50 at Week 12 or later then they will be withdrawn from the study.

5.4 Rationale for study design and selection of dose

PS0018 is a 48-week open-label extension study for eligible subjects who participated in PS0016, a Phase 2a, randomized, subject-blind, Investigator-blind study in adult subjects with moderate to severe chronic plaque psoriasis. This study will allow the collection of further data on the long-term safety, tolerability, and efficacy of bimekizumab in this subject population and will provide continued access to bimekizumab.

Bimekizumab will initially be administered at a dose of 160mg Q4W subcutaneously (sc) during the 48 week Open Label Treatment Period. There will be an option to increase the dose to 320mg Q4W at the discretion of the Investigator if the subject's PASI response is ≥50% to <75% reduction from the Baseline of PS0016 at Week 12 or later. If the subject's disease is adequately controlled on the 320mg Q4W dose, they may return to 160mg Q4W at the discretion of the Investigator. The decision to return to 160mg Q4W dosing should be based upon treatment response, tolerability, and Investigator discretion, with the aim to use the dosing regimen that achieves the optimal benefit-risk for each subject. If a subject does not achieve a PASI50 at Week 12 or later then they will be withdrawn from the study.

The rationale for the selection of the 160mg Q4W dose for this study is based on the following:

- The optimal therapeutic dose of bimekizumab will not yet be known at the time subjects begin entering PS0018 from PS0016.
- The 160mg Q4W dose is within the range of doses that have already been explored by iv administration. This dose was selected based on modeling using the currently available data and may be modified, if appropriate, as further data are collected on the optimal dose of bimekizumab.
- The 160mg Q4W starting dose in PS0018 will provide data to evaluate the safety and efficacy of a dose reduction.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent form is signed and dated by the subject.
2. Subject is considered reliable and capable of adhering to the protocol and visit schedule according to the judgment of the Investigator.
3. Subject completes all dosing requirements in PS0016 without meeting any withdrawal criteria.
4. **Female** subjects must be postmenopausal (at least 1 year; to be confirmed hormonally at the PS0018 Baseline Visit, if less than 2 years since last menstrual period), permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) or, if of childbearing potential, must be willing to use a highly effective method of contraception up until 20 weeks after last administration of study medication (anticipated 5 half-lives), and have a negative

pregnancy test at Visit 1 (Baseline) 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, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence if it is in accordance with a subject's preferred and common lifestyle. Subjects who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse until 20 weeks after the last dose of study medication. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.

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

6.2 Exclusion criteria

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

1. Subject has previously participated in this study.
2. Female subjects who plan to become pregnant during the study or within 20 weeks following last dose of study medication. Male subjects who are planning a partner pregnancy during the study or within 20 weeks following the last dose.
3. Subject has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the subject's ability to participate in this study. Note: For any subject with an ongoing serious adverse event (SAE), or a history of serious infections (including herpes zoster or hospitalizations) in PS0016, the Medical Monitor must be consulted prior to the subject's entry into PS0018.
4. Subject has any current sign or symptom that may indicate a medically significant infection.
5. Subject has current clinically active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, tuberculosis (TB), nontuberculous mycobacteria (NTMB), Blastomyces, Aspergillus, or Candidiasis (systemic). Any subject diagnosed with Histoplasmosis, Coccidiodes, Paracoccidiodes, Pneumocystis, TB, NTMB, Blastomyces, Aspergillus, or Candidiasis (systemic) during PS0016 is excluded from PS0018 even if treatment has been completed.
6. Any subject who meets any withdrawal criteria in the feeder study (PS0016) is excluded from participating in the open-label extension study (PS0018).

6.3 Withdrawal criteria

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

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

1. Subject withdraws his/her consent.
2. There is confirmation of a pregnancy in a female subject during the study, as evidenced by a positive pregnancy test.
3. The Sponsor or a regulatory agency requests withdrawal of the subject.
4. Subject develops an illness that in the opinion of the Investigator would interfere with his/her continued participation if the risk of continuing participation outweighs the potential benefit.
5. Subject develops erythrodermic, guttate, or pustular form of psoriasis.
6. Subjects considered to have either a suspected new latent tuberculosis (LTB) infection or who develop an active TB or NTMB infection during the study (including but not limited to, conversion demonstrated by interferon-gamma release assay [IGRA] or other diagnostic means) must be immediately discontinued from study medication; an Early Withdrawal Visit must be scheduled as soon as possible, but not later than the next regular visit.

   Confirmed active TB is 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.
7. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
8. Subject uses prohibited concomitant medications that may present a risk to the safety of the subject in the opinion of the Investigator and/or the Medical Monitor.
9. Subject experiences an AE as described below:
   - Any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above AE that is assessed as related to study drug in the opinion of the Investigator.
     - If the event is deemed to be not related to study drug by the Investigator, the subject may remain in the study after approval by the Medical Monitor.
   - Any CTCAE Grade 2 event that is evaluated as related to study drug in the opinion of the Investigator, is persistent, and falls into any of the following system organ classes (SOCs): “Blood and lymphatic disorders,” “Cardiac disorders,” or “Vascular disorders.”
     - Persistent is defined as lasting 28 days or more, which spans at least 2 scheduled injections.

10. Subject has a clinical laboratory value meeting the following criteria:
    - CTCAE Grade 3 and above: subjects must be withdrawn regardless of relationship to study drug or duration of event.
    - CTCAE Grade 2
        - Subjects may remain in the study if the event is transient. If a subject has a Grade 2 laboratory abnormality, a retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat value is below Grade 2, the subject may receive the next scheduled study treatment. If the value on the repeat is still Grade 2 or above, a second repeat test must be performed and results made available prior to the next scheduled study treatment. If this second repeat value is still Grade 2 or above, the subject must be withdrawn.
11. Subject has active suicidal ideation as indicated by a positive response ("Yes") to questions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated Columbia-Suicide Severity Rating Scale (C-SSRS). The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
12. Subjects with a HADS-D score ≥15 must be withdrawn. Any subject who develops a HADS-D score of >10 during the study should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.
13. Subject does not achieve a PASI50 at Week 12 or later following open-label treatment in PS0018.
14. Subjects with newly diagnosed Inflammatory Bowel Disease (IBD) or with IBD flares during the study must:
    - Be referred, as appropriate, to a healthcare professional treating IBD, such as a gastroenterologist
    - Discontinue the IMP and be followed-up until resolution of active IBD symptoms

    If IBD flares increase in severity or frequency during the study, the Investigator should use clinical judgment in deciding whether the subject should continue in the study and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.

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

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

6.3.1 PDILI IMP discontinuation criteria

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

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

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

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

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

Evaluation of PDILI must be initiated as described in Section 9.7.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

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

6.4 Study stopping rules

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

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

- A pattern of AEs occurs that contraindicates the further dosing of enrolled / additional subjects, including (but not limited to):
  - More than 1 subject meets any individual Withdrawal Criteria 6, 9, 10, 11 or 12 (as provided in Section 6.3), regardless of whether they met the same or different criteria.
  - Once a second subject meets any of those criteria, referral to the DMC may not be delayed while awaiting the outcome of either case.

If the above criteria are reached, the DMC will meet as soon as possible to determine whether discontinuation or suspension of the study should occur, and to determine what investigations, analyses, procedural amendments, or other actions should occur, before making any recommendation regarding the possibility of recommencing the study. Further details on the role of the DMC are provided in Section 9.8.7.

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

7 STUDY TREATMENT

7.1 Description of investigational medicinal product

The IMP used in this study is bimekizumab.

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

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

7.2 Treatments to be administered

During the Treatment Period, all subjects will receive bimekizumab 160mg Q4W sc administered for up to 48 weeks in an open-label manner. Subjects should not receive their first dose in PS0018 until at least 4 weeks (+/-3 days) after their last dose in PS0016. At the discretion of the Investigator, and if the subject does not achieve a PASI75 response (75% reduction in the PASI score from the Baseline of PS0016) at Week 12, the bimekizumab dose in PS0018 may be increased to 320mg Q4W sc. If the subject's disease is adequately controlled on the 320mg Q4W dose, they may return to 160mg Q4W. The decision to return to 160mg Q4W dosing should be based upon treatment response, tolerability, and Investigator discretion, with the aim to use the dosing regimen that achieves the optimal benefit-risk for each subject.

The study medication is to be administered in the clinic by study site staff as 1 sc injection for the 160mg dose or 2 sc injections for the 320mg dose. Suitable areas for sc injections are the lateral abdominal wall and upper outer thigh. Injection sites should be rotated and injections should not be given into areas where the skin is tender, bruised, red, or hard.

The minimum time between doses should be no less than 24 days and no more than 32 days for Q4W dosing.

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

7.3 Packaging

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

7.4 Labeling

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

7.5 Handling and storage requirements

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

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

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

Study drug will be shipped to the study sites in temperature controlled containers. Out-of-range shipping or storage conditions must be brought to the attention of the Sponsor or designee, as per instructions contained in the IMP Handling Manual. 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 (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

The 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 SOPs or returned to UCB (or designee). Onsite destruction of used kits only may be allowed with prior approval from the Sponsor or designee after reconciliation. Investigational medicinal product intended for the study cannot be used for any other purpose than that described in this protocol.

7.7 Procedures for monitoring subject compliance

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

7.8 Concomitant medication(s)/treatment(s)

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

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

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

7.8.1 Permitted concomitant treatments (medications and therapies)

Topical medications

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

Subjects will be allowed to use topical medications (corticosteroids, retinoids, Vitamin D analogs coal tar, etc) as needed during this open-label extension.

Other medications

Subjects who were already receiving an established nonsteroidal anti-inflammatory drug (NSAID) regimen during PS0016 may continue their use during this 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 be done with caution. Intra-articular injections for arthritis of the knee are allowed.

Subjects who were already receiving an established anti-depressant regimen during PS0016 may continue their use during this study.

7.8.2 Prohibited concomitant treatments (medications and therapies)

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

Table 7–1: Prohibited psoriasis medications during PS0018

Drug
Systemic retinoids
Systemic treatment (non-biological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) systemic fumarate systemic corticosteroids phototherapy or chemophototherapy
Anti-TNFs: infliximab (including biosimilar), golimumab etanercept (including biosimilar) certolizumab pegol adalimumab (including biosimilar)
Other biologics and other systemic therapies: apremilast ustekinumab
Anti-IL-17 therapy
Any other antipsoriatic agent (systemic)
Any other antipsoriatic agent (topical) under investigation

IL=interleukin; TNF=tumor necrosis factor

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

Vaccines

Administration of live (including attenuated) vaccines is not allowed during the conduct of the study or for 20 weeks after the last dose of study drug. Administration of inactivated vaccines is allowed during the study at the discretion of the Investigator.

7.9 Blinding

This is an open-label extension study and no blinding will be performed. All subjects' treatment assignments during PS0016 will remain blinded until database lock of PS0016.

7.10 Randomization and numbering of subjects

This is an open-label extension study and no randomization will be performed. All subjects will receive bimekizumab 160mg Q4W sc with an option to increase the dose to 320mg Q4W at the discretion of the Investigator (see Section 7.2 for further details).

Subjects will continue with the 5-digit subject numbers assigned by the interactive voice or web response system (IXRS) in the preceding study.

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 provided in the sections that follow.

- Visit windows of ±3 days on either side of the scheduled dosing are permitted for all visits other than the SFU Visit (see below); however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to the first dose (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 time between doses should be no less than 24 days and no more than 32 days for Q4W dosing.
- 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).

8.1 Baseline Visit

The Baseline assessments noted with an * will be obtained at the final visit of PS0016 and do not need to be recorded on the eCRF for this study.

All procedures or assessments will be performed prior to administration of study drug, unless otherwise noted. The following procedures or assessments will be performed:

- Ensure that a separate Informed Consent Form was completed by the subject for PS0018 (must be done prior to any PS0018 study procedures)
- Confirm that a TB test (IGRA) was performed at the final visit of PS0016 and the results were negative
- Assessment of inclusion/exclusion criteria
- Vital signs (blood pressure, pulse rate, and temperature)*
- Body weight*
- Physical examination*
- Record 12-lead ECG*
- C-SSRS*
- TB questionnaire*
- PASI*
- IGA*
- BSA*
- HADS*
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)*

  - Bimekizumab plasma concentration*
  - Anti-bimekizumab antibodies*
- Obtain urine sample for:
  - Standard safety laboratory tests (urinalysis)*
  - Urine pregnancy test for women of childbearing potential*
- Concomitant medications
- Record adverse events (AEs)
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

8.2 Week 4 (±3 days); and Week 28 (±3 days)

All procedures or assessments will be performed prior to administration of study drug, unless otherwise noted. The following procedures or assessments will be performed:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- PASI
- IGA
- BSA
- Obtain blood samples for:
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

8.3 Week 8 (±3 days); Week 16 (±3 days); and Week 40 (±3 days)

All procedures or assessments will be performed prior to administration of study drug (if applicable), unless otherwise noted. The following procedures or assessments will be performed:

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

- IGA
- BSA
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests (urinalysis)
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

8.4 Week 12 (±3 days)

The following procedures or assessments will be performed prior to administration of study drug (if applicable):

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- TB questionnaire
- PASI
- IGA
- BSA
- HADS
- Obtain blood samples for:
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS

- Study medication administration (after all other visit assessments are completed)

8.5 Week 20 (±3 days); and Week 44 (±3 days)

The following procedures or assessments will be performed prior to administration of study drug (if applicable):

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- PASI
- IGA
- BSA
- Obtain urine sample for:
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

8.6 Week 24 (±3 days)

The following procedures or assessments will be performed prior to administration of study drug (if applicable):

- Vital signs (blood pressure, pulse rate, and temperature)
- Record 12-lead ECG
- C-SSRS
- TB questionnaire
- PASI
- IGA
- BSA
- HADS
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
- Obtain urine samples for:
  - Standard safety laboratory tests (urinalysis)
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications

- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

8.7 Week 32 (±3 days)

All procedures or assessments will be performed prior to administration of study drug (if applicable), unless otherwise noted. The following procedures or assessments will be performed:

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- PASI
- IGA
- BSA
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
- Obtain urine sample for:
  - Standard safety laboratory tests (urinalysis)
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

8.8 Week 36 (±3 days)

The following procedures or assessments will be performed prior to administration of study drug (if applicable):

- Vital signs (blood pressure, pulse rate, and temperature)
- C-SSRS
- TB questionnaire
- PASI
- IGA
- BSA
- HADS
- Obtain urine sample for:
  - Urine pregnancy test for women of childbearing potential

- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

8.9 Week 48 (±3 days) Study Exit/Early Withdrawal

The following procedures or assessments will be performed:

- Vital signs (blood pressure, pulse rate, and temperature)
- Body weight
- Physical examination
- Record 12-lead ECG
- C-SSRS
- TB questionnaire
- PASI
- IGA
- BSA
- HADS
- Obtain blood samples for:
  - TB test (IGRA; QuantiFERON TB GOLD test is recommended)
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests (urinalysis)
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs

8.10 SFU Visit (20 weeks after the last dose; -3/+7 days)

The following procedures or assessments will be performed:

- Vital signs (blood pressure, pulse rate, and temperature)
- Body weight
- Physical examination

- C-SSRS
- Record 12-lead ECG
- PASI
- IGA
- Obtain blood samples for:
  - TB test (IGRA; QuantiFERON TB GOLD test is recommended)
  - Standard safety laboratory tests (hematology and biochemistry)
  - Serum pregnancy test for women of childbearing potential
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests (urinalysis)
- Concomitant medications
- Record AEs (including assessment for development of other forms of psoriasis)

8.11 Early Withdrawal Visit

Subjects withdrawing early from the study (see Section 6.3) will undergo the same assessments as the Week 48 Visit (see Section 8.9) and will enter the SFU Period.

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

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

- Vital signs
- Physical examination
- Record 12-lead ECG
- C-SSRS
- If medically indicated, obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - The blood sample may also be used for PK assessments, if needed

- Obtain urine sample for standard safety laboratory tests (urinalysis; including urine pregnancy test)
- Concomitant medications
- Record AEs

9 ASSESSMENT OF SAFETY

9.1 Adverse events

9.1.1 Definition of AE

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

In order to ensure complete safety data collection, all AEs occurring during the study (ie, after the signing of the Informed Consent form), including any pretreatment and 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.

9.1.2 Procedures for reporting and recording AEs

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

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

In addition, the Investigator should review any self-assessment procedures employed in the study.

9.1.3 Description of AEs

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

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

9.1.4 Follow up of AEs

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. Further details regarding follow up of PDILI events are provided in Section 9.7.1.4.

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.

9.1.5 Rule for repetition of an AE

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

9.1.6 Pregnancy

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

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

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

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

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should

be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/Contract Research Organization (CRO) contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective 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.

9.1.7 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.

9.1.8 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).

9.1.9 Safety signal detection

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

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

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

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

9.2 Serious adverse events

9.2.1 Definition of SAE

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 9.5], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

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

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

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

9.2.2 Procedures for reporting SAEs

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 SAE 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.

9.2.3 Follow up of SAEs

An SAE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. Further details regarding follow up of PDILI events is provided in Section 9.7.1.4.

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

9.3 Immediate reporting of AEs

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the definitions in Section 9.2.1 regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AEs of special interest as defined in Section 9.5

9.4 Anticipated SAEs

The following Anticipated SAEs (Table 9–1) are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will

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

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 9.2.2.

Table 9–1: Anticipated SAEs 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.

9.5 Adverse events of special interest

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

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

9.6 Adverse events for special monitoring

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

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB; see Section 9.8.1), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the C-SSRS; see Section 9.8.6), depression and anxiety (assessed using the HADS; see Section 12.4), major cardiovascular events, and liver function test changes/enzyme elevations (ALT, AST, bilirubin; see Section 9.7.1), malignancies, and inflammatory bowel diseases.

9.7 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. Laboratory parameters to be measured are listed in Table 9–2.

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

Table 9–2: Laboratory measurements

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

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

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

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

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

9.7.1 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 9.5), and, if applicable, also reported as an SAE (see Section 9.2.1).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 9-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 9.7.1.1). 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 9.7.1.4).

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 even if a subsequent alternative diagnosis fully explains the hepatic findings.

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

Table 9-3 summarizes the approach to investigate PDILI.

Table 9-3: Required investigations and follow-up for PDILI

Laboratory value		Symptoms [a] of hepatitis or hypersensitivity	Immediate		Follow up	
ALT or AST	**Total bilirubin**		**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 9.7.1.3); 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				
≥5xULN	NA	NA	Need for hepatology consult to be discussed (required if ALT or AST ≥8xULN). Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.			

Table 9-3: Required investigations and follow-up for PDILI

Laboratory value		Symptoms [a] of hepatitis or hypersensitivity	Immediate		Follow up	
ALT or AST	**Total bilirubin**		**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN (and ≥2x baseline) and <5xULN (and ≥2x baseline)	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow up requirements). [c]	Further investigation – immediate IMP discontinuation not required (see Section 9.7.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase. • Liver chemistry values remain ≥3xULN (and ≥2x baseline) after 2 weeks of monitoring without evidence of resolution.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 9.7.1.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks. [d] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • Discontinue IMP if levels remain ≥3xULN (and ≥2x baseline) without evidence of resolution [d] • Continue to monitor until values normalize, stabilize, or return to within baseline values. [d]

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

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

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

[c] Details provided in Section 9.7.1.1. 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.

9.7.1.1 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 9.7.1.3) and SAE report (if applicable).

9.7.1.2 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 9-3 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.

9.7.1.3 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 include, but are not limited to, those listed in Table 9-4 (laboratory measurements) and Table 9-5 (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 laboratory measurements to be assessed are presented in Table 9-4.

Table 9-4: PDILI laboratory measurements

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

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

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

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

Additional information to be collected is presented in Table 9-5.

Table 9-5: 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

9.7.1.4 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 9-3. 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.

9.8 Other safety measurements

9.8.1 Assessment and management of TB and TB risk factors

All subjects will be assessed for TB through physical examination for signs and symptoms of TB, laboratory testing (Section 9.8.1.1), and subject questionnaire (Section 9.8.1.3). A chest x-ray can be performed in PS0018, if warranted, to confirm or exclude TB (Section 9.8.1.2).

At the Baseline Visit of PS0018, all subjects will undergo physical examination for signs and symptoms of TB and must be confirmed to have undergone an IGRA test (QuantiFERON TB GOLD is recommended) in PS0016 with negative results. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB.

Exclusion criteria at Baseline of PS0018

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

a. Known TB infection whether present or past is defined as:
   - Active TB infection or clinical signs and symptoms suspicious for TB (pulmonary or extra-pulmonary)
   - History of active TB infection involving any organ system or findings in other organ systems consistent with TB infection, unless adequately treated and proven to be fully recovered upon consult with a TB specialist
   - Any evidence by radiography or other imaging modalities consistent with previously active TB infection that is not reported in the subject's medical history
b. High risk of acquiring TB infection is defined as:
   - Known exposure to another person with active TB infection within the 3 months prior to enrollment
   - Time spent in a healthcare delivery setting or institution where individuals infected with TB are housed and where the risk of transmission of infection is high
c. Latent TB infection is defined as:
   - The absence of signs, symptoms (ie, evidence of organ-specific involvement), or physical findings suggestive of TB infection with a positive IGRA test (or 2 indeterminate IGRA test results) and a chest x-ray (or other imaging) without evidence of TB infection. If the result of the IGRA test is indeterminate, the particular IGRA test previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be enrolled in the study. The retest must be done prior to entry in PS0018.

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

Signs and Symptoms

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

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

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

Latent TB infection is defined in the "Exclusion Criteria" above. If the result of the IGRA is indeterminate, the particular IGRA previously performed may be repeated once; if positive or indeterminate on retest, the subject may not be enrolled in the study without further evaluation by a TB specialist. In the event of an indeterminate test result, the retest must be done prior to the next visit. If LTB infection or active TB is identified, subject must undergo appropriate study specified withdrawal procedures. Laboratory diagnosis should be undertaken via mycobacteria culture media (or if available by preferred nucleic acid amplification test such as the Xpert MTB RIF test) and the result must be negative for TB inducing pathogens.

Test Conversion

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

LTB

In case the evaluation by the appropriate specialist indicates a new LTB infection during the study, a prophylactic TB treatment should be initiated and the subject must be withdrawn from the study. Every related action should be discussed in advance with the Medical Monitor.

Once withdrawn from study treatment, subjects should return for the Week 48/Withdrawal Visit, complete all Early Withdrawal Visit assessments, and complete a SFU Visit (20 weeks after the last dose of study medication).

Active TB or NTMB infection

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

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

9.8.1.1 TB assessment by IGRA

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD is recommended) will be performed at the final visit of PS0016 and should be repeated at Week 48/Early Withdrawal Visit and the SFU visit for all subjects. The test results will be reported as positive, negative, or indeterminate. UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, the subject must undergo appropriate study-specified withdrawal

procedures. In the event of an indeterminate test result, the retest must be done prior to the next visit.

9.8.1.2 Chest x-ray for TB

Chest x-ray will be performed in PS0018 only when required to confirm or exclude TB. Any new clinically significant findings on chest x-ray must be documented in the source documents and the eCRF as an AE.

9.8.1.3 TB questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed at the Baseline Visit of PS0018, and at the Week 12, Week 24, Week 36, and Week 48/Withdrawal Visit. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] or to any of the other questions within the questionnaire at any visit should trigger further careful assessment to determine if subject has LTB or active TB.

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

9.8.1.4 TB management

LTB infection and active TB identified during study

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

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

The subject should be transferred to the care of his/her physician and managed according to the best available standard of care. Subjects identified as having converted to active TB during the study must be withdrawn and scheduled to return for the Week 48/Withdrawal Visit as soon as possible, but no later than the next scheduled study visit, and complete all Week 48/Withdrawal Visit assessments.

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

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

9.8.2 Pregnancy testing

Pregnancy testing will consist of serum testing at the SFU Visit and urine testing at all other visits.

The Baseline Visit urine pregnancy test result must be negative prior to enrollment of the subject. A negative urine pregnancy test result should be obtained immediately prior to each administration of study drug and at all subsequent visits. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

9.8.3 Vital signs

Vital signs will be collected at every visit and will include systolic and diastolic blood pressure, 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.

Body weight will be measured at the time points specified in the schedule of study assessments (Table 5–1).

9.8.4 12-lead ECGs

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

9.8.5 Physical examination

The physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; respiratory; cardiovascular; GI; musculoskeletal; hepatic; neurological (including limb reflexes); and mental status. Physical examination will be performed at the time points specified in the schedule of study assessments (Table 5–1). Findings considered clinically significant changes since the physical examination at the Screening Visit of PS0016 will be recorded as AEs.

9.8.6 Assessment of suicidal ideation and behavior

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

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

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

9.8.7 Data Monitoring Committee

The DMC membership includes clinicians knowledgeable about the disease or the treatment. The DMC will include a statistician, and at a minimum, specialists in dermatology and infectious disease. All members have experience and expertise in clinical trials. Board members may not participate in the study as principal or co-Investigators, or as study subject care physicians. The duration of membership for the DMC will be inclusive of planned analyses for PS0018. The DMC may also be asked to provide a review of final study results, as deemed appropriate.

The detailed role, scope, responsibilities, and complete procedures, as well as the identity of the DMC members, will be described in a separate charter document.

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

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

10 ASSESSMENT OF PHARMACOKINETIC VARIABLES

Blood samples for measurement of PK (Section 4.2) 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.

11 ASSESSMENT OF IMMUNOLOGICAL VARIABLES

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 EFFICACY

12.1 Psoriasis Area and Severity Index

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

The degree of involvement is estimated across 4 body areas; head, upper limbs, trunk, and lower limbs and then transferred into a grade (Table 12–1).

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 12–1: Body areas for calculation of percent BSA for PASI

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

BSA=body surface area; PASI=Psoriasis Area and Severity Index

[a] Where 0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected.

The PASI50, PASI75, PASI90, and PASI100 responses are based on at least 50%, 75%, 90%, and 100% improvement in the PASI score. The improvement will be based on changes from the PASI score at the Baseline of PS0016.

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

12.2 Investigator's Global Assessment

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

The Investigator will assess the overall severity of psoriasis using the following 5-point scale:

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

12.3 BSA affected by psoriasis

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

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

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

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

12.4 Hospital Anxiety and Depression Scale

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

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 Clinical Project Manager of the Sponsor within 24 hours and follow any local regulatory requirements.

13.2 Monitoring

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

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

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

Monitoring visits will provide UCB (or designee) with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of eCRFs, ensure that all protocol requirements, applicable authorities regulations, and Investigator's obligations are being fulfilled, and resolve any inconsistencies in the study records.

13.2.1 Definition of source data

All source documents must be accurate, clear, unambiguous, permanent, and capable of being audited. Source documentation should be made using some permanent form of recording (ink, typing, printing, optical disc). They should not be obscured by correction fluid or have temporary attachments (such as removable self-stick notes). Photocopies of eCRFs are not considered acceptable source documents. Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, ECG or other printouts, completed scales, or QOL questionnaires, for example. Source documents should be kept in a secure, limited access area.

The Sponsor or designee will review to ensure that computerized source documents produced by the site are compliant with Food and Drug Administration (FDA) Part 11 requirements and document appropriately. Source documents that are computer generated and stored electronically that are not FDA Part 11 compliant, must be printed for review by the monitor (eg, ECG reports). Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the subject's source documents. The Investigator will facilitate the process for enabling the monitor to compare the content of the printout and the data stored in the computer to ensure all data are consistent.

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

13.2.2 Source data verification

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

13.3 Data handling

13.3.1 eCRF completion

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

Serious AE reporting will be done using the SAE Form (see Section 9.2.2) while also entering the event in the appropriate eCRF section. The safety database and the clinical database will be reconciled during the study and discrepancies will be corrected as needed.

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

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

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

13.3.2 Database entry and reconciliation

Case Report Forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system. Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. This study is performed using EDC: the data are entered into the eCRFs once and are subsequently verified.

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

13.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject 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 study master file.

13.6 Audit and inspection

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

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

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

13.7 Good Clinical Practices

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

14 STATISTICS

A description of statistical methods is presented below and will be described in more detail in the Statistical Analysis Plan (SAP).

14.1 Definition of analysis sets

The Enrolled Set (ES) will consist of all subjects who have given informed consent for PS0018.

The Safety Set (SS) will consist of all subjects who receive at least 1 dose of the study medication in PS0018.

The Full Analysis Set (FAS) will consist of all enrolled subjects who receive at least 1 dose of the study medication and have a valid efficacy measurement for PASI at Baseline of PS0018.

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all enrolled subjects who receive at least 1 dose of the study medication and provide at least 1 quantifiable plasma concentration postdose in PS0018.

14.2 Planned safety analyses

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

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA®). Treatment-emergent AEs will be defined as events that have a start date on or following the first administration of study treatment in PS0018 through the final administration of study treatment +140 days (covering the 20-week SFU Period). Treatment-emergent AEs will be categorized to treatment group based on the dose being received at the time of onset of the event. Tables will include columns for bimekizumab 320mg Q4W, bimekizumab 160mg Q4W, and All bimekizumab (ie, either dose of bimekizumab).

Change from Baseline safety variables will be defined relative to the Baseline measurement from PS0016.

14.2.1 Primary safety analysis

All TEAEs will be summarized descriptively by treatment group, primary system organ class (SOC), high level term (HLT), and preferred term (PT). This summary will include the exposure adjusted incidence rate (EAIR) with associated 95% confidence interval and the exposure adjusted event rate (EAER).

For EAIR, the numerator will be the total number of subjects experiencing the AE. The denominator will be 100 subject-years; that is, the total summation of individual subject-years at risk up to the first occurrence of the AE for subjects with that AE, and the total subject-years at risk for those subjects not experiencing that AE, divided by 100. Exposure adjusted incidence rates will be presented with a 95% exact confidence interval based upon the Chi-Square distribution (Ulm, 1990).

For EAERs, the numerator will be the number of AEs including repeat occurrences in individual subjects; the denominator will be 100 subject-years. That is, the total summation of individual subject-years at risk divided by 100. No confidence interval will be computed for EAER.

Subject exposure at risk in days will be defined as date of last administration of study medication – date of first administration of study medication +140 days (ie, the duration of the SFU Period). If a subject dies, patient exposure at risk is censored at the date of death. The sum of these exposure days at risk across subjects is converted to years for the EAIR and EAER calculations described above.

14.2.2 Other safety analyses

Additional tables will summarize TEAEs by intensity and relationship to study medication, TEAEs leading to withdrawal from the study, treatment-emergent SAEs, and deaths.

In order to evaluate if there is any difference in the TEAE profile of subjects who have dose adjustments, additional summaries will be generated and are described further here. With respect to dose adjustments, subjects will be classified into 1 of the following 3 groups:

- Nonadjusters – This group consists of subjects who do not experience a dose adjustment during the study.
- Single adjusters – This group consists of subjects who experience just one dose adjustment during the study. Per the protocol, if just a single adjustment occurs, then that adjustment must be to go from bimekizumab 160mg Q4W to 320mg Q4W.
- Multiple adjusters – This group consists of subjects who experience more than 1 dose adjustment during the study. This means that the subjects in this group dose adjust from

bimekizumab 160mg Q4W to 320mg Q4W and then adjust back to 160mg Q4W (with further dose adjustments possible).

Summaries based on these 3 groups will be done by PS0016 randomized treatment group for the TEAE overview, incidence of TEAEs (by SOC, HLT, and PT), and incidence of treatment-emergent SAEs.

Extent of exposure to study medication in PS0018 will be summarized using descriptive statistics. As with the primary summaries of TEAEs, extent of exposure will be presented with columns for bimekizumab 160mg Q4W, bimekizumab 320mg Q4W, and All bimekizumab.

Change from Baseline in laboratory values, ECGs, and vital signs will be presented using descriptive statistics by PS0016 randomized treatment group and overall. As these variables are summarized over time and the initial values can be impacted by the randomized treatment in PS0016, the presentation by PS0016 randomized treatment group is intended to provide perspective on the change in these values starting with the initial PS0016 randomization through the 48-week Open-Label Treatment Period of PS0018. The table presentations will display descriptive statistics for the PS0016 Baseline and the observed and change from PS0016 Baseline results by scheduled visit for PS0018.

14.3 Planned PK 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.

14.4 Planned immunological analyses

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

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

14.5 Planned efficacy analyses

Efficacy variables will be summarized based on the FAS. The summaries described in this section will provide data on maintenance of effect of open-label bimekizumab over 48 weeks. Additionally, it will allow an assessment of the impact of dose adjustments on efficacy results.

Responder efficacy variables (PASI50, PASI75, PASI90, PASI100, IGA score of 0 or 1, and HADS normal scores) will be summarized descriptively using counts and percentages by scheduled visit and PS0016 randomized treatment group and overall. The PASI responder variables are derived relative to the PS0016 Baseline. Missing data will be handled by using nonresponder imputation (NRI), meaning that subjects that discontinue early or who have missing data at a given time point are imputed as though they did not achieve the given response. Supportive summaries will be based on observed case data.

Continuous efficacy variables based on the change from Baseline (PASI, BSA, and HADS) will be summarized using descriptive statistics by scheduled visit and PS0016 randomized treatment group and overall. The table presentations will display descriptive statistics for the PS0016 Baseline and the observed and change from PS0016 Baseline results by scheduled visit for PS0018. Figures for selected variables will also be generated in order to demonstrate the kinetics of response over time. Missing data will be handled by using multiple imputation (MI) via the

Markov-Chain Monte Carlo (MCMC) method. Supportive summaries will be based on observed case data.

In addition to the summaries described above, the impact of dose adjustment on efficacy will be considered. This will be done primarily by summarizing efficacy variables by the 3 adjuster groups as defined in Section 14.2.2. Furthermore, a supportive analysis specifically for single adjusters will be performed in which PASI score will be summarized by visit, where Baseline is recalibrated for each individual subject and defined as the visit where the bimekizumab 320mg Q4W dose is initiated. The visits summarized will be in weeks relative to when the 320mg Q4W dose was started as opposed to the scheduled week of the PS0018 assessment. These summaries will be based on observed data only.

14.6 Planned interim analysis and data monitoring

A DMC will review the safety data on a recurring basis as outlined in the DMC charter.

14.7 Determination of sample size

Up to 45 subjects are anticipated to enroll in PS0018. This number is based on the fact that 45 subjects are planned to be randomized in the feeder study, PS0016. The calculations to reach that sample size are outlined in the PS0016 protocol. As the primary objective of this study is to assess the long-term safety and tolerability of bimekizumab 160mg Q4W, the number of subjects anticipated is based on the number of subjects completing PS0016 and meeting eligibility requirements for PS0018.

15 ETHICS AND REGULATORY REQUIREMENTS

15.1 Informed consent

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

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

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

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

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

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

15.2 Subject identification cards

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

15.3 IRBs and IECs

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

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

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

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

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

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

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

15.4 Subject privacy

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

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

15.5 Protocol amendments

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

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

16 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

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18 APPENDICES

18.1 Protocol Amendment 1

Rationale for the amendment

The purpose of this amendment is to revise the following:

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

Specific changes

Change #1 Serious adverse event reporting

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA:** +1 800 880 6949 or +1 866 890 3175 **Canada:** +1 877 582 8842
Email	**Global:** DS_ICT@ucb.com

Has been changed to

Serious adverse event reporting (24h)	
Fax	**Europe and Rest of the World:** +32 2 386 24 21 **USA and Canada:** +1 800 880 6949 or +1 866 890 3175 ~~**Canada: +1 877 582 8842**~~
Email	**Global:** DS_ICT@ucb.com

Change #2 List of Abbreviations

The table row with PtGADA and its definition was deleted

Change #3 Section 1 Summary

Original text:

Pharmacokinetic variables are plasma concentrations of bimekizumab. The immunological variable is anti-bimekizumab antibody levels prior to and following study treatment. The efficacy assessments are PASI, Investigator's Global Assessment (IGA), body surface area (BSA) affected by psoriasis, Patient's Global Assessment of Disease Activity (PtGADA), and the Hospital Anxiety and Depression Scale (HADS); a detailed list of efficacy variables is presented in Section 4.4.

Has been changed to:

Pharmacokinetic variables are plasma concentrations of bimekizumab. The immunological variable is anti-bimekizumab antibody levels prior to and following study treatment. The efficacy assessments are PASI, Investigator's Global Assessment (IGA), body surface area (BSA) affected by psoriasis, ~~Patient's Global Assessment of Disease Activity (PtGADA),~~ and the Hospital Anxiety and Depression Scale (HADS); a detailed list of efficacy variables is presented in Section 4.4.

Change #4 Section 4.4 Efficacy variables

The variable "Change from Baseline in the PtGADA for the arthritis visual analog scale (VAS)" was deleted.

Change #5 Table 5-1 Schedule of study assessments

The table row for the PtGADA assessment was deleted.

The footnote with PtGADA abbreviation definition was deleted.

Change #6 Section 8.1 Baseline Visit

PtGADA assessment was deleted.

Change #7 Section 8.4 Week 12 (±3 days)

PtGADA assessment was deleted.

Change #8 Section 8.6 Week 24 (±3 days)

PtGADA assessment was deleted.

Change #9 Section 8.7 Week 36 (±3 days)

PtGADA assessment was deleted.

Change #10 Section 8.8 Week 48 (±3 days)

PtGADA assessment was deleted.

Change #11 Section 12 Assessment of Efficacy

The subsection discussing the PtGADA (Section 12.4 PtGADA for the arthritis VAS) was deleted.

Change #12 Section 14.5 Planned efficacy analyses

Original text:

Continuous efficacy variables based on the change from Baseline (PASI, BSA, PtGADA, and HADS) will be summarized using descriptive statistics by scheduled visit and PS0016 randomized treatment group and overall.

Has been changed to:

Continuous efficacy variables based on the change from Baseline (PASI, BSA, ~~PtGADA,~~ and HADS) will be summarized using descriptive statistics by scheduled visit and PS0016 randomized treatment group and overall.

18.2 Protocol Amendment 2

Rationale for the amendment

The purpose of this amendment is the following:

- Revise the timepoints for the blood sample for anti-bimekizumab antibodies assessment and blood sample for bimekizumab plasma concentrations assessment
- Specify the study stopping rules

Specific changes

Change #1

Table 5-1 Schedule of study assessments

For the Blood sample for bimekizumab plasma concentrations assessment, the "X" in the Wk 24 column and the "X" in the Wk 32 column were deleted. An "X" was added to the Wk 28 column.

Change #2

Table 5-1 Schedule of study assessments

For the Blood sample for anti-bimekizumab antibodies assessment, the "X" in the Wk 24 column and the "X" in the Wk 32 column were deleted. An "X" was added to the Wk 28 column.

Change #3

Section 6.4 Study stopping rules was added

6.4 Study stopping rules

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

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

- A pattern of AEs occurs that contraindicates the further dosing of enrolled / additional subjects, including (but not limited to):
  - More than 1 subject meets any individual Withdrawal Criteria 6, 9, 10, 11 or 12 (as provided in Section 6.3), regardless of whether they met the same or different criteria.
  - Once a second subject meets any of those criteria, referral to the DMC may not be delayed while awaiting the outcome of either case.

  If the above criteria are reached, the DMC will meet as soon as possible to determine whether discontinuation or suspension of the study should occur, and to determine what investigations, analyses, procedural amendments, or other actions should occur, before making any recommendation regarding the possibility of recommencing the study. Further details on the role of the DMC are provided in Section 9.8.7.
- If the Sponsor or its designees judges it necessary for medical, safety, regulatory, or any other reasons consistent with applicable laws, regulations, and GCP.

Change #4

The section heading

8.2 Week 4 (±3 days)

was changed to

8.2 Week 4 (±3 days); and Week 28 (±3 days)

Change #5

The section heading

8.3 Week 8 (±3 days); Week 16 (±3 days); Week 32 (±3 days); and Week 40 (±3 days)

was changed to

8.3 Week 8 (±3 days); Week 16 (±3 days); and Week 40 (±3 days)

Change #6

The section heading

8.5 Week 20 (±3 days); Week 28 (±3 days); and Week 44 (±3 days)

was changed to

8.5 Week 20 (±3 days); and Week 44 (±3 days)

Change #7

Section 8.6 Week 24 (±3 days)

The following procedures or assessments will be performed prior to administration of study drug (if applicable):

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

was changed to

The following procedures or assessments will be performed prior to administration of study drug (if applicable):

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

Change #8

Section 8.7 Week 32 (±3 days) was added:

8.7 Week 32 (±3 days)

All procedures or assessments will be performed prior to administration of study drug (if applicable), unless otherwise noted. The following procedures or assessments will be performed:

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

- BSA
- Obtain blood samples for:
  - Standard safety laboratory tests (hematology and biochemistry)
- Obtain urine sample for:
  - Standard safety laboratory tests (urinalysis)
  - Urine pregnancy test for women of childbearing potential
- Concomitant medications
- Record AEs
- Contact the IXRS
- Study medication administration (after all other visit assessments are completed)

18.3 Protocol Amendment 3

Rationale for the amendment

The purpose of this amendment is to revise the withdrawal criteria to provide instructions for the management of subjects with newly diagnosed IBD or with IBD flares during the study. In addition, the study contact information was updated.

Modifications and changes

Specific changes

Change #1

Sponsor Study Physician

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

Was Changed to:

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

Change #2

Clinical Trial Biostatistician

Name:	[redacted]
Address:	UCB Biosciences, 8010 Arco Corporation Drive, Raleigh, NC 27617

Phone:	[redacted]
Fax:	[redacted]

Was changed to:

Name:	[redacted]
Address:	UCB Biosciences, 8010 Arco Corporation Drive, Raleigh, NC 27617
Phone:	[redacted]
Fax:	[redacted]

Change #3

List of Abbreviations

Inflammatory Bowel Disease (IBD) was added to the list

Change #4

Section 6.3 Withdrawal criteria

The following was added to the withdrawal criteria:

14. Subjects with newly diagnosed Inflammatory Bowel Disease (IBD) or with IBD flares during the study must:

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

If IBD flares increase in severity or frequency during the study, the Investigator should use clinical judgment in deciding whether the subject should continue in the study and contact the Medical Monitor and UCB study physician to confirm the subject's suitability for continued participation in the study.

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.

PS0018 Protocol Amendment 3 - Phase 2, open-label extension

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	26-Feb-2018 23:02 GMT+01
[redacted]	Clinical Approval	27-Feb-2018 09:06 GMT+01
[redacted]	Clinical Approval	27-Feb-2018 13:33 GMT+01
[redacted]	Clinical Approval	01-Mar-2018 10:00 GMT+01