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

## PROTOCOL PS0041 AMENDMENT 2

## PHASE 3

## SHORT TITLE:

A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque psoriasis

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

**Regulatory agency identifying number:**

| | |
|---|---|
| NCT Number: | Not applicable. |

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| Document history | | |
|---|---|---|
| **Document** | **Date** | **Type of amendment** |
| Protocol amendment 2 | 19 Apr 2023 | Not substantial |
| Protocol amendment 1 | 08 Feb 2023 | Substantial |
| Original Protocol | 10 Oct 2022 | Not applicable |

**Amendment 2 (19 Apr 2023)**

**Overall Rationale for the Amendment**

The purpose of this amendment is to provide further clarification on the inclusion criteria and to be fully aligned with the pivotal global studies.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.1 Inclusion criteria | Revised inclusion criterion #4 | Revised to align with global pivotal studies in psoriasis |

# SAFETY REPORTING OF ADVERSE EVENTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES

| Safety reporting of adverse events (24h) | |
|---|---|
| **Email** | **Global**: DS_ICT@ucb.com |
| **Fax** | +32 2 386 24 21 |

| Reporting of device deficiencies (24h) | |
|---|---|
| **Email** | **Global:** qactscomplaints@ucb.com |

# TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol title:** A Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque psoriasis

**Short title:** A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque psoriasis

**Rationale:** The purpose of this study is to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque psoriasis (PSO) who are candidates for systemic PSO therapy and/or phototherapy. Following the completion of the global pivotal Phase 3 program of bimekizumab in moderate to severe plaque PSO, the aim of this study is to demonstrate the efficacy and safety of bimekizumab in adult Chinese study participants with moderate to severe plaque PSO.

**Objectives and endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| Compare the efficacy of bimekizumab administered sc for 16 weeks versus placebo in the treatment of study participants with moderate to severe plaque PSO | **Co-primary endpoint 1:**<br>• Participant-level outcome: PASI90 response at Week 16<br>**Co-primary endpoint 2:**<br>• Participant-level outcome: IGA 0/1 response at Week 16 |
| **Secondary** | |
| **Key secondary** | |
| Evaluate the efficacy of bimekizumab compared with placebo at achieving response (PASI75) at 4 weeks of treatment | • Participant-level outcome: PASI75 response at Week 4 |
| Evaluate the efficacy of bimekizumab compared with placebo at achieving complete clearance (PASI100) at 16 weeks of treatment | • Participant-level outcome: PASI100 response at Week 16 |

| Objectives | Endpoints |
|---|---|
| **Additional secondary** | |
| Evaluate the effect of bimekizumab compared with placebo on itch, pain, and scaling, as assessed by the PSD (P-SIM) response, at 16 weeks of treatment | Reported by study participants using the PSD (also published as P-SIM [Gottlieb et al, 2020]):<br>• Participant-level outcome: PSD (P-SIM) response for itch at Week 16<br>• Participant-level outcome: PSD (P-SIM) response for pain at Week 16<br>• Participant-level outcome: PSD (P-SIM) response for scaling at Week 16 |
| Assess the safety of bimekizumab through 16 weeks of treatment | • Incidence of TEAEs through Week 16<br>• Incidence of serious TEAEs through Week 16<br>• Incidence of TEAEs leading to permanent discontinuation of IMP through Week 16 |
| **Tertiary** | |
| Assess the efficacy of bimekizumab in the treatment of study participants with moderate to severe plaque PSO over time | • IGA 0 response over time<br>• IGA 0/1 response over time<br>• PASI75 response over time<br>• PASI90 response over time<br>• PASI100 response over time<br>• Percentage of study participants with absolute PASI score ≤1, ≤2, ≤3, and ≤5 over time<br>• Time to PASI75, PASI90, and PASI100 response |
| Assess the effect of bimekizumab on scalp PSO over time in study participants with scalp PSO at Baseline | • Scalp IGA 0/1 response over time |
| Evaluate the effect of bimekizumab over time on itch, pain, and scaling, and other items assessed by the PSD (P-SIM) | • For each PSD (P-SIM) item score: change from Baseline over time |
| Assess the effect of bimekizumab on health-related QoL over time | • DLQI 0/1 response over time |
| Assess the PK of bimekizumab over time | • Plasma bimekizumab concentrations over time |
| Assess the immunogenicity of bimekizumab prior to and following IMP administration | • Anti-bimekizumab antibody levels prior to and following IMP administration |

| Objectives | Endpoints |
|---|---|
| Assess the safety and tolerability of bimekizumab throughout the study | • Severity and frequency of TEAEs<br>• Selected safety topics of interest TEAEs<br>• Change from Baseline in clinical laboratory values (chemistry, hematology)<br>• Change from Baseline in vital signs<br>• Clinically significant changes in physical examination findings |

DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; IMP=investigational medicinal product; P-SIM=Psoriasis Symptom and Impact Measure; PASI=Psoriasis Area and Severity Index; PK=pharmacokinetic(s); PSD=Patient Symptom Diary; PSO=psoriasis; Q4W=every 4 weeks; QoL=quality of life; sc=subcutaneous(ly); scalp IGA=scalp-specific IGA; TEAE=treatment-emergent adverse event

Note: During the 16-week Initial Treatment Period, study participants will receive either bimekizumab 320mg Q4W sc or placebo Q4W sc. During the Maintenance Treatment Period, study participants will receive treatment as described in Section 4.1.

Note: The PASI75/90/100 response is defined as a 75% or greater/90% or greater/100% improvement from Baseline in the PASI score.

Note: The IGA 0/1 response is defined as an IGA response of clear (0) or almost clear (1) with ≥2-category improvement relative to Baseline.

Note: The PSD (P-SIM) response for itch/pain/scaling is defined as a score that has improved (decreased) by ≥4 points from Baseline (using weekly averages), and the study participant has not discontinued IMP.

Note: The IGA 0 response is defined as an IGA response of clear (0) with ≥2-category improvement relative to Baseline.

Note: The scalp IGA 0/1 response is defined as a scalp IGA response of clear (0) or almost clear (1) with a ≥2-category improvement from Baseline.

Note: The DLQI 0/1 response is defined as a DQLI total score equal to 0 or 1.

## Overall design

PS0041 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque PSO.

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

During the 16-week Initial Treatment Period, approximately 120 Chinese adult study participants will be randomized 3:1 to receive the following blinded investigational medicinal product (IMP) regimens:

- Bimekizumab 320mg administered subcutaneously (sc) every 4 weeks (Q4W) (90 study participants)
- Placebo administered sc Q4W (30 study participants)

After completion of the 16-week Initial Treatment Period, study participants will enter the 16-week Maintenance Treatment Period and study participants will return to the clinic Q4W.

The treatment during the Maintenance Treatment Period (Week 16 to Week 32) will be based on the following rules:

- Study participants in the bimekizumab 320mg Q4W arm will receive bimekizumab 320mg every 8 weeks (Q8W). These study participants will also receive placebo injections at visits in between dosing with bimekizumab to maintain blinding procedures.
- Study participants in the placebo arm will receive bimekizumab 320mg Q4W.

Investigational medicinal product will be administered in the clinic by sc injection.

After completion of the 16-week Maintenance Treatment Period, study participants will enter the Safety Follow-Up (SFU) Period after the final dose of IMP.

Study participants withdrawing early from the study will undergo the Premature End of Treatment (PEOT) Visit assessments and will enter the 17-week SFU Period.

All study participants, including those withdrawn from IMP, will have a SFU Visit 17 weeks after the final dose of IMP.

A study participant will be considered to have completed the study if he/she completes all scheduled visits, up to and including Week 32 (regardless of completion of the SFU Visit).

The end of the study is defined as the date of the final study participant's final visit in the study (including the SFU Visit).

**Number of participants**

Approximately 120 Chinese adult study participants will be randomly assigned to IMP for an estimated total of 90 evaluable study participants in the bimekizumab 320mg group and 30 study participants in the placebo group.

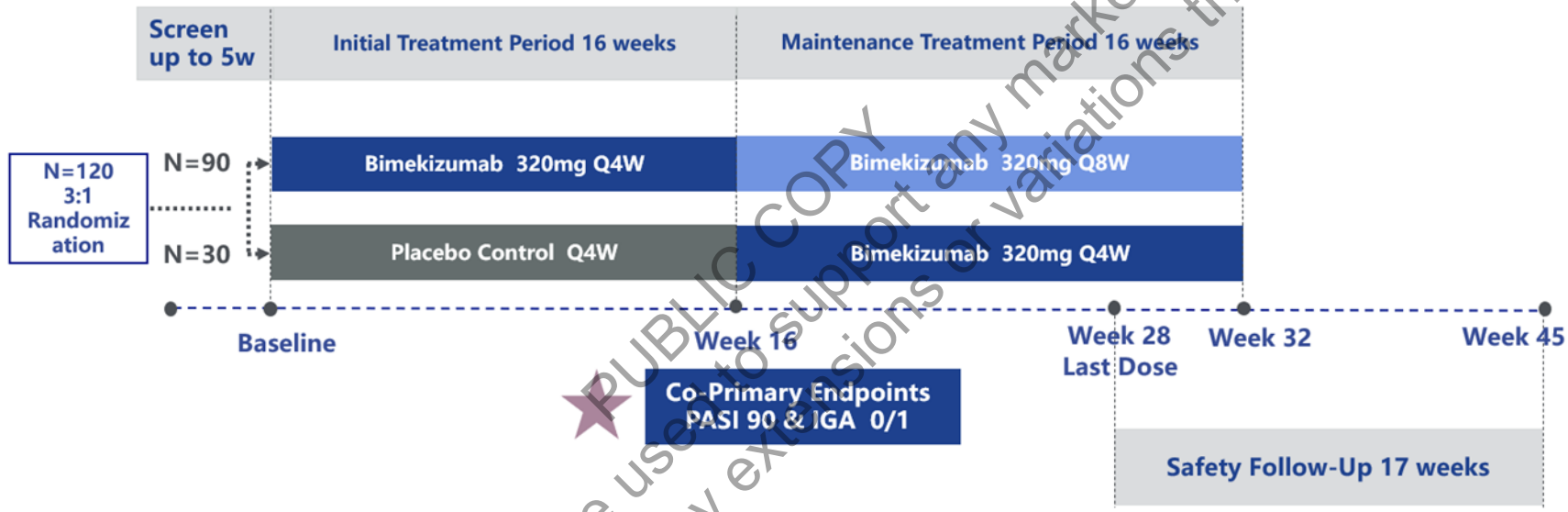
**Treatment groups and duration**

Study participants will be randomized 3:1 to 2 dose groups: bimekizumab 320mg or placebo. This study will include 4 periods: Screening Period (up to 5 weeks), Initial Treatment Period (16 weeks), Maintenance Treatment Period (16 weeks), and SFU Period (17 weeks after the final dose of IMP).

## 1.2 Schema

The study schematic is shown in Figure 1-1.

**Figure 1-1: Study schematic**




IGA 0/1=Investigator's Global Assessment response clear (0) or almost clear (1) with ≥2-category improvement relative to Baseline; PASI90=90% or greater improvement from Baseline in the Psoriasis Area and Severity Index score; Q4W=every 4 weeks; Q8W=every 8 weeks; w=week

## 1.3 Schedule of Activities

### Table 1-1: Schedule of Activities

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

## Table 1-1: Schedule of Activities

| Visit[a]/ Week / Protocol activity | Screening | Initial Treatment Period (weeks after first dose) | | | | | | | Maintenance Treatment Period (weeks after first dose) | | | | SFU[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline (first dose) | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32/ PEOT | |
| Urinalysis | X | X | | | | | | X | | | | X | X |
| ECG | X | | | | | | | | | | | | |
| Pregnancy testing[g] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Hepatitis B and C testing[h] | X | | | | | | | | | | | | |
| HIV testing[i] | X | | | | | | | | | | | | |
| Chest x-ray/CT scan [j] | X | | | | | | | | | | | | |
| IGRA TB test | X | | | | | | | | | | X | | |
| TB questionnaire | X | X | | | | | | X | | | X | X | |
| Blood sample for BKZ plasma concentration | | X | X | | | X | | X | | X | | X | |
| Blood sample for anti-BKZ antibodies | | X | | | | X | | X | | X | | X | X |
| PASI | X | X | X | X | X | X | X | X | X | X | X | X | |
| IGA | X | X | X | X | X | X | X | X | X | X | X | X | |
| Percentage of BSA | X | X | X | X | X | X | X | X | X | X | X | X | |
| Scalp IGA[k] | | X | X | X | X | X | X | X | | | | X | |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X |

## Table 1-1: Schedule of Activities

| Visit[a]/ Week / Protocol activity | Screening | Initial Treatment Period (weeks after first dose) | | | | | | | Maintenance Treatment Period (weeks after first dose) | | | | SFU[b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Baseline (first dose) | 1 | 2 | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32/ PEOT | |
| AEs/ADE and device deficiency assessment | X | X | X | X | X | X | X | X | X | X | X | X | X |
| IRT[l] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| BKZ or placebo administration[m,n] | | X | | | X | X | X | X | X | X | X | | |

Ab=antibody; ADE=adverse device effect; AE=adverse event; BKZ=bimekizumab; BSA=body surface area; CT=computed axial tomography; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eCRF=electronic Case Report Form; HBcAb=anti-hepatitis B core antibody; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; P-SIM=Psoriasis Symptom and Impact Measure; PASI=Psoriasis Area and Severity Index; PEOT=Premature End of Treatment; PSD=Patient Symptom Diary; Q4W=every 4 weeks; Q8W=every 8 weeks; scalp IGA=scalp-specific IGA; SFU=Safety Follow-Up; TB=tuberculosis

Note: All assessments should be performed prior to IMP administration. The IMP administration is the starting point for the next administration period. Thus, the assessments in Week 16 and Week 32 belong to the previous treatment period.

[a] For visits from the first dose of IMP through Week 32, the visit window is ±4 days from the scheduled visit. For the SFU Visit, the visit window is ±7 days from the scheduled visit.

[b] The SFU Visit will occur 17 weeks after the final dose of IMP.

[c] Ensure no significant changes in medical history.

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

[e] The physical examination will be performed as described in Section 8.2.3.

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

[g] Pregnancy testing will consist of serum testing at Screening. A urine pregnancy test will be administered at all other visits.

[h] Study participants who have evidence of or test positive for hepatitis B or C are excluded from the study, per Exclusion Criterion #9 (Section 5.2). A positive test for HBV is defined as: 1) positive for HBsAg **or** 2) positive for HBcAb. A positive test for HCV is defined as: 1) positive for anti-HCV Ab **and** 2) positive via a confirmatory test for HCV (eg, HCV polymerase chain reaction).

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

[j] Screening chest x-ray/CT scan must occur within 3 months prior to Screening Visit.

## Table 1-1: Schedule of Activities

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

[k] The scalp IGA will be assessed for all study participants at Baseline. The scalp IGA will only be assessed at post-Baseline visits for those study participants with scalp involvement (scalp IGA score >0) at Baseline.
[l] Investigational medicinal product administration is based on randomization.
[m] To protect the blinding of the dosing regimen during the Maintenance Treatment Period, study participants receiving bimekizumab 320mg Q8W will also receive placebo injections at visits in between dosing so that all participants receive injections Q4W.
[n] After a study participant completes the Week 16 assessments, which are the last assessments of the Initial Treatment Period, the dose of IMP for the Maintenance Treatment Period will be administered according to the randomization scheme. The final assessments of the Maintenance Treatment Period will be performed at Week 32. No IMP will be administered at Week 32.

# 2 INTRODUCTION

## 2.1 Study rationale

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. Therapy for patients with PSO varies according to the severity of disease. Limited or mild disease is often treated with topical therapies such as corticosteroids and vitamin D analogs. Patients with more severe disease are often treated with phototherapy, methotrexate, cyclosporine, or biologic agents, such as tumor necrosis factor (TNF) antagonists, interleukin (IL)-12/23 inhibitors, IL-23p19 inhibitors, and IL-17A inhibitors.

Bimekizumab is a humanized, full-length monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) subclass with 2 identical antigen-binding regions that potently and selectively bind and neutralize IL-17A, IL-17F, and IL-17AF cytokines. This property makes bimekizumab distinct from the other IL-17-targeting agents, like secukinumab and ixekizumab (selective anti-IL-17A cytokine targeting mAb) or brodalumab (anti-IL-17 receptor targeting mAb). Interleukin-17A and IL-17F are key proinflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases. Therefore, bimekizumab permits an evaluation of the potential for additional efficacy, which may be conferred by dual inhibition of both cytokines, in patients suffering from diseases in which both cytokines are active. Bimekizumab was granted marketing authorization in the European Union and was approved in Great Britain, Canada, Saudi Arabia, and Australia for the treatment of moderate to severe plaque PSO in adults who are candidates for systemic therapy. In Japan, bimekizumab was approved for the treatment of plaque PSO, generalized pustular PSO, and psoriatic erythroderma. Bimekizumab is currently under review in other regions for moderate to severe plaque PSO. The completed Phase 3 bimekizumab plaque PSO studies provided [redacted] evidence of efficacy and an acceptable safety profile. UCB is also developing bimekizumab for the treatment of adults with psoriatic arthritis (PsA), axial spondyloarthritis, and hidradenitis suppurativa. Additionally, UCB has initiated the pediatric PSO program with a Phase 2 pharmacokinetics (PK) and safety study.

The purpose of this study is to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque PSO who are candidates for systemic PSO therapy and/or phototherapy. Following the completion of the global pivotal Phase 3 program of bimekizumab in moderate to severe plaque PSO, the aim of this study is to demonstrate the efficacy and safety of bimekizumab in adult Chinese study participants with moderate to severe plaque PSO.

## 2.2 Background

Psoriasis is a common, chronic inflammatory disease characterized by inflammation and keratinocyte proliferation. Plaque PSO, the most common form of the disease, is typified by areas of red, inflamed skin, often covered with thick, micaceous, silver-colored scales on extensor surfaces. Plaques may be pruritic and painful as the skin cracks and bleeds. In severe cases, plaques grow and merge into one another, covering large areas.

In addition to the impact on skin, PSO has a multitude of psychosocial and emotional effects on patients, including increased self-consciousness, frustration, fatigue, depression, and suicidal

ideation. As a result, patients frequently report sleeping problems, difficulties at work, problems interacting with family members, disrupted leisure activities, and sexual difficulties (Dowlatshahi et al, 2014; Gottlieb, 2005; Mukhtar et al, 2004; Ortonne, 2004; Krueger et al, 2001).

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

The reported prevalence of PSO in countries ranges between 0.09% and 11.43%, with ≥100 million individuals affected worldwide (WHO report on psoriasis, 2016). There are a variety of forms of PSO, including plaque, guttate, inverse, pustular, and erythrodermic. Plaque PSO (PSO vulgaris) is the most common, comprising approximately 80% to 90% of all cases. It is estimated that approximately 80% of patients with plaque PSO have mild to moderate disease, while 20% of patients have more severe disease, which affects either greater than 5% of BSA or is located on high impact areas including the scalp, genitals, hands, and nails (Boehncke and Schön, 2015; Menter et al, 2008).

Descriptions of nonclinical and clinical bimekizumab data, including the status of ongoing studies, are provided in the current version of the Investigator's Brochure (IB).

### 2.2.1 Current situation in China

A nationwide survey of mainland China in 1984 revealed that the prevalence of PSO was 0.16%, meaning there could be about 2 million patients with PSO in China, given its population of 1.33 billion people as reported in the 2010 census (Shao et al, 1987). Since then, some epidemiological studies have been conducted in single cities or regions of China, mostly without statistically appropriate sampling design and data analysis (Li et al, 2013; Ding et al, 2012; Wang et al, 2012; Xu et al, 2001). The most recent study, conducted in 6 preselected cities in 2008, found that the prevalence of PSO was 0.47%, meaning there could be about 6 million patients with PSO in China, a slight increase compared with the prevalence in 1984 (Ding et al, 2012).

In China, the treatment options are similar to options available globally. Limited or mild disease is often treated with corticosteroids, vitamin D analogs, and retinoids. Patients with more severe disease are often treated with photochemotherapy, immunosuppressants, or biologic agents. Biologics available in China include TNFα inhibitors (adalimumab) and IL inhibitors (ixekizumab, secukinumab, brodalumab, guselkumab, and ustekinumab). Some traditional Chinese medicines are also used to treat PSO, but there is a lack evidence for their efficacy and safety in this indication.

The unmet needs in Chinese PSO patients are largely the same as unmet needs globally. These include therapy cessation due to an increased risk of developing serious infections, risk of malignancies, lack of response to therapy, or loss of response over time.

Descriptions of nonclinical and clinical bimekizumab data, including the status of ongoing studies, are provided in the current version of the IB.

## 2.3 Benefit/risk assessment

Across the 3 pivotal Phase 3 studies (PS0008, PS0009, and PS0013; comparison against adalimumab or ustekinumab or placebo) and the Phase 3b study PS0015 (comparison against secukinumab), bimekizumab 320mg Q4W was effective for the PASI90, PASI100, and IGA 0/1 response endpoints in all prespecified subgroups, including, but not limited to, age, gender, race, body weight, Baseline disease severity, antidrug antibody (ADAb) status, neutralizing antibody status, prior biologic exposure (including prior anti-TNF and anti-IL-17 exposure), and geographic region. There were no meaningful differences observed between subgroups of bimekizumab-treated study participants at Week 16 or at later time points, indicating that the safety profile of bimekizumab does not differ based on age, gender, race, or body weight. Therefore, although data were not collected from Chinese study participants in the completed global pivotal Phase 3 program, the benefits and risks of bimekizumab administration in Chinese adult study participants are expected to be similar to results in adult study participants with plaque PSO to date.

In all studies of bimekizumab in moderate to severe plaque PSO mentioned above, study participants achieved and maintained skin clearance across multiple efficacy endpoints, as assessed by PASI (change from Baseline and by various levels of response) and IGA responses, after up to 56 weeks of bimekizumab 320mg sc treatment administered Q4W or bimekizumab 320mg sc treatment administered Q4W for an initial 16 weeks followed by Q8W maintenance treatment. The observed safety data were as expected considering the mechanism of action of bimekizumab and the population under investigation. The vast majority of adverse events (AEs) were nonserious, mild to moderate, and did not lead to IMP discontinuation. The most commonly reported treatment-emergent AEs (TEAEs) in bimekizumab-treated study participants were nasopharyngitis, oral candidiasis, and upper respiratory tract infection.

Prespecified safety topics of interest for the study are as follows: infections (serious, opportunistic, fungal, and tuberculosis [TB]), neutropenia, hypersensitivity, injection site reactions, neuropsychiatric AEs (including suicidal ideation and behavior [SIB]), major CV events, liver function test (LFT) changes/enzyme elevations, malignancies, and inflammatory bowel disease (IBD).

These are based on findings from the bimekizumab clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action. There are no specific AE reporting requirements for these topics; however, special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB) are in place.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of bimekizumab may be found in the current version of the IB.

# 3 OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| Compare the efficacy of bimekizumab administered sc for 16 weeks versus placebo in the treatment of study participants with moderate to severe plaque PSO | **Co-primary endpoint 1:**<br>• Participant-level outcome: PASI90 response at Week 16<br>**Co-primary endpoint 2:**<br>• Participant-level outcome: IGA 0/1 response at Week 16 |
| **Secondary** | |
| **Key secondary** | |
| Evaluate the efficacy of bimekizumab compared with placebo at achieving response (PASI75) at 4 weeks of treatment | • Participant-level outcome: PASI75 response at Week 4 |
| Evaluate the efficacy of bimekizumab compared with placebo at achieving complete clearance (PASI100) at 16 weeks of treatment | • Participant-level outcome: PASI100 response at Week 16 |
| **Additional secondary** | |
| Evaluate the effect of bimekizumab compared with placebo on itch, pain, and scaling, as assessed by the PSD (P-SIM) response, at 16 weeks of treatment | Reported by study participants using the PSD (also published as P-SIM [Gottlieb et al, 2020]):<br>• Participant-level outcome: PSD (P-SIM) response for itch at Week 16<br>• Participant-level outcome: PSD (P-SIM) response for pain at Week 16<br>• Participant-level outcome: PSD (P-SIM) response for scaling at Week 16 |
| Assess the safety of bimekizumab through 16 weeks of treatment | • Incidence of TEAEs through Week 16<br>• Incidence of serious TEAEs through Week 16<br>• Incidence of TEAEs leading to permanent discontinuation of IMP through Week 16 |
| **Tertiary** | |
| Assess the efficacy of bimekizumab in the treatment of study participants with moderate to severe plaque PSO over time | • IGA 0 response over time<br>• IGA 0/1 response over time<br>• PASI75 response over time<br>• PASI90 response over time<br>• PASI100 response over time<br>• Percentage of study participants with absolute PASI score ≤1, ≤2, ≤3, and ≤5 over time |

| Objectives | Endpoints |
|---|---|
| | • Time to PASI75, PASI90, and PASI100 response |
| Assess the effect of bimekizumab on scalp PSO over time in study participants with scalp PSO at Baseline | • Scalp IGA 0/1 response over time |
| Evaluate the effect of bimekizumab over time on itch, pain, and scaling, and other items assessed by the PSD (P-SIM) | • For each PSD (P-SIM) item score: change from Baseline over time |
| Assess the effect of bimekizumab on health-related QoL over time | • DLQI 0/1 response over time |
| Assess the PK of bimekizumab over time | • Plasma bimekizumab concentrations over time |
| Assess the immunogenicity of bimekizumab prior to and following IMP administration | • Anti-bimekizumab antibody levels prior to and following IMP administration |
| Assess the safety and tolerability of bimekizumab throughout the study | • Severity and frequency of TEAEs<br>• Selected safety topics of interest TEAEs<br>• Change from Baseline in clinical laboratory values (chemistry, hematology)<br>• Change from Baseline in vital signs<br>• Clinically significant changes in physical examination findings |

DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; IMP=investigational medicinal product; P-SIM=Psoriasis Symptom and Impact Measure; PASI=Psoriasis Area and Severity Index; PK=pharmacokinetic(s); PSD=Patient Symptom Diary; PSO=psoriasis; Q4W=every 4 weeks; QoL=quality of life; sc=subcutaneous(ly); scalp IGA=scalp-specific IGA; TEAE=treatment-emergent adverse event

Note: During the 16-week Initial Treatment Period, study participants will receive either bimekizumab 320mg Q4W sc or placebo Q4W sc. During the Maintenance Treatment Period, study participants will receive treatment as described in Section 4.1.

Note: The PASI75/90/100 response is defined as a 75% or greater/90% or greater/100% improvement from Baseline in the PASI score.

Note: The IGA 0/1 response is defined as an IGA response of clear (0) or almost clear (1) with ≥2-category improvement relative to Baseline.

Note: The PSD (P-SIM) response for itch/pain/scaling is defined as a score that has improved (decreased) by ≥4 points from Baseline (using weekly averages), and the study participant has not discontinued IMP.

Note: The IGA 0 response is defined as an IGA response of clear (0) with ≥2-category improvement relative to Baseline.

Note: The scalp IGA 0/1 response is defined as a scalp IGA response of clear (0) or almost clear (1) with a ≥2-category improvement from Baseline.

Note: The DLQI 0/1 response is defined as a DQLI total score equal to 0 or 1.

# 4 STUDY DESIGN

## 4.1 Overall design

PS0041 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in Chinese adult study participants with moderate to severe plaque PSO.

The study population consists of Chinese adult study participants (≥18 years of age) with a diagnosis of moderate to severe plaque PSO (Baseline PASI ≥12 and BSA affected by PSO ≥10% and IGA score ≥3 on a 5-point scale) who are candidates for systemic PSO therapy and/or phototherapy.

This study will include 4 periods: Screening Period (up to 5 weeks), Initial Treatment Period (16 weeks), Maintenance Treatment Period (16 weeks), and SFU Period (17 weeks after the final dose of IMP [Figure 1-1]).

**Screening Period**

The Screening Period will last up to a total of 5 weeks (for example, in cases where a laboratory assessment needs to be repeated or to allow washout of prohibited medications). During the Screening Period, eligible study participants will be informed about the study and sign the Informed Consent Form (ICF). Following signed informed consent, all screening procedures and laboratory tests (hematology, urine, and biochemistry) will be performed per the Schedule of Activities (SoA) (Table 1-1). A study participant newly diagnosed with a latent TB infection (LTBI) as a result of a positive IGRA screening test, may be rescreened once and enrolled after receiving ≥4 weeks of appropriate LTBI therapy and after consultation with the Medical Monitor. Further details of rescreening are provided in the exclusion criteria (Section 5.2).

After completion of the Screening Period, eligible study participants will be allowed to enroll into the study.

**Initial Treatment Period**

During the 16-week Initial Treatment Period, approximately 120 Chinese adult study participants will be randomized 3:1 to receive the following blinded IMP regimens:

- Bimekizumab 320mg administered sc Q4W (90 study participants)
- Placebo administered sc Q4W (30 study participants)

Investigational medicinal product will be administered in the clinic by sc injection at the visits specified in the SoA (Table 1-1). Study participants withdrawing early from the study will undergo the PEOT Visit assessments and will enter the SFU Period.

**Maintenance Treatment Period**

After completion of the Week 16 assessments, which are the last assessments in the 16-week Initial Treatment Period, study participants will enter the 16-week Maintenance Treatment Period. The first dose of IMP will be administered at Week 16 after all assessments are performed. During the Maintenance Treatment Period, study participants will return to the clinic Q4W up to Week 32 to maintain the study blind.

The treatment during the Maintenance Treatment Period (Week 16 to Week 32) will be based on the following rules:

- Study participants in the bimekizumab 320mg Q4W arm will receive bimekizumab 320mg Q8W. These study participants will also receive placebo injections at visits between dosing with bimekizumab to maintain blinding procedures.
- Study participants in the placebo arm will receive bimekizumab 320mg Q4W.

**Safety Follow-Up Period**

After completion of the 16-week Maintenance Treatment Period, study participants will enter the SFU Period after the final dose of IMP.

Study participants withdrawing early from the study will undergo the PEOT Visit assessments and will enter the SFU Period.

All study participants, including those withdrawn from IMP, will have a SFU Visit 17 weeks after the final dose of IMP.

## 4.2 Scientific rationale for study design

[redacted]

## 4.3 Justification for dose

[redacted]

## 4.4 End of study definition

A study participant will be considered to have completed the study if he/she completes all scheduled visits, up to and including Week 32 (regardless of completion of the SFU Visit).

The end of the study is defined as the date of the final study participant's final visit in the study (including the SFU Visit).

# 5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

## 5.1 Inclusion criteria

To be eligible to participate in this study, all of the following criteria must be met at Screening and at the Baseline Visit:

1. Study participant has provided informed consent.
2. Study participant is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, or IMP intake according to the judgment of the Investigator.
3. Study participant is Chinese male or female ≥18 years of age.
4. Study participant has plaque PSO for ≥6 months prior to the Screening Visit.
5. Study participant has PASI ≥12 and BSA affected by PSO ≥10% and IGA score ≥3 on a 5-point scale.
6. Study participant is a candidate for systemic PSO therapy and/or phototherapy.

7. Female study participants must be:
   - Postmenopausal: Menopause is defined as 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause.
   - Permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy).
   - Or, if of childbearing potential (and engaged in sexual activity that could result in procreation), must be willing to use a highly effective method of contraception throughout the duration of the study until 17 weeks after last administration of IMP and have a negative pregnancy test at Visit 1 (Screening) and prior to first dose. The following methods are considered highly effective when used consistently and correctly:
     - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal).
     - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
     - Intrauterine device.
     - Intrauterine hormone-releasing system.
     - Vasectomized partner.
     - Abstinence as a form of birth control is generally not allowed in the study unless abstinence is in accordance with a study participant's preferred and common lifestyle. Study personnel must confirm the continued use of abstinence is in accordance with the study participant's lifestyle at regular intervals during the study.

   Refer to Section 10.4 (Appendix 4) for further information about contraceptive guidance.
8. Study participant agrees not to change their usual sun exposure during the course of the study and to use ultraviolet A/ultraviolet B sunscreens if unavoidable exposure occurs.

## 5.2 Exclusion criteria

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

1. Female study participant who is breastfeeding, pregnant, or plans to become pregnant during the study or within 17 weeks following the final dose of IMP.
2. Study participant previously participated in a bimekizumab clinical study and received ≥1 dose of the IMP (including placebo).
3. Study participant previously participated in another study of a medication (systemic) under investigation within the last 12 weeks or at least 5 half-lives relative to Baseline, whichever is greater, or is currently participating in another study of a medication (systemic) under investigation.
4. Study participant previously participated in another study of a topical medication under investigation within the last 4 weeks relative to Baseline or is currently participating in another study of a topical medication under investigation.

5. Study participant previously participated in another study of a medical device under investigation within the last 4 weeks relative to Baseline or is currently participating in another study of a medical device under investigation.
6. Study participant has a known hypersensitivity to any excipients of bimekizumab.
7. Study participant has a form of PSO other than chronic plaque-type (eg, pustular, erythrodermic, guttate, or drug-induced PSO).
8. Study participant has an active infection or history of infection(s) as follows:
   - Any active systemic infection (except common cold) within 14 days prior to Baseline.
   - A serious infection, defined as requiring hospitalization or intravenous anti-infectives within 2 months prior to the first dose of IMP.
   - Recurrent or chronic infections that, in the opinion of the Investigator, might cause this study to be detrimental to the study participant.
   - Known history of opportunistic infections. Opportunistic infections are infections caused by uncommon pathogens (eg, pneumocystis carinii, cryptococcosis) or unusually severe infections caused by common pathogens (eg, cytomegalovirus, herpes zoster, candida).
9. Study participant has concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection. Study participants who have evidence of, or tested positive for, hepatitis B or hepatitis C are excluded.
   - A positive test for the hepatitis B virus (HBV) is defined as: 1) positive for hepatitis B surface antigen (HBsAg+), or 2) positive for anti-hepatitis B core antibody (HBcAb+).
   - A positive test for the hepatitis C virus (HCV) is defined as: 1) positive for hepatitis C antibody (anti-HCV Ab), and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).
10. Study participant has received any live (includes attenuated) vaccination within the 8 weeks prior to Baseline (eg, inactivated influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted).
11. Study participant has received Bacillus Calmette-Guerin vaccinations within 1 year prior to IMP administration.
12. Study participant has known TB infection, is at high risk of acquiring TB infection, or has current or history of nontuberculous mycobacterium (NTMB) infection. A study participant newly diagnosed with LTBI as a result of a positive IGRA screening test may be rescreened once and enrolled after receiving ≥4 weeks of appropriate LTBI therapy, after consultation with the Medical Monitor, and if no evidence of therapy-related hepatotoxicity has occurred prior to the first injection (alanine aminotransferase [ALT]/aspartate aminotransferase [AST] remain ≤2 times upper limit of normal [ULN]).

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

Refer to Section 8.2.5.2 for details on TB assessments to be performed at Screening.

13. Study participant has a history of a lymphoproliferative disorder, including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
14. Study participant has any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or ductal carcinoma in situ of the breast.
15. Study participant has a diagnosis of inflammatory conditions other than PSO vulgaris or PsA, including, but not limited to, rheumatoid arthritis, sarcoidosis, inflammatory bowel disease, or systemic lupus erythematosus.
16. Study participant has had major surgery (including joint surgery) within the 6 months prior to Screening or has planned major surgery within 6 months after entering the study.
17. Study participant has any systemic disease (eg, renal failure, heart failure, hypertension, liver disease, diabetes, anemia) considered by the Investigator to be uncontrolled, unstable, or likely to progress to a clinically significant degree during the course of the study.
18. Study participant has had myocardial infarction or stroke within the 3 months prior to the first dose of IMP.
19. Study participant has laboratory abnormalities at Screening, including any of the following:
    - ≥3.0×ULN of any of the following: ALT, AST, alkaline phosphatase (ALP); or >ULN total bilirubin (≥1.5×ULN total bilirubin if known Gilbert's syndrome)
    - White blood cell count $<3.00\times10^3/\mu L$
    - Absolute neutrophil count $<1.5\times10^3/\mu L$
    - Lymphocyte count $<0.5\times10^9/L$
    - Hemoglobin <8.5g/dL
    - Any other laboratory abnormality, which, in the opinion of the Investigator, will prevent the study participant from completing the study or will interfere with the interpretation of the study results

    Individual screening tests for which the results are in error, borderline, or indeterminate for inclusion in the study can be repeated once.
20. Study participant has any other condition, including medical or psychiatric, which, in the Investigator's judgment, would make the study participant unsuitable for inclusion in the study.
21. Study participant has experienced primary failure to an IL-17 response modifier. Primary failure is defined as a study participant who did not respond to a biologic agent within 12 weeks.
22. Study participant has a history of chronic alcohol or drug abuse within 6 months prior to Screening as evaluated by the Investigator based on medical history, site interview, and/or results of the specified urine drug screen.

23. Study participant has presence of significant uncontrolled neuropsychiatric disorder, including major severe depression, active suicidal ideation, or positive suicide behavior, diagnosed by physicians. Study participants with history of suicide attempt within the 5 years prior to the Screening Visit must be excluded. Study participants with history of suicide attempt more than 5 years prior to the Screening Visit must be evaluated by a mental health care practitioner before enrollment.
24. Study participant is a member of Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
25. Study participant is a UCB employee or employee of third-party organizations involved in the study.

## 5.3 Screen failures

Screen failures are defined as study participants who consent to participate in the clinical study but are not subsequently randomized to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure study participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

For individuals who do not meet the criteria for participation in this study (ie, screen failures), 1 rescreening may be allowed following consultation with and approval by the Medical Monitor. Rescreened study participants should be assigned a new study participant number. Reasons for rescreening include, but are not limited to, the following:

- Study participant needs to complete a full course of therapy for LTBI and can be rescreened after completion of 4 weeks of prophylaxis prior to the first dose of IMP, as described in the exclusion criteria (Section 5.2).
- Individual laboratory screening tests for which the results are exclusionary can be retested following consultation with and approval by the Medical Monitor.
- Eligibility assessments could not be completed as planned (eg, for technical reasons) within the defined Screening Period without consultation with and approval by the Medical Monitor.
- Study participant does not meet the required washout period for concomitant medications without consultation with and approval by the Medical Monitor (Section 6.5.2).

For randomized study participants with a Baseline result >ULN for ALT, AST, ALP, or total bilirubin, a Baseline diagnosis and/or the cause of any clinically meaningful elevation must be understood and recorded in the electronic Case Report Form (eCRF).

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

# 6 STUDY TREATMENTS

Investigational medicinal product is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 6.1 Treatments administered

During the 16-week Initial Treatment Period, eligible study participants will be randomized in a 3:1 ratio to receive the following blinded IMP regimens: bimekizumab 320mg Q4W or placebo (Table 6-1). For bimekizumab treatment assignments during the Maintenance Treatment Period, see Section 4.1.

Suitable areas for sc injections are the lateral abdominal wall, upper arm, and upper outer thigh. Study participants will receive 2 injections of IMP per dosing visit, and each of the injections should be administered at a separate injection site (eg, 1 injection in each arm or 1 in arm and 1 in thigh). Injection sites should be rotated at each visit, and injections should not be given into a PSO plaque or areas where the skin is tender, bruised, erythematous, or indurated. The injection should last approximately 10 to 15 seconds.

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

**Table 6-1: Treatments administered**

| Arm name | Bimekizumab | Placebo |
|---|---|---|
| **IMP name** | Bimekizumab 320mg Q4W/Q8W | Placebo |
| **Type** | Biologic | N/A |
| **Dose formulation** | 1mL PFS | 1mL PFS |
| **Unit dose strength(s)** | 160mg/mL (55mM sodium acetate, 220mM glycine, 0.04% polysorbate 80 at pH 5.0) | 0.9% sodium chloride aqueous solution (physiological saline, preservative-free) of pharmacopoeia (USP/Ph.Eur) quality |
| **Dosage levels** | 320mg Q4W/Q8W | Placebo Q4W |
| **Route of administration** | sc injection | sc injection |
| **Use** | Active | Placebo comparator |
| **IMP** | IMP | IMP |
| **Sourcing** | Provided centrally by the Sponsor | Provided centrally by the Sponsor |
| **Packaging and labeling** | Each PFS will be labeled as required by China. | Each PFS will be labeled as required by China. |
| **Former name** | UCB4940 | N/A |

IMP=investigational medicinal product; N/A=not applicable; PFS=prefilled syringe; Ph.Eur=European Pharmacopoeia; Q4W=every 4 weeks; Q8W=every 8 weeks; sc=subcutaneous; USP=United States Pharmacopoeia

The dosing scheme is presented in Table 6-2.

**Table 6-2: Dosing scheme**

| Dose assignment | Baseline (first dose) | Initial Treatment Period (weeks after first dose) | | | | Maintenance Treatment Period (weeks after first dose) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 4 | 8 | 12 | 16 | 20 | 24 | 28 | 32 |
| Bimekizumab 320mg Q4W/Q8W | ●● | ●● | ●● | ●● | ●● | ○○ | ●● | ○○ | NA |
| Placebo/ bimekizumab 320mg Q4W | ○○ | ○○ | ○○ | ○○ | ●● | ●● | ●● | ●● | NA |

●=bimekizumab; IMP=investigational medicinal product; ○=placebo; NA=not applicable; Q4W=every 4 weeks; Q8W=every 8 weeks

Note: After a study participant completes the Week 16 assessments, which are the last assessments of the Initial Treatment Period, the dose of IMP for the Maintenance Treatment Period will be administered according to the randomization scheme. The final assessments of the Maintenance Treatment Period will be performed at Week 32. No IMP will be administered at Week 32.

### 6.1.1 Medical devices

The UCB-manufactured medical device provided for use in this study is the 1mL PFS.

Instructions for medical device use are provided in the IMP Handling Manual.

All adverse device effects (ADEs) and device deficiency (including malfunction use error and inadequate labeling) shall be documented and reported by the Investigator throughout the study (see Section 8.3.9) and appropriately managed by the Sponsor.

## 6.2 Preparation, handling, storage, and accountability requirements

Unblinded study staff will be responsible for preparation of the clinical study material, including recording the administration information on source documents and administration of the IMP as sc injections. The unblinded personnel will not be involved in the study in any way other than assuring the medication is taken from the correct kit and administering the IMP to the study participants.

Only study participants enrolled in the study may receive IMP, and only authorized site staff may supply or administer IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all IMP received and any discrepancies are reported and resolved before use of the IMP.

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

Further guidance and information for the final disposition of unused IMP are provided in the IMP Handling Manual.

### 6.2.1 Drug accountability

During the Initial Treatment Period and Maintenance Treatment Period of this study, the IMP will be administered in the clinic, and compliance will be determined at the visit by study personnel.

The Drug Accountability Form will be used to record IMP dispensing and return information on a by-participant 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.

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

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

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 IMP accountability at the study site to an appropriate pharmacist/designee.

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

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

## 6.3 Measures to minimize bias: randomization and blinding

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

At the Screening Visit, each study participant will be assigned a 5-digit number that serves as the study participant identifier throughout the study. The study participant number will be required in all communication between the Investigator or designee and the IRT regarding a particular study participant. Once a study participant number has been assigned, it must not be reassigned.

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

Study participant numbers, randomization numbers, and kit numbers will be tracked via the IRT.

### 6.3.1 Procedures for maintaining and breaking the treatment blind

#### 6.3.1.1 Maintenance of study treatment blind

All study participant treatment details (bimekizumab or placebo) will be allocated and maintained by the IRT system.

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

Unblinded study staff will be delegated the responsibility to receive, inventory, and destroy the used IMP. The packaging identifies each kit by a unique number. Unblinded study staff will be responsible for preparation (breaking tamper proof sticker on kit, etc) of the IMP, including recording the administration information on source documents. To protect the blinding of the dosing regimen during the Maintenance Treatment Period, study participants receiving bimekizumab 320mg Q8W will also receive placebo injections at visits in between dosing so that all participants receive injections Q4W.

#### 6.3.1.2 Breaking the treatment blind in an emergency situation

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

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

## 6.4 Treatment compliance

During the Initial Treatment Period and Maintenance Treatment Period of this study, the IMP 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 (Section 6.2.1).

If a study participant is noncompliant with the study procedures or medications, in the opinion of the Investigator, then the study participant should be withdrawn as described in Section 7.2.

## 6.5 Concomitant medication(s)/treatment(s)

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

### 6.5.1 Permitted concomitant treatments (medications and therapies)

#### 6.5.1.1 Topical medications

The following concomitant topical medications are permitted during the study:

- Study participants may continue to use topical moisturizers or emollients, bath oils, or oatmeal bath preparations for skin conditions during the study, as needed (PRN). Over-the-counter shampoos for the treatment of scalp PSO are also permitted.
- Mild and low potency topical steroids will be permitted for use limited to the face, axilla, and/or genitalia, PRN. These topical medications should not be used within approximately 24 hours prior to study visits requiring IGA and PASI measures.

#### 6.5.1.2 Other medications

Study participants who are receiving an established regimen for depression should remain on stable dosing prior to Baseline and throughout the study. Medication used to treat depression should be stable for 4 weeks prior to Baseline.

### 6.5.2 Prohibited concomitant treatments (medications and therapies)

For prohibited prior medications, refer to the exclusion criteria (Section 5.2).

Prohibited concomitant medications and therapies are outlined in Table 6-3.

**Table 6-3: Prohibited concomitant treatments (medications and therapies)**

| Drug | Washout period relative to Baseline Visit |
|---|---|
| Topicals, except for those permitted | 2 weeks |
| Systemic retinoids | 1 month |
| Systemic treatment (nonbiological):<br>systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)<br>fumaric acid esters specifically used for the treatment of PSO<br>systemic corticosteroids<br>phototherapy | 1 month |
| Anti-TNFs: | |
| etanercept (including biosimilar) | 1 month |
| infliximab (including biosimilar)<br>golimumab<br>certolizumab pegol<br>adalimumab (including biosimilar) | 3 months |
| Other biologics and other systemic therapies, eg: | |
| ustekinumab | 3 months |
| apremilast, tofacitinib | 2 weeks |
| guselkumab | 3 months |
| rituximab | 3 months |
| Anti-IL-17 therapy[a]:<br>secukinumab<br>ixekizumab<br>brodalumab | 3 months |
| Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved) | 3 months or 5 half-lives, whichever is greater |
| Any other antipsoriatic agent (systemic) not listed above | 3 months or 5 half-lives, whichever is greater |
| Any other antipsoriatic agent (topical) under investigation | 1 month |
| Traditional systemic Chinese medicine treatments for PSO and/or PsA | 1 month |

IL-17=interleukin 17; PsA=psoriatic arthritis; PSO=psoriasis; TNF=tumor necrosis factor
[a] Bimekizumab is prohibited per exclusion criteria (Section 5.2).

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

### 6.5.3 Vaccines

Administration of live (including attenuated) vaccines is not allowed during the conduct of the study and for 17 weeks after the final dose of IMP. Administration of inactivated vaccines is allowed during the study at the discretion of the Investigator in consultation with the Medical Monitor.

Administration of any other type of vaccine that is not a live or inactivated vaccine must be discussed with the Medical Monitor.

### 6.5.4 Rescue medication

No rescue medication is planned.

## 6.6 Dose modification

No dose modifications are allowed during the Initial Treatment Period or Maintenance Treatment Period.

## 6.7 Criteria for study hold or dosing stoppage

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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) should also be informed and provided with the 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 or destruction of all unused IMP and other material in accordance with UCB procedures for the study.

## 6.8 Treatment after the end of the study

After the end of PS0041, study participants can switch to alternative treatments.

# 7 DISCONTINUATION OF IMP AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of IMP

A study participant should be withdrawn from IMP and will be asked to come back for the SFU Visit 17 weeks after the final dose of IMP if any of the following events occur:

1. Study participant 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.

2. Study participant develops erythrodermic, guttate, or pustular form of PSO.
3. Study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
4. Study participant uses prohibited concomitant medications (as defined in Section 6.5.2) that may present a risk to the safety of the study participant or the integrity of the study data, in the opinion of the Investigator and/or the Medical Monitor.
5. Study participant has a clinical laboratory value meeting any of the following criteria:
   - Hepatotoxicity as described in Section 7.1.1.
   - A laboratory value meeting any of the following criteria:
     - Absolute neutrophil count $<1.0\times10^3/\mu L$
     - Absolute lymphocyte count $<0.5\times10^3/\mu L$

   A study participant may remain in the study if the result is transient. A retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat absolute neutrophil count or absolute lymphocyte count is still below the allowable values, the study participant must be withdrawn. If the repeat absolute neutrophil count or absolute lymphocyte count is above the allowable values, the study participant may continue in the study.
6. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test. See Section 10.4 (Appendix 4) for more information regarding pregnancies.
7. Study participant experiences a severe AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the Investigator, merits the discontinuation of IMP and appropriate measures being taken.
8. Study participant considered as having either a suspected new LTBI or who develops an active TB or NTMB infection during the study must be immediately discontinued from IMP, and a PEOT Visit must be scheduled as soon as possible, but not later than the next regular visit.

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

   Confirmed active TB is an SAE and must be captured 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 described in Section 10.3 (Appendix 3) until such time as the TB infection resolves.

   Additional information on TB policies is provided in (Section 8.2.5).
9. Study participants with newly diagnosed IBD during the study must discontinue IMP.
10. Study participant has SIB and/or any evidence of major depression. Study participants **must be referred** immediately to a mental health care professional for further assessment of any SIB and/or any evidence of major depression. Withdrawal is mandatory for suicidal behavior and/or a confirmed diagnosis of severe major depression. Otherwise, a withdrawal decision

will be based on the Investigator's assessment of benefit/risk in consultation with the Medical Monitor.

Investigators should attempt to obtain information on study participants in the case of withdrawal or discontinuation. For study participants considered as lost to follow up, the Investigator should make an effort (≥1 phone call and 1 written message to the study participant) 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 study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal or discontinuation.

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

### 7.1.1 Potential drug-induced liver injury IMP discontinuation criteria

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

Immediate and permanent discontinuation of IMP is required for study participants with either of the following PDILI criteria:

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

Immediate discontinuation of IMP is required for study participants with the following PDILI criterion:

- Study participants with ALT or AST ≥3×ULN who exhibit temporally associated symptoms of hepatitis or hypersensitivity. Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness. Hypersensitivity symptoms may include fever (without clear alternative cause), rash, or eosinophilia.

  If a nondrug-related cause for the symptoms can be confirmed, these study participants may resume IMP administration after discussion with the responsible UCB Study Physician, but only when the requirements for rechallenge with IMP (as provided in Section 10.6 [Appendix 6]) are met.

Study participants with the PDILI criterion below may be allowed to continue on IMP at the discretion of the Investigator:

- Study participants with ALT or AST ≥5×ULN and <8×ULN, total bilirubin <2×ULN, and no eosinophilia, 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 10.6 [Appendix 6]), with repeat tests performed in 2 weeks. Upon retest, if ALT or AST values have reduced to <5×ULN, the study participant can continue with the study. However, if ALT or AST values remain ≥5×ULN and <8×ULN after retest, IMP should be temporarily withheld, and study participant should undergo a repeat test in 2 weeks. If ALT or AST values remain

≥5×ULN even after the second retest, then the study participant should be permanently withdrawn from the study and should be followed for PDILI.

If a study participant is unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

Investigators should attempt to obtain information on study participants in the case of IMP discontinuation to complete the final evaluation. Study participants 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 study participant withdrawal (if applicable), must be recorded in the source documents. The eCRF must document the primary reason for IMP discontinuation.

Specific assessments and follow-up actions for PDILI are provided in Section 10.6 (Appendix 6).

#### 7.1.1.1 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10-3. 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 Medical Monitor and UCB Study Physician, as needed.

### 7.1.2 Clinical laboratory criteria

Study participants should be monitored for absolute neutrophil count and/or absolute lymphocyte count as described in Section 7.1.

### 7.1.3 Temporary discontinuation of IMP

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 participants from any immediate hazard to their health and safety. In this case, this action should be taken immediately, without prior notification of the regulatory authority, IRB/IEC, or Sponsor.

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

Any study participant who develops a clinically important infection or recurrent infection not responsive to standard therapy during the study must discontinue IMP until resolution of the infection. The Investigator should use clinical judgement in deciding whether the study participant should restart IMP and should contact the Medical Monitor and UCB Study Physician to confirm the study participant's suitability for continued participation in the study.

### 7.1.4 IMP restart/rechallenge

The criteria for IMP restart/rechallenge are described in Section 10.6.2.1.

## 7.2 Participant discontinuation/withdrawal from the study

If a study participant is unable to attend a visit due to the coronavirus disease 2019 (COVID-19) pandemic, study-specific contingencies will be followed (Section 9.5), and the study participant should not be withdrawn.

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

A study participant should be withdrawn from the study and will be encouraged to come back for the SFU Visit 17 weeks after final dose of IMP if the study participant withdraws his/her consent or the Sponsor or a regulatory agency requests withdrawal of the study participant.

A study participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

If a study participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a study participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

See the SoA (Table 1-1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Refer to Section 7.1 for additional study participant discontinuation/withdrawal criteria.

### 7.3 Lost to follow up

A study participant will be considered lost to follow up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a study participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the study participant and reschedule the missed visit as soon as possible, counsel the study participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the study participant wishes to and/or should continue in the study.
- Before a study participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the study participant (≥1 phone call and 1 written message to the study participant) 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 study participant, must be recorded in the source documents. The eCRF must document the primary reason for withdrawal.

Should the study participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow up documented in the eCRF.

## 8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Table 1-1).

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the study participant should continue or discontinue IMP.

Adherence to the study design requirements, including those specified in the SoA (Table 1-1), is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential study participants meet all eligibility criteria at the Baseline Visit for randomization. The Investigator will maintain a screening log to record details of all study participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the study participant's routine clinical management (eg, chest x-ray and computed axial tomography [CT] scan) and obtained before signing of the ICF may be utilized for Screening or Baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1-1).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Some study-specific investigations may not be possible to conduct according to the study protocol during a pandemic or other exceptional circumstances (eg, hurricanes) due to the need to implement safety measures and guidance from regulatory authorities. In such a situation, which may be accompanied by local or global containment or other measures, sites may need to prohibit access to study participants and study-related personnel. Study participants' visits to the study site may be replaced by contingency measures. These measures are primarily established to ensure the continued safety of study participants during the course of the study and to maintain the study participants' treatment schedules, if the Investigator considers it appropriate. The contingency measures will be described in a contingency plan which will be maintained by UCB for the respective study. The contingency measures are shared with the Investigator and the respective study-related personnel as soon as there are indications that it is necessary to implement any of the measures.



## 8.1 Efficacy assessments

### 8.1.1 PASI

The PASI is the most commonly used and validated assessment for grading the severity of PSO in clinical studies (Feldman, 2004). The PASI quantifies the severity and extent of the disease and weighs these with the percentage of BSA involvement. The PASI will be completed by the Investigator electronically at the visits specified in the SoA (Table 1-1).

The percent area of involvement (BSA%) will be estimated across 4 body areas: head, upper extremities, trunk, and lower extremities. Assessors will enter the degree of involvement for a given region on a scale of 0 to 6 (0=none; 1=1% to <10% affected; 2=10% to <30% affected; 3=30% to <50% affected; 4=50% to <70% affected; 5=70% to <90% affected; 6=90% to 100% affected) (Table 8-1).

The Investigator will assess 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 8-1: Body areas for calculation of percent BSA for PASI**

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

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

The PASI75, PASI90, and PASI100 responses are based on ≥75%, ≥90%, and 100% improvement in the PASI score, respectively. The total BSA affected by PSO will be entered as a percentage from 0 to 100.

### 8.1.2 IGA

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

The Investigator will assess the overall severity of PSO using the 5-point scale presented in Table 8-2.

**Table 8-2: Five-point IGA**

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

IGA=Investigator's Global Assessment; PSO=psoriasis

### 8.1.3 Patient Symptom Diary (Psoriasis-Symptom and Impact Measure)

UCB developed a new electronic patient-reported outcome (ePRO) measure that will be used to assess key symptoms relevant to study participants with moderate to severe plaque PSO.

The Patient Symptom Diary (PSD) (Psoriasis-Symptom and Impact Measure [P-SIM]) consists of 14 items, measuring the following PSO-related signs, symptoms, and functional impacts:

[redacted]. Each item is assessed for severity/impact level on a 0 to 10 scale, where 0 means no symptoms or impact and 10 means very severe symptoms or worst impact. The PSD (P-SIM) will be assessed at the clinic during scheduled study visits as specified in the SoA (Table 1-1).

[redacted]

### 8.1.4 Scalp IGA

A static IGA for scalp PSO will be used to assess disease severity on the scalp. Scalp lesions will be assessed in terms of clinical signs of redness, thickness, and scaliness using the 5-point scale presented in Table 8-3.

The scalp IGA will be assessed for all study participants at Baseline. The scalp IGA will be completed by the Investigator electronically. Only study participants with a scalp IGA score >0 at Baseline will have the scalp IGA assessed at later visits as specified in the SoA (Table 1-1).

**Table 8-3: Scalp IGA**

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

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

### 8.1.5 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a questionnaire designed for use in adult study participants with PSO. The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect study participants' health-related quality of life (QoL). This instrument asks study participants about symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. It has been shown to be valid and reproducible in study participants with PSO. The DLQI score ranges from 0 to 30, with higher

scores indicating lower health-related QoL. A 4-point change in the DLQI score (DLQI response) has been reported to be meaningful for the study participant (within-participant minimal important difference), while a DLQI absolute score of 0 or 1 indicates no or small impact of the disease on health-related QoL (Basra et al, 2015; Hongbo et al, 2005).

Study participants will be asked to complete the DLQI at the visits specified in the SoA (Table 1-1).

The DLQI should be completed in a quiet place prior to any discussion regarding study-related issues, disease status, or treatment effect with the Investigator/site staff, and prior to any procedures.

## 8.2 Safety assessments

### 8.2.1 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2) must be conducted in accordance with the laboratory manual and the SoA (Table 1-1). See Section 10.2 and the SoA for the list, timing, and frequency of clinical laboratory tests to be performed. Blood samples will be collected prior to dosing for measurement of hematology and biochemistry laboratory measurements as well as interferon-gamma release assay (IGRA) assessments (see Section 8.2.5.3.4) as specified in the SoA (Table 1-1).

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the study participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 17 weeks after the final dose of IMP should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

### 8.2.2 Vital signs

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

Vital signs should be assessed prior to IMP administration and prior to any blood collection.

### 8.2.3 Physical examination

The physical examination will include general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the respiratory, CV, gastrointestinal (GI), musculoskeletal, hepatic, and neurological (including limb reflexes) systems; and mental status. All physical examinations will

also include evaluation of signs and symptoms of active TB and risk for exposure to TB (Section 8.2.5.3). Findings considered clinically significant changes since the physical examination at the Screening Visit will be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

### 8.2.4 12-lead electrocardiogram

Twelve-lead standard electrocardiograms (ECGs) will be recorded at the Screening Visit. Full details of ECG recording will be provided in the ECG Manual.

### 8.2.5 Assessment and management of TB and TB risk factors

All study participants will be assessed for TB through physical examination for signs and symptoms of TB (Section 8.2.5.3.1), laboratory testing (Section 8.2.1), chest x-ray/CT scan (Section 8.2.5.3.2), and TB questionnaire (Section 8.2.5.3.3).

#### 8.2.5.1 Definitions

Study participants with known active TB disease, at high risk of acquiring TB infection, or with untreated LTBI (ie, pending anti-TB prophylactic course) or current or history of NTMB infection are excluded from the study.

a. Known TB infection whether present or past is defined as:
   - Active TB disease or clinical signs and symptoms strongly suggestive of TB (pulmonary or extrapulmonary)
   - History of active TB disease involving any organ system or findings in other organ systems consistent with TB, 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 disease that is not reported in the study participant's medical history

b. High risk of acquiring TB infection is defined as:
   - Known close exposure (eg, sleeping in the same room) to another person with active TB infection within 3 months prior to Screening
   - Time spent within 3 months prior to Screening in a health care delivery setting or institution where individuals infected with TB are housed or where the risk of transmission of infection is high

c. Latent TB infection is defined as an infection by *Mycobacterium tuberculosis* with:
   - A positive IGRA (or 2 indeterminate IGRAs), AND
   - Chest imaging (or other imaging) negative for TB infection, AND
   - Absence of signs, symptoms (eg, evidence of organ-specific involvement), or physical findings suggestive of TB infection.

d. Pulmonary NTMB infection is defined as a group of lung or extrapulmonary infections caused by mycobacteria different from *Mycobacterium tuberculosis (M. tuberculosis)* infections.

#### 8.2.5.2 Assessments at Screening

At Screening, all study participants will have an IGRA test (QuantiFERON Gold Plus TB test is recommended), a chest x-ray (unless already performed within 3 months of Screening; CT scan of the chest at Screening or within 3 months prior to Screening is acceptable, if available), and examination for signs and symptoms of TB. In addition, each study participant will complete a TB questionnaire directed at potential exposure to TB and symptoms of TB.

Study participants diagnosed with active TB during Screening will be excluded from the study. Study participants with LTBI diagnosed during Screening must complete a full course of prophylaxis and can be rescreened after completion of 4 weeks of prophylaxis prior to the first dose of IMP, as described in the exclusion criteria (Section 5.2).

A decision tree for IGRA TB results at Screening, including study participant eligibility, retesting requirements, and treatment requirements at Screening, is shown in Figure 8-1.

## Figure 8-1: Decision tree for IGRA TB results at Screening


IGRA=interferon-gamma release assay; IMP=investigational medicinal product; LTBI=latent tuberculosis infection; TB=tuberculosis

[a] Interferon-gamma release assay retest must be done during the protocol-defined Screening window.

[b] Study participants with LTBI diagnosed during Screening must complete a course of prophylaxis. Study participants can be rescreened after completion of 4 weeks of prophylaxis prior to the first dose of IMP.

#### 8.2.5.3 Assessment and reporting of TB and TB risk factors during the study

##### 8.2.5.3.1 Physical examination

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

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

Some common symptoms that the study participant 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, and abdominal pain (mimicking IBD). Unusual presentations should always be considered.

##### 8.2.5.3.2 Chest x-ray/CT scan for TB

Chest radiographic imaging is performed at Screening, and results must be available at Baseline before first IMP administration unless a chest x-ray or CT scan is available within 3 months prior to Screening.

Additional chest x-rays or other imaging tests should be performed when positive signs and symptoms indicate pulmonary infection, including potential TB infection, or when close exposure to persons with TB is documented.

##### 8.2.5.3.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed as described in the SoA (Table 1-1). The questionnaire will assist with the identification of study participants who may require therapy for TB.

A study participant who answers "Yes" at Screening to the question [redacted] should not be allowed into the study pending further assessments (including TB specialist consult). A "Yes" response to any of the questions in the TB questionnaire during the study may trigger further assessment to determine if the study participant has either LTBI and must receive TB prophylactic therapy prior to continuing IMP, or active TB infection and must be withdrawn from the study.

##### 8.2.5.3.4 Interferon-gamma release assay test conversion

The IGRA is a whole blood testing methodology for diagnosing *M. tuberculosis* infection. It has become the gold standard, but it does not help in differentiating LTBI from active TB disease.

Tuberculosis test conversion is defined as a positive or indeterminate (and confirmed indeterminate on repeat) IGRA result for the current test when previous IGRA test results were negative. All study participants with positive or indeterminate IGRA test results must immediately stop IMP administration. In case of an IGRA test conversion, the study participant

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. Where medically relevant, additional assessments (eg, blood tests or IGRA, chest x-rays, or other imaging) should be performed and documented. Such conversions should be reported as AEs as described in the protocol. The AE term should be updated with the final diagnosis once available.

#### 8.2.5.3.5 Latent TB

If evaluation by the appropriate specialist diagnoses a new LTBI, a TB prophylactic therapy in accordance with applicable clinical guidelines should be immediately initiated.

Study participants who initiate treatment for LTBI during the Screening Period must repeat initial screening laboratory parameters, all physical examinations, and questionnaires prior to randomization in the study and must continue the full course of TB prophylactic therapy. Study participants can be rescreened after completion of 4 weeks of prophylaxis prior to the first dose of IMP.

If no TB prophylactic therapy is initiated for the newly diagnosed LTBI during Screening, the study participant must not be enrolled into the study. Every related action should be discussed in advance with the Medical Monitor.

Any study participant who develops LTBI during the study must discontinue further administration of IMP, and a PEOT Visit must be scheduled as soon as possible, but not later than the next regular visit. The study participant must be permanently withdrawn if the study participant is diagnosed with LTBI with no initiation of prophylactic treatment, prematurely discontinues prophylactic treatment, or, in the opinion of the Investigator or Sponsor, is noncompliant with prophylactic TB therapy. Once withdrawn, the PEOT Visit must be scheduled as soon as possible, and the study participant should be encouraged to keep the SFU Visit. Latent TB infection must be reported as an AE. Follow-up reports should be completed as described in Section 10.3 (Appendix 3) until the LTBI resolves.

#### 8.2.5.3.6 Active TB or NTMB infection

Study participants who develop active TB or NTMB infection during the study must be withdrawn from the study. The study participant must be immediately permanently discontinued from IMP, and a PEOT Visit must be scheduled as soon as possible, but no later than the next scheduled visit. The study participant should be encouraged to keep the SFU Visit as specified by the protocol. Treatment for active TB or NTMB should be started immediately.

Confirmed active TB is always considered an SAE. UCB's process requires that these must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements (Section 10.3 [Appendix 3]). Follow-up reports should be completed as per protocol requirement until the TB infection resolves.

#### 8.2.5.3.7 Tuberculosis management of LTBI, active TB, or other NTMB infection identified during study

During the study, study participants who develop evidence of LTBI, active TB, or NTMB infection must immediately stop further administration of IMP and will be referred to a TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Study participants diagnosed with active TB or LTBI should receive appropriate TB or prophylaxis

therapy. The study participant should be transferred to the care of his/her physician and managed according to the standard of care.

Study participants identified as having active TB during the study must be withdrawn and scheduled to return for the PEOT Visit as soon as possible, but no later than the next scheduled study visit, and complete all PEOT assessments. The study participant should be encouraged to complete a SFU Visit after the final dose of IMP.

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

Additional details on TB detection and management are provided in the UCB TB Detection Procedure Guideline.

## 8.3 Adverse events and SAEs

Adverse events will be reported by the study participant.

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the IMP or study procedures, or that caused the study participant to discontinue the IMP or the study (Section 7).

### 8.3.1 Time period and frequency for collecting AE and SAE information

All AEs and SAEs will be collected from the signing of the ICF until the SFU Visit at the visits specified in the SoA (Table 1-1).

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Section 10.3 (Appendix 3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

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 17 weeks from the final dose of IMP for each study participant and to also inform study participants 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.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

### 8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the study participant is the preferred method to inquire about AE occurrences.

### 8.3.3 Follow up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each study participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study participant is lost to follow up (as defined in Section 7.3). Further details of follow-up procedures are provided in Section 10.3 (Appendix 3).

### 8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of study participants and the safety of an IMP under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of IMP under clinical investigation. The Sponsor will comply with Chinese regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigator.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

### 8.3.5 Pregnancy

Details of all pregnancies in female study participants and female partners of male study participants will be collected after the start of IMP and until the SFU Visit.

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 24 hours of receipt of the information and should follow the procedures outlined in Section 10.4 (Appendix 4).

The female study participant should be discontinued from the IMP as soon as pregnancy is known (by positive pregnancy test), and the following should be completed:

- The study participant should return for a PEOT visit.
- The study participant should immediately stop the intake of IMP.
- A SFU Visit should be scheduled 17 weeks after the study participant has discontinued IMP.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### 8.3.6 AEs of special interest

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

administration of a UCB product/compound. For bimekizumab, the following event requires immediate reporting (within 24 hours regardless of seriousness) to UCB:

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

### 8.3.7 Other safety topics of interest

Prespecified safety topics of interest for this study are as follows: infections (serious, opportunistic, fungal, and TB), neutropenia, hypersensitivity, injection site reactions, neuropsychiatric AEs (including SIB), major CV events, LFT changes/enzyme elevations, malignancies, and IBD.

These safety topics of interest are based on findings from the bimekizumab clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action. There are no specific AE reporting requirements for these topics, however, special monitoring, additional data collection activities, and/or enhanced signal detection activities within UCB are in place.

The reporting requirements for events relating to TB are as follows:

- Interferon-gamma release assay test conversion, defined as a positive or indeterminate (and confirmed indeterminate on repeat) IGRA result for the current test when previous IGRA test results were negative, should be reported as an AE (Section 8.2.5.3.4). The AE term would need to be updated with final diagnosis once available.
- Latent TB infection must be reported as an AE (Section 8.2.5.3.5). Follow-up reports should be completed as described in Section 10.3 (Appendix 3) until the LTBI resolves.
- Confirmed active TB is always considered an SAE and must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements (Section 10.3 [Appendix 3]). Follow-up reports should be completed as described in Section 10.3 (Appendix 3) until the TB infection resolves (Section 8.2.5.3.6).

### 8.3.8 Anticipated SAEs

Anticipated SAEs (ie, serious AEs that are anticipated to occur in the study population at some frequency that is independent of drug exposure) for this study are presented in Table 8-4.

This list does not change the Investigator's obligation to report all SAEs (including anticipated SAEs) as detailed in Section 10.3 (Appendix 3).

**Table 8-4: Anticipated SAEs for study participants with moderate to severe plaque PSO**

| MedDRA system organ 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; PSO=psoriasis; 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 participant.

### 8.3.9 Medical device AEs and device deficiencies

The device is used in this study for the purposes of IMP administration (Section 6.1.1). In order to fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

Adverse events will be reported according to the ISO 14155:2020, while recognizing and following requirements, including reporting timelines specified in other specific laws, regulations, directives, standards and/or guidelines.

The definition of an ADE, serious adverse device effect (SADE), and medical device deficiency can be found in Section 10.7 (Appendix 7).

NOTE: Events fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Section 10.3 (Appendix 3).

#### 8.3.9.1 Time period for detecting medical device deficiencies

Adverse device effects and device deficiencies will be detected, documented, and reported during all periods of the study in which the device is used.

If the Investigator learns of any deficiency at any time after a study participant has been discharged from the study and such event(s) is considered reasonably related to a device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting device deficiency is provided in Section 10.7 (Appendix 7).

#### 8.3.9.2 Follow up of ADEs and device deficiencies

Follow up applies to all study participants, including those who discontinue IMP and/or the study.

The Investigator is responsible for ensuring that follow up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.

New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

#### 8.3.9.3 Prompt reporting of ADEs and device deficiencies to Sponsor

Adverse device effects and device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of an ADE or device deficiency.

The Sponsor will be the contact for the receipt of ADE and device deficiency reports. The Adverse Event and Device Deficiency Report Form will be sent to the Sponsor.

#### 8.3.9.4 Regulatory reporting requirements for ADEs and device deficiencies

The Investigator will promptly report all ADEs and device deficiencies occurring with any medical device provided for use in the study to the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to devices being used in clinical studies.

The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of ADEs and device deficiencies to the IRB/IEC.

## 8.4 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, study participants, regulatory authorities, and IRBs/IECs will be informed appropriately and as early as possible.

The UCB Study Physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety (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 results) for which data will be periodically reviewed during the course of the study.

## 8.5 Treatment of overdose

For this study, any dose of bimekizumab greater than that prescribed in the protocol (ie, 320mg) will be considered an overdose. Overdose events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess IMP itself is an AE or SAE (eg, suicide attempt).

UCB does not recommend specific treatment for an overdose. Any signs or symptoms of adverse reactions should be treated symptomatically as per standard care by the Investigator.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately
2. Closely monitor the study participant for any AE/SAE and laboratory abnormalities until bimekizumab can no longer be detected systemically (≥90 days)

3. Obtain a plasma sample for PK analysis as soon as possible after the final dose of IMP if requested by the Medical Monitor (determined on a case-by-case basis)
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the study participant.

## 8.6 Pharmacokinetics

Blood samples will be collected prior to dosing for measurement of plasma concentrations of bimekizumab at the visits specified in the SoA (Table 1-1).

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of bimekizumab. Samples collected for analyses of bimekizumab plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Study participant confidentiality will be maintained. At visits during which blood samples for the determination of plasma concentrations of bimekizumab will be taken, 1 sample of sufficient volume can be used.

Drug concentration information that may unblind the study will not be reported to any blinded study personnel as long as the study remains blinded.

## 8.7 Biomarkers

Biomarkers are not evaluated in this study.

## 8.8 Immunogenicity assessments

Antibodies to bimekizumab will be evaluated in plasma samples collected from all study participants at the visits specified in the SoA (Table 1-1). Additionally, plasma samples should also be collected at the final visit from study participants who discontinue IMP or withdraw from the study. These samples will be tested by the Sponsor or Sponsor's designee.

A tier-based approach will be used, consisting of consecutive screening, confirmatory, and titration methods. Plasma samples will be screened for antibodies binding to bimekizumab, and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to bimekizumab and/or further characterize the immunogenicity of bimekizumab.

The detection and characterization of antibodies to bimekizumab will be performed using validated assay methods by or under the supervision of the Sponsor. The procedures for sample analysis and the relevant validation results will be described in a separate bioanalytical report. All samples collected for detection of antibodies to IMP will also be evaluated for bimekizumab plasma concentration to enable interpretation of the antibody data. Confirmed positive antibody samples will be further characterized for their ability to neutralize the activity of bimekizumab. Samples may be stored for a maximum of 20 years (or according to local regulations) following the last study participant's last visit for the study at a facility selected by the Sponsor, to enable further analysis of immune responses to bimekizumab.

## 8.9 Medical resource utilization and health economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

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

## 9.1 Definition of analysis sets

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

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

The Safety Set (SS) will consist of all study participants who receive ≥1 dose of IMP.

The Full Analysis Set (FAS) will consist of all randomized study participants who receive ≥1 dose of IMP and have a valid measurement for each of the co-primary efficacy endpoints at Baseline.

The Active Medication Set (AMS) will consist of all study participants who receive ≥1 dose of active IMP (bimekizumab).

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

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized study participants who receive ≥1 dose of IMP and provide ≥1 quantifiable plasma concentration postdose without important protocol deviations that would affect the concentration.

## 9.2 General statistical considerations

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

All analyses will be performed using SAS® version 9.3 or later (SAS Institute, Cary, NC, US).

The statistical analysis of the co-primary efficacy endpoints will be performed using a Type I error rate at a 2-sided alpha level of 0.05.

### 9.2.1 Multiplicity

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

The hypotheses ($H_1$, $H_2$, $H_3$, $H_4$) comparing bimekizumab versus placebo will be tested at a 2-sided alpha level of 0.05.

The first 2 hypotheses ($H_1$ and $H_2$) will separately test whether bimekizumab is superior to placebo for PASI90 response and IGA 0/1 response at Week 16. These are the hypothesis tests

corresponding to the co-primary endpoints. If both null hypotheses are rejected at a 2-sided alpha level of 0.05, that alpha will be passed to the next test in the sequence, allowing the testing procedure to proceed.

The hypotheses associated with the subsequent tests ($H_3$ and $H_4$) are for the 2 key secondary efficacy endpoints and are based on testing for superiority relative to placebo. See Table 9-1 for details on this procedure.

**Table 9-1: Sequence of hypothesis testing**

| Hypothesis | Test |
|---|---|
| $H_1$ and $H_2$ | PASI90 and IGA 0/1 response at Week 16 |
| $H_3$ | PASI75 response at Week 4 |
| $H_4$ | PASI100 response at Week 16 |

H=hypothesis; IGA 0/1=Investigator's Global Assessment response clear (0) or almost clear (1) with ≥2-category improvement relative to Baseline; PASI=Psoriasis Area and Severity Index; PASI75/90/100=75% or greater/90% or greater/100% improvement from Baseline in the PASI score

## 9.3 Planned efficacy/outcome analyses

### 9.3.1 Analysis of the primary efficacy/primary endpoints

The co-primary efficacy endpoints for this study will be PASI90 response and IGA 0/1 response at Week 16.

The co-primary efficacy endpoints will be analyzed for all study participants in the RS.

The co-primary efficacy endpoints will be derived as follows:

- PASI90 responder at Week 16: PASI score at Week 16 has improved by ≥90% from Baseline, and the study participant has not discontinued IMP prior to Week 16.
- IGA 0/1 responder at Week 16: IGA score at Week 16 is 0 or 1 (clear or almost clear) with ≥2-category improvement from Baseline in the IGA score, and the study participant has not discontinued IMP prior to Week 16.

The evaluation of superiority (bimekizumab versus placebo treatment comparison) will be based on the Cochran-Mantel-Haenszel (CMH) test. Treatment comparisons will be made based on the CMH test using the p-value for the general association. Odds ratios and 95% confidence intervals (CIs) based on the CMH method will also be presented.

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

#### 9.3.1.1 Sensitivity analyses

The primary efficacy analysis described in Section 9.3.1 will be repeated using the FAS and PPS with the NRI method similar to the primary analysis (Section 9.3.1). Observed case summaries (excluding study participants with missing PASI/IGA data at Week 16) will also be provided as a sensitivity analysis to the primary analysis method.

Additional sensitivity analyses of the co-primary endpoints for handling missing data will also be performed and are described in detail in Section 9.6.

### 9.3.2 Secondary efficacy endpoint analyses

The secondary efficacy endpoints will be analyzed for all study participants in the RS using the NRI method similar to the primary analysis (Section 9.3.1).

For the binary secondary efficacy endpoints assessing the superiority of bimekizumab versus placebo, the CMH test as specified for the primary analysis will be implemented (Section 9.3.1).

For all secondary efficacy endpoints, observed case summaries will also be presented.

#### 9.3.2.1 Key secondary efficacy endpoint analyses

The binary key secondary efficacy endpoints will be derived as follows:

- PASI75 responder at Week 4: PASI score at Week 4 has improved by ≥75% from Baseline, and the study participant has not discontinued IMP prior to Week 4.
- PASI100 responder at Week 16: PASI score at Week 16 has improved by 100% from Baseline (ie, PASI complete response), and the study participant has not discontinued IMP prior to Week 16.

The key secondary efficacy endpoints (PASI75 response at Week 4 and PASI100 response at Week 16) will be analyzed using the same method as for the co-primary endpoints by using RS and NRI method (Section 9.3.1). In addition, analyses will be repeated using the FAS and the NRI method. Observed case summaries will also be provided as a sensitivity analysis. Missing data for these variables will also be imputed using multiple imputation (MI) similar to the sensitivity analyses for the co-primary endpoints. Further details on multiple imputation are described in Section 9.6.

#### 9.3.2.2 Additional secondary efficacy endpoint analyses

The additional secondary efficacy endpoints will be derived as follows:

- PSD (P-SIM) responder for itch at Week 16: Itch score has improved (decreased) by ≥4 points from Baseline to Week 16, and the study participant has not discontinued IMP prior to Week 16. This will be assessed only in study participants with a Baseline itch score ≥4.
- PSD (P-SIM) responder for pain at Week 16: Pain score has improved (decreased) by ≥4 points from Baseline to Week 16, and the study participant has not discontinued IMP prior to Week 16. This will be assessed only in study participants with a Baseline pain score ≥4.
- PSD (P-SIM) responder for scaling at Week 16: Scaling score has improved (decreased) by ≥4 points from Baseline to Week 16, and the study participant has not discontinued IMP

prior to Week 16. This will be assessed only in study participants with a Baseline scaling score ≥4.

[redacted]

### 9.3.3 Tertiary efficacy endpoint analyses

The tertiary efficacy endpoints in the Initial Treatment Period and the Overall Treatment Period (Initial Treatment Period+Maintenance Treatment Period) will be analyzed for all study participants in the RS.

Binary (responder) endpoints will be summarized using frequency tables by treatment group for each visit. Continuous endpoints will be summarized using descriptive statistics by treatment group for each visit.

Time to PASI75/90/100 response during the Initial Treatment Period will be estimated and presented using the Kaplan-Meier product-limit method for each treatment group. Time to a given response will be defined as the length in days from the first dose of IMP until the first date when the response is achieved. Study participants who discontinue IMP prior to achieving a response will be censored at the date of IMP discontinuation. Study participants who reach the Week 16 visit without achieving the given PASI response will be censored at the date of the Week 16 visit. Study participants will be censored at Baseline (Day 0) if there is no Baseline PASI assessment or no post-Baseline PASI assessment. The median time to response, including the 2-sided 95% CI, will be calculated for each treatment group. Comparisons of bimekizumab versus placebo will be analyzed using a log-rank test.

All binary tertiary efficacy endpoints will be summarized based on imputed data (NRI), unless otherwise stated in the SAP. In some cases, endpoints may also be summarized based on observed case data (ie, study participants with missing data or who have prematurely discontinued IMP are treated as missing). Should there be no missing data for a study endpoint, then only observed case data will be presented. Continuous variables will be summarized using descriptive statistics by treatment group for each visit based on observed case.

## 9.4 Planned safety and other analyses

### 9.4.1 Safety analyses

Safety endpoints will be analyzed for all study participants in the SS. The AMS will be used for summaries of safety that include data from the Initial Treatment Period and/or Maintenance Treatment Period. Further details will be specified in the SAP.

#### 9.4.1.1 AEs

Adverse events will be coded according to the most recent Medical Dictionary for Regulatory Activities. Treatment-emergent AEs are defined as those AEs that have a start date on or following the first dose of IMP.

The frequency of all TEAEs will be presented for each treatment group separately by SOC, high level term (HLT), and preferred term. The data will be displayed as number of study participants experiencing the TEAE, percentage of study participants, and number of TEAEs.

Additional tables will summarize TEAEs by severity and relationship to IMP, TEAEs leading to study discontinuation, serious TEAEs, deaths, and TEAEs categorized as safety topics of interest and AESIs. Definitions for categorizing TEAEs as safety topics of interest and AESIs will be provided in the SAP.

If a TEAE occurs on the date of a study treatment switch, the event will be attributed to the original study treatment (the "preswitch" treatment). The only exceptions are for the following types of events, which will be attributed to the new study treatment:

- Events that fulfill the anaphylaxis criteria for acute events (the criteria for acute anaphylaxis events will be provided in the SAP)
- Events that fulfill the hypersensitivity reaction criteria (the algorithm for defining a hypersensitivity reaction will be provided in the SAP)
- Events with an HLT of "Administration site reactions NEC"
- Events with an HLT of "Injection site reactions"

Further details of TEAE summaries will be provided in the SAP.

Extent of exposure will be presented descriptively by treatment group.

#### 9.4.1.2 Hematology/biochemistry

Treatment-emergent markedly abnormal (TEMA) laboratory values are those that have an assessment date on or following first dose of IMP.

Laboratory assessments will be analyzed by visit. Absolute values and changes from Baseline in each laboratory parameter will be presented descriptively for each treatment group. The incidence rate of TEMA laboratory values at the parameter level will also be presented descriptively for each treatment group. Definitions for markedly abnormal laboratory values will be provided in the SAP.

#### 9.4.1.3 Vital signs

Vital signs will be summarized by visit. Absolute values and change from Baseline in systolic and diastolic BP and pulse rate will be presented descriptively by visit for each treatment group.

Markedly abnormal vital signs will be summarized. Definitions of markedly abnormal vital signs will be provided in the SAP.

#### 9.4.1.4 Physical examination

Clinically significant changes from Baseline in physical examination findings will be reported as AEs and included in the TEAE summarization described in Section 9.4.1.1.

### 9.4.2 PK and ADAb analyses

Plasma bimekizumab concentrations will be summarized for the PK-PPS at each time point using descriptive statistics. In addition, PK model-based analyses may be performed and reported separately.

Antidrug antibody data will be evaluated for each study participant in the SS, and rates of ADAb-positive study participants will be calculated. Neutralizing ADAb data will also be evaluated. Further details will be provided in the SAP.

## 9.5 Handling of protocol deviations

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

Important protocol deviations may lead to exclusion from the PPS or PK-PPS (Section 9.1).

Summaries of all important protocol deviations will be produced.

## 9.6 Handling of dropouts or missing data

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

[redacted]

[redacted]

There may be cases where the multiple imputation model fails to converge. In such situations, the last observation carried forward (LOCF) approach will instead be used to impute the missing data. If LOCF is used instead of multiple imputation for this reason, this will be clearly specified in the corresponding table summary. Note that for LOCF imputation, any missing data or data collected following discontinuation of IMP will be imputed with the most recent previous value.

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

Pharmacokinetic analyses will be based on observed data; no imputation will be used. However, if plasma concentration measurements are below the lower level of quantification (LLOQ), then for calculation of the derived statistics the result will be set to half of the LLOQ.

## 9.7 Planned analysis and data monitoring

A primary analysis will be performed after all randomized study participants have completed the Week 32 assessments, and a final analysis and clinical study report (CSR) will be prepared once all data (through the SFU Visit) have been collected after study completion and database lock.

## 9.8 Determination of sample size

[redacted]

[redacted]

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

## 10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

### 10.1.1 Regulatory and ethical considerations

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

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, ICF, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other study participant-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 study participants or others, and any protocol deviations, to eliminate immediate hazards to study participants.

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 study participants. 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 study participant 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 China. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

### 10.1.2 Financial disclosure

Insurance coverage will be handled according to local requirements.

Finance and insurance are addressed in the Investigator and/or contract research organization (CRO) agreements, as applicable.

### 10.1.3 Informed consent process

Study participant'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 study participant in both oral and written form by the Investigator (or designee). Each study participant will have the opportunity to discuss the study and its alternatives with the Investigator.

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

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

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

### 10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the study participant's confidentiality. Throughout this study, all data forwarded to UCB (or designee) will be identified only by the study participant 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 study participant'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 study participant's study participation, and autopsy reports for deaths occurring during the study).

The study participant must be informed that personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the study participant.

The study participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

### 10.1.5 Data quality assurance

All study participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, contemporaneous, original, and attributable from source documents; that the safety and rights of study participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements.

All essential documents must be retained by the Investigator for the minimum retention period mandatory under the applicable local laws and regulations. The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

#### 10.1.5.1 eCRF completion

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

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

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

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

Detailed instructions will be provided in the eCRF Completion Guidelines.

### 10.1.6 Source documents

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

Source documents are original records in which raw data are first recorded. These may include hospital/clinic/general practitioner records, charts, diaries, x-rays/CT scans, laboratory results,

printouts, pharmacy records, care records, ECG or other printouts, completed scales, QoL questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Electronic PRO measures and the TB questionnaire will be completed by each study participant and will be collected via electronic device.

Source documents that are computer generated and stored electronically must be printed for review by the monitor. Once printed, these copies should be signed and dated by the Investigator and become a permanent part of the study participant'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 must be saved and stored as instructed by UCB (or designee).

### 10.1.7 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of study participants by the Investigator
- Discontinuation of further bimekizumab development

### 10.1.8 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

## 10.2 Appendix 2: Clinical laboratory tests

- The tests detailed in Table 10-1 will be performed by the central laboratory, with the exception of urine dipsticks and urine pregnancy tests, which will be performed locally at the site.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either IMP administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either an IMP decision or response evaluation, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of study participants are detailed in Section 5.1 and Section 5.2, respectively.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

## Table 10-1: Protocol-required safety laboratory assessments

| Laboratory assessments | Parameters | | | |
|---|---|---|---|---|
| Hematology | Platelet count<br>RBC count<br>Hemoglobin<br>Hematocrit | RBC indices:<br>MCV<br>MCH<br>MCHC | | WBC count with differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils |
| Clinical chemistry[a] | BUN | Potassium | AST | Total bilirubin |
| | Creatinine | Sodium | ALT | Glucose (nonfasting) |
| | Calcium | Alkaline phosphatase | Lipid panel | Chloride |
| | | GGT | LDH | |
| Routine urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick<br>• Microscopic examination (if protein, blood, nitrite, or leukocyte esterase is abnormal) | | | |
| Other Screening tests | • Serum hCG pregnancy test (as needed for WOCBP) by central laboratory at Screening and urine pregnancy test locally for all assessments after Screening<br>• IGRA testing<br>• Urine drug screen<br>• Serology (HIV antibody, HBsAg, and hepatitis C virus antibody)<br>Specific details regarding the handling and processing of serum chemistry, hematology, and urinalysis samples are provided in the study laboratory manuals.<br>All study-required laboratory assessments will be performed by the central laboratory, with the exception of urine dipsticks and urine pregnancy tests, which will be performed locally at the site.<br>The results of each test must be entered into the eCRF. | | | |

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; eCRF=electronic Case Report Form; GGT=gamma glutamyltransferase; HBsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell count; ULN=upper limit of normal; WBC=white blood cell count; WOCBP=woman of childbearing potential

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are provided in Section 7.1.1 and Appendix 6 (Section 10.6). All events of ALT ≥3×ULN and bilirubin ≥2×ULN (>35% direct bilirubin) or ALT ≥3×ULN and INR >1.5, if INR measured, may indicate severe liver injury (potential Hy's Law) and must be reported as an SAE.

Investigators must document their review of each laboratory safety report.

Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

## 10.3 Appendix 3: Adverse events – Definitions and procedures for recording, evaluating, follow up, and reporting

**Definition of AE**

| **AE definition** |
|---|
| • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of IMP, whether or not considered related to the IMP.<br>• NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of IMP. |

| **Events <u>meeting</u> the AE definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).<br>• Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.<br>• New conditions detected or diagnosed after IMP administration even though they may have been present before the start of the study.<br>• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.<br>• Signs, symptoms, or the clinical sequelae of a suspected overdose of either IMP or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.<br>• "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. |

| **Events <u>NOT</u> meeting the AE definition** |
|---|
| • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the study participant's condition.<br>• The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the study participant's condition.<br>• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.<br>• Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).<br>• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. |

**Definition of SAE**

If an event is not an AE per definition above, then it cannot be a SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **A SAE is defined as any untoward medical occurrence that, at any dose:** |
|---|
| **a. Results in death** |
| **b. Is life-threatening**<br>The term 'life-threatening' in the definition of 'serious' refers to an event in which the study participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. |
| **c. Requires inpatient hospitalization or prolongation of existing hospitalization**<br>In general, hospitalization signifies that the study participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.<br>Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE. |
| **d. Results in persistent disability/incapacity**<br>• The term disability means a substantial disruption of a person's ability to conduct normal life functions.<br>• This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption. |
| **e. Is a congenital anomaly/birth defect** |
| **f. Important medical events:**<br>• Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the study participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.<br>• Examples of such events include, but are not limited to, potential Hy's law, invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse. |

## Recording and follow up of AE and/or SAE

**AE and SAE recording**

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the study participant's medical records to UCB in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all study participant identifiers, with the exception of the study participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Assessment of intensity**

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the study participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets ≥1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe (eg, a severe AE may be either serious or not serious, depending on whether these criteria are also met).

The National Cancer Institute Common Terminology Criteria for Adverse Events should be used as a supportive standardization instrument to evaluate AEs and SAEs, but the final intensity grading by the Investigator must be mild, moderate, or severe.

**Assessment of causality**

- The Investigator is obligated to assess the relationship between IMP and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to IMP administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which a SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow up of AEs and SAEs**

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- 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 study participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- If a study participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any postmortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

## Reporting of SAE

**SAE reporting to UCB via an electronic data collection tool**

- The primary mechanism for reporting a SAE to UCB will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UCB Study Physician by telephone.
- Contacts for SAE reporting can be found in SAFETY REPORTING OF ADVERSE EVENTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES.

**SAE reporting to UCB via paper CRF**

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the UCB Study Physician.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SAFETY REPORTING OF ADVERSE EVENTS (SERIOUS AND NONSERIOUS) AND DEVICE DEFICIENCIES.

## 10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

### Definitions

**Woman of childbearing potential (WOCBP)**: A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the following categories **are not considered WOCBP**:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's review of the study participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

**Contraception guidance**

**Female study participants**

Female study participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10-2.

## Table 10-2: Highly effective contraceptive methods

| |
|---|
| **Highly effective contraceptive methods that are user dependent**[a]<br>Failure rate of <1% per year when used consistently and correctly. |
| Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Intravaginal<br>• Transdermal |
| Progestogen only hormonal contraception associated with inhibition of ovulation<br>• Oral<br>• Injectable |
| **Highly effective methods that are user independent** |
| Implantable progestogen-only hormonal contraception associated with inhibition of ovulation<br>• IUD<br>• IUS<br>• Bilateral tubal occlusion |
| **Vasectomized partner**<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. |
| **Sexual abstinence**<br>Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the IMP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the study participant. |

IMP=investigational medicinal product; IUD=intrauterine device; IUS=intrauterine hormone-releasing system; WOCBP=woman of childbearing potential

Note: In case of newly started contraception pills/IUDs, Investigator should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as to when these newly started methods would become effective.

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for study participants participating in clinical studies.

### Pregnancy testing

- Woman of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test.
- Additional pregnancy testing should be performed as indicated in the SoA (Table 1-1) and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

**Male study participants with partners who become pregnant**

- The Investigator will attempt to collect pregnancy information on any male study participant's female partner who becomes pregnant while the male study participant is in this study. This applies only to male study participants who receive bimekizumab. If the study participant is later found to be on placebo, then pregnancy data collection can stop.
- In cases where the partner of a male study participant enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the study participant 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/CRO contract monitor for the study. The Investigator will complete the information in the eCRF only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent Form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.
- After obtaining the necessary signed informed consent from the pregnant female partner (and/or parent/legal representative), the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of receipt of the information. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow up will be ≥30 days after the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

**Female study participants who become pregnant**

- Any female study participant who becomes pregnant while participating in the study will discontinue IMP (see Section 8.3.5).
- The Investigator will collect pregnancy information on any female study participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of receipt of the information. The study participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the study participant and the neonate, and the information will be forwarded to the Sponsor. Generally, the follow up will be ≥30 days after the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the IMP by the Investigator will be reported to the Sponsor as described in Section 8.3.5. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

## 10.5 Appendix 5: Genetics

Not applicable.

## 10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments and IMP rechallenge guidelines

The PDILI IMP discontinuation criteria for this study are provided in Section 7.1.1, 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 receipt of the information. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 8.3.6), and, if applicable, also reported as an SAE (see Section 8.3.4).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10-4 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 10.6.1). 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 7.1.1.1).

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 7.1.1), IMP must be permanently discontinued unless a subsequent alternative diagnosis fully explains the hepatic findings. If a subsequent alternative diagnosis fully explains the hepatic findings, and the requirements provided in Section 10.6.2.1 are met, rechallenge with IMP may be appropriate.

The approach to investigate PDILI is summarized in Table 10-3.

## Table 10-3: Required investigations and follow up for PDILI

| Laboratory value | | | Immediate | | Follow up | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |
| ≥3×ULN | ≥2×ULN[b] | N/A | Hepatology consult[c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and study participant discussed with Medical Monitor ASAP. | Immediate IMP discontinuation[d] | Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 10.6.3); recommended to occur at the site with HCP. | Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values.[e] |
| ≥3×ULN | N/A | Yes | | | | |
| ≥8×ULN | N/A | N/A | Need for hepatology consult to be discussed (required if ALT or AST ≥8×ULN) Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and study participant discussed with Medical Monitor ASAP. | | | |
| ≥5×ULN (and ≥2× Baseline) and <8×ULN | <2×ULN | No | Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see | Further investigation – immediate IMP discontinuation not | 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 10.6.3). | Monitoring of liver chemistry values at least twice per week for 2 weeks.[e] • Immediate IMP discontinuation required if liver |

## Table 10-3: Required investigations and follow up for PDILI

| Laboratory value | | | Immediate | | Follow up | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |
| | | | follow-up requirements).[c] | required (see Section 10.6.2).<br><br>IMP discontinuation required if any of the following occur:<br>• Study participant cannot comply with monitoring schedule.<br>• Liver chemistry values continue to increase.<br>• Liver chemistry values remain ≥5×ULN (and ≥2× Baseline) after 4 weeks of monitoring without evidence of resolution. | | chemistry values continue to increase.<br>After 2 weeks of monitoring liver chemistry values:<br>• ALT or AST remains ≥5×ULN to <8×ULN, IMP should be temporarily withheld, and study participant should undergo repeat test in 2 weeks.<br>• Continue IMP if ALT or AST values <5×ULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within Baseline values.<br>• If ALT or AST remains ≥5×ULN after second retest, immediate IMP discontinuation required.<br>• Continue to monitor until values normalize, stabilize, or return to within Baseline values.[e] |

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

## Table 10-3: Required investigations and follow up for PDILI

| Laboratory value | | | Immediate | | Follow up | |
|---|---|---|---|---|---|---|
| **ALT or AST** | **Total bilirubin** | **Symptoms[a] of hepatitis or hypersensitivity** | **Consultation requirements** | **Actions** | **Testing** | **Evaluation** |

[a] Hepatitis symptoms include fatigue, nausea, vomiting, and right upper quadrant pain or tenderness; hypersensitivity symptoms include eosinophilia, rash, and fever (without clear alternative cause).
[b] If the study participant also has ≥2×ULN ALP, the possibility of an indication of biliary obstruction should be discussed with the Medical Monitor.
[c] Details provided in Section 10.6.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist but may be a gastroenterologist.
[d] Details are provided in Section 10.6.2.
[e] Unless an alternative monitoring schedule is agreed by the Investigator and responsible UCB Study Physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and responsible UCB Study Physician, as needed.

### 10.6.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor or UCB Study Physician within 24 hours (eg, by laboratory alert), and the study participant must be discussed with the Medical Monitor or UCB Study Physician as soon as possible. If required, the study participant 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 10.6.3) and SAE report (if applicable).

### 10.6.2 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 7.1.1 and Table 10-3 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.

#### 10.6.2.1 IMP restart/rechallenge

Study participants who are immediately discontinued from IMP due to having met certain criteria for PDILI (as described in Section 7.1.1 and Table 10-3), but for whom an alternative diagnosis is confirmed, ie, drug-induced liver injury is excluded, can rarely restart IMP. Rechallenge with IMP can occur only if ALL of the following requirements are met:

- The results of additional testing and monitoring described in Section 10.6.3 and Section 7.1.1.1 confirm a nondrug-related cause for the abnormal hepatic laboratory parameters and any associated symptoms (ie, a subsequent alternative diagnosis fully explains the hepatic findings).
- No alternative treatment options are available to the study participant.
- The study participant has shown clear therapeutic benefit from the IMP.
- Study participant's ALT or AST elevations do not exceed ≥5×ULN.
- Study participant's total bilirubin is <2×ULN.
- Study participant has no signs or symptoms of hypersensitivity or hepatitis.
- The rechallenge is approved by the UCB Study Physician and a hepatologist. The hepatologist must be external to UCB. It is recommended that the hepatologist be a local hepatology expert or the hepatologist treating the study participant.
- Study participant agrees to the Investigator-recommended monitoring plan and understands his/her individual benefit/risk for restarting IMP and this is adequately documented.

### 10.6.3 Testing: identification/exclusion of alternative etiology

The measurements and additional information required for the assessment of PDILI events when there is a reasonable possibility that they may have been caused by the IMP are detailed in Table 10-4 (laboratory measurements) and Table 10-5 (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 study participant 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.

**Table 10-4: PDILI laboratory measurements**

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

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBcAb-IgM=anti-hepatitis B core antibody-IgM; HBsAg=hepatitis B surface antigen; IgM=immunoglobulin M; INR=international normalized ratio; PDILI=potential drug-induced liver injury; PK=pharmacokinetics; RNA=ribonucleic acid; ULN=upper limit of normal; WOCBP=woman of childbearing potential

[a] Tests in addition to the specified analytes may be performed based on the Investigator's medical judgment and study participant history.

[b] Measured only for study participants with ALT >8×ULN, 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, rash, and fever (without clear alternative cause).

[c] For WOCBP.

### Table 10-5: PDILI information to be collected

| New or updated information |
|---|
| • Concomitant prescriptions and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included. |
| • Pertinent medical history, including the following:<br>– History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis, or other "fatty liver disease")<br>– Adverse reactions to drugs<br>– Allergies<br>– Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency)<br>– Recent travel<br>– 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

## 10.7 Appendix 7: Medical device AEs, ADEs, SAEs, and device deficiencies: definition and procedures for recording, evaluating, follow up, and reporting

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the Investigator and the Sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of Sponsor medical devices.

### 10.7.1 Definition of AE and adverse device effect

| **AE and ADE Definition** |
|---|
| • An AE is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.<br>• An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device. |

### 10.7.2 Definition of SAE, SADE, and USADE

If an event is not an AE per definition above, then it cannot be a SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

| **A SAE is an AE that:** |
|---|
| a. Led to death |
| b. Led to serious deterioration in the health of the participant, that either resulted in:<br>1. A life-threatening illness or injury. The term life-threatening in the definition of serious refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.<br>2. A permanent impairment of a body structure or a body function.<br>3. Inpatient or prolonged hospitalization, planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a SAE.<br>4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function. |
| c. Led to fetal distress, fetal death, or a congenital abnormality or birth defect |
| **SADE definition** |
| • A SADE is defined as an ADE that has resulted in any of the consequences characteristic of a SAE. |
| **USADE definition** |
| • An unanticipated serious adverse device effect (USADE) is a SADE which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report (see Section 8.3.9). |

### 10.7.3 Definition of device deficiency

| **Device deficiency definition** |
|---|
| • A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling. |

### 10.7.4 Recording and follow up of AE and/or SAE and device deficiencies

**AE, SAE, and device deficiency recording**

- When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice, and on the appropriate form of the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to UCB in lieu of completion of the AE/SAE/device deficiency eCRF page.
- There may be instances when copies of medical records for certain cases are requested by UCB. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to UCB.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence. The Investigator should complete a Product Complaint Form for all reported device deficiencies.

**Assessment of intensity**

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.
- An event is defined as serious when it meets ≥1 of the predefined outcomes as described in the definition of a SAE, NOT when it is rated as severe.

**Assessment of causality**

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The Investigator will also consult the IB in his/her assessment.
- For each AE/SAE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which a SAE has occurred and the Investigator has minimal information to include in the initial report to UCB. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to UCB.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

**Follow up of AE/SAE/device deficiency**

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by UCB to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide UCB with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

## 10.8 Appendix 8: Rapid alert procedures

Not applicable.

## 10.9 Appendix 9: Country-specific requirements

Not applicable.

## 10.10 Appendix 10: Abbreviations and trademarks

| | |
|---|---|
| ADAb | antidrug antibody |
| ADE | adverse device effect |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AMS | Active Medication Set |
| AST | aspartate aminotransferase |
| BP | blood pressure |
| BSA | body surface area |
| CT | computed axial tomography |
| CI | confidence interval |
| CMH | Cochran-Mantel-Haenszel |
| COVID-19 | coronavirus disease 2019 |
| CPM | Clinical Project Manager |
| CRO | contract research organization |
| CSR | clinical study report |
| CV | cardiovascular |
| DLQI | Dermatology Life Quality Index |
| ECG | electrocardiogram |
| eCRF | electronic Case Report Form |
| ePRO | electronic patient-reported outcome |
| ES | Enrolled Set |
| FAS | Full Analysis Set |
| FSH | follicle stimulating hormone |
| GCP | Good Clinical Practice |
| GI | gastrointestinal |
| HBcAb | anti-hepatitis B core antibody |
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |

| | |
|---|---|
| HIV | human immunodeficiency virus |
| HLT | high level term |
| HRT | hormonal replacement therapy |
| IB | Investigator's Brochure |
| IBD | inflammatory bowel disease |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonisation |
| IEC | Independent Ethics Committee |
| IGA | Investigator's Global Assessment |
| IGA 0 | Investigator's Global Assessment response clear (0) with a ≥2-category improvement relative to Baseline |
| IGA 0/1 | Investigator's Global Assessment response clear (0) or almost clear (1) with a ≥2-category improvement relative to Baseline |
| IgG1 | immunoglobulin G1 |
| IGRA | interferon-gamma release assay |
| IL | interleukin |
| IMP | investigational medicinal product |
| IRB | Institutional Review Board |
| IRT | interactive response technology |
| LFT | liver function test |
| LLOQ | lower level of quantification |
| LTBI | latent tuberculosis infection |
| LOCF | last observation carried forward |
| mAb | monoclonal antibody |
| MAR | missing at random |
| MCMC | Markov-Chain Monte Carlo |
| MI | multiple imputation |
| *M. tuberculosis* | *Mycobacterium tuberculosis* |
| NRI | nonresponder imputation |
| NTMB | nontuberculous mycobacterium |
| P-SIM | Psoriasis-Symptom and Impact Measure |
| PASI | Psoriasis Area and Severity Index |

| | |
|---|---|
| PASI75/90/100 | 75% or greater/90% or greater/100% improvement from Baseline in the Psoriasis Area and Severity Index score |
| PD | pharmacodynamic(s) |
| PDILI | potential drug-induced liver injury |
| PEOT | Premature End of Treatment |
| PK | pharmacokinetic(s) |
| PK-PPS | Pharmacokinetics Per-Protocol Set |
| PPS | Per-Protocol Set |
| PRN | as needed, pro re nata |
| PS | Patient Safety |
| PsA | psoriatic arthritis |
| PSD | Patient Symptom Diary |
| PSO | psoriasis |
| Q4W | every 4 weeks |
| Q8W | every 8 weeks |
| QoL | quality of life |
| RS | Randomized Set |
| SADE | serious adverse device effect |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| sc | subcutaneous |
| SFU | Safety Follow-Up |
| SIB | suicidal ideation and behavior |
| SoA | Schedule of Activities |
| SOC | system organ class |
| SS | Safety Set |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| TEMA | treatment-emergent markedly abnormal |
| TNF | tumor necrosis factor |
| ULN | upper limit of normal |
| USADE | unanticipated serious adverse device effect |
| WOCBP | woman of childbearing potential |

## 10.11 Appendix 11: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

**Amendment 1 (08 Feb 2023)**

**Overall Rationale for the Amendment**

The original protocol dated 10 Oct 2022 was only distributed to vendors for study setup purposes; it was not shared with any regulatory agency.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis<br>1.2 Schema<br>4.1 Overall design<br>9.8 Determination of sample size | Increased number of study participants to be enrolled | Updated following discussions with CDE to provide sufficient safety exposures |
| 9.3 Planned efficacy/outcome analyses | Deleted protocol subsection 9.3.1 "efficacy estimands" from the document; subsequent subsections were renumbered | Updated to be consistent with terminology in global pivotal studies |
| 9.3.2.1 Sensitivity analyses<br>9.3.3.1 Key secondary efficacy endpoint analyses<br>9.6 Handling of dropouts or missing data | Added an additional sensitivity analysis for missing data | Added additional analyses applicable for the increased sample size |
| 9.6 Handling of dropouts or missing data | Added text to clarify planned sensitivity analyses | Updated to be consistent with terminology in global pivotal studies |
| 5.2 Exclusion Criteria (exclusion criteria #7) | Removed the term vulgaris | Clarified the exclusion criteria |
| 1.1 Synopsis<br>1.3 Schedule of activities<br>3 Objectives and endpoints | Added PSD (P-SIM) assessment to visit Week 32 and added PSD (P-SIM) assessment over time to tertiary objectives and endpoints | Updated to assess efficacy of bimekizumab after Q8W dosing |
| 9.7 Planned analysis and data monitoring | Changed the 16-week data analysis and respective CSR to a 32-week data analysis and CSR | Updated following discussions with CDE to assess efficacy of bimekizumab Q4W and Q8W dosing up to Week 32 |
| 1.1 Synopsis<br>1.2 Schema<br>1.3 Schedule of activities<br>4 Study design<br>6.1 Treatments administered | Replaced the 2-stage, 40-week Maintenance Treatment Period with a 16-week Maintenance Treatment Period | Bimekizumab treatment for 16 weeks in the Maintenance Treatment Period is sufficient to provide evidence for maintained efficacy and safety |

CDE=Center for Drug Evaluation; CSR=clinical study report; PSD=patient symptom diary; P-SIM=Psoriasis Symptom and Impact Measure; Q4W=every 4 weeks; Q8W=every 8 weeks

# 11 REFERENCES

Basra MK, Salek MS, Camilleri L, Sturkey R, Finlay AY. Determining the minimal clinically important difference and responsiveness of the Dermatology Life Quality Index (DLQI): further data. Dermatology. 2015;230(1):27–33.

Boehncke WH, Schön MP. Psoriasis. Lancet. 2015;386:983-94.

Christophers E, Barker JN, Griffiths CE, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. J Eur Acad Dermatol Venereol. 2010;24:548–54.

Ding X, Wang T, Shen Y, et al. Prevalence of psoriasis in China: a population-based study in six cities. Eur J Dermatol. 2012;22:663–7.

Dowlatshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. J Invest Dermatol. 2014;134:1542–51.

Feldman SR. A quantitative definition of severe psoriasis for use in clinical trials. J Dermatolog Treat. 2004;15(1):27–9.

Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. JAMA. 2006;296:1735–41.

Gisondi P, Tessari G, Conti A, et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol. 2007;157:68–73.

Gottlieb AB. Psoriasis: Emerging therapeutic strategies. Nat Rev Drug Discov. 2005;4:19–34.

Gottlieb AB, Ciaravino V, Cioffi C, Peterson L, Warren RB. Development and content validation of the Psoriasis Symptoms and Impacts Measure (P-SIM) for assessment of plaque psoriasis. Dermatol Ther (Heidelb). 2020 Dec;10(6):1255–72.

Hongbo Y, Thomas CL, Harrison MA, Salek MS, Finlay AY. Translating the science of quality of life into practice: What do dermatology life quality index scores mean? J Invest Dermatol. 2005 Oct;125(4):659–64.

International Council for Harmonisation [ICH] Addendum, 2019.

Krueger G, Koo J, Lebwohl M, Menter A, Stern RS, Rolstad T. The impact of psoriasis on quality of Life. Results of a 1998 National Psoriasis Foundation patient-membership survey. Arch Dermatol. 2001;137:280–4.

Li MJ, Wang P, Cai M, et al. Prevalence and risk factors of psoriasis in Hainan Province: an epidemiological survey. Chin J Dermatol. 2013;46:157–9.

Mallinckrodt CH, Lin Q, Lipkovich I, Molenberghs G. A structured approach to choosing estimands and estimators in longitudinal clinical trials. Pharm Stat. 2012;11:456-61.

Menter A, Gottlieb A, Feldman SR, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826–50.

Mukhtar R, Choi J, Koo JY. Quality of life issues in psoriasis. Dermatol Clin. 2004;22:389–95.

Ortonne JP. Redefining clinical response in psoriasis: targeting the pathological basis of disease. J Drugs Dermatol. 2004;3:13–20.

Rubin D.B. 1987. Multiple Imputation for Nonresponse in Surveys. New York: John Wiley and Sons.

Shao CG, Zhang GW, Wang GC. Distribution of psoriasis in China: a nationwide screening. Proceedings of the Chinese Academy of Medical Sciences and the Peking Union Medical College. 1987;2:59–65.

Wang RL, Cao LS, Zhou C, et al. Prevalence of 15 skin diseases in adolescents from Liangshan Prefecture in Sichuan Province. Chin J Dermatol. 2012;45:270–2.

World Health Organization. Global report on psoriasis. 2016. World Health Organization. https://apps.who.int/iris/handle/10665/204417.

Xu Y, Tong Z, Shen S. An epidemiological survey of psoriasis among rural residents in Suzhou, Anhui Province. Acta Universitatis Medicinalis Anhui. 2001;36:483–5.

Yeung H, Takeshita J, Mehta NN, et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA Dermatol. 2013;149:1173–9.

# 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, according to Clinical Trial Regulation EU 536/2014, and according to current Good Clinical Practice.

# Approval Signatures

**Name:** ps0041-protocol-amend-2

**Version:** 1.0

**Document Number:** CLIN-000223425

**Title:** PS0041 Protocol Amendment 2

**Approved Date:** 20 Apr 2023



| Document Approvals | |
|---|---|
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 20-Apr-2023 00:51:19 GMT+0000 |
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 20-Apr-2023 03:25:28 GMT+0000 |
| Approval<br>Verdict: Approved | Name: [redacted]<br>Capacity: Clinical<br>Date of Signature: 20-Apr-2023 06:52:42 GMT+0000 |