# A MULTICENTER, OPEN-LABEL, RANDOMIZED STUDY TO ASSESS THE PHARMACOKINETICS, SAFETY, AND EFFICACY OF TWO DOSES OF BIMEKIZUMAB IN ADOLESCENT STUDY PARTICIPANTS WITH MODERATE TO SEVERE PLAQUE PSORIASIS

# PROTOCOL PS0020 AMENDMENT 1

# PHASE 2

# SHORT TITLE:

An open-label, randomized study to evaluate the pharmacokinetics, safety, and efficacy of 2 doses of bimekizumab in adolescent study participants with moderate to severe plaque psoriasis

Sponsor:

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**Regulatory agency identifying number(s):**

| | |
|---|---|
| EudraCT Number: | 2020-001724-34 |
| IND Number: | 128707 |

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| Document History | | |
|---|---|---|
| **Document** | **Date** | **Type of amendment** |
| Original Protocol | 30 Jun 2020 | Not applicable |
| Amendment 1 | 10 Nov 2020 | Not applicable |

**Amendment 1 (**10 Nov 2020**)**

**Overall Rationale for the Amendment**

This amendment addresses recommendations from the Food and Drug Administration for the addition of screening and monitoring of suicidal ideation/behavior and depression, including the use of specific assessment scales. Additional changes include, but are not limited to, clarification of withdrawal criteria, clarification of footnotes in the Schedule of Activities, and updates to the planned analysis.

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 1.1 Synopsis, overall design section | In second bullet in list of study periods, sc added as administration route for bimekizumab. | Clarification |
| | In fourth paragraph, deleted “who do not tolerate IMP or” from second last section to be consistent with changes in withdrawal criteria. | Clarification |
| | In seventh paragraph, safety topics of interest, additional topics being monitored, and additional safety assessments were updated. | Clarification |
| 1.3 Schedule of Activities, Table 1-1 Schedule of Study Assessments – Initial Treatment Period | Added new row for C-SSRS. | Addition |
| | Added new row for PHQ-9. | Addition |
| | Footnote g has been revised to the type of samples to collect for viral antibodies. | Clarification |
| | Footnote i has been revised to clarify timing of recent radiograph of the chest prior to Screening. | Clarification |
| | New footnote l has been added to the Baseline (W0) column for the Hematology/chemistry/urine row to clarify performance of these assessments at this visit. | Clarification |

| | | |
|---|---|---|
| | Column heading changed from Screening (Day -35 to 0) to Screening (Day -35 to -10) and new footnote m has been added. | Correction to ensure time for shipping of IMP to site |
| 1.3 Schedule of Activities, Table 1-2 Schedule of Study Assessments – Open-label Extension Period | Added new row for C-SSRS. | Addition |
| | Added new row for PHQ-9. | Addition |
| 2.3 Benefit/risk assessment | In third paragraph, safety topics of interest, additional topics being monitored, and additional safety assessments were updated. | Clarification |
| | Measures to minimize burden of participation in the study have been added. | Addition |
| 4.1 Study design | In second bullet in list of study periods, sc added as administration route for bimekizumab. | Clarification |
| | In eighth paragraph, safety topics of interest, additional topics being monitored, and additional safety assessments were updated. | Clarification |
| 5.2 Exclusion criteria | Exclusion criterion 3, which excluded participants with a history of suicidality or depression, has been replaced with new exclusion criteria 30, 31, and 32. These have been added to incorporate SIB and depression scale scores and to clarify exclusion of participants with active suicidal ideation, positive suicide behavior, severe depression, or history of psychiatric inpatient hospitalization. | Clarification and addition |
| | Exclusion criterion 8, second bullet, has been renumbered as 8a. It has been changed to allow rescreening after completion of 8 weeks of prophylaxis, to delete the requirement for a washout period for prophylactic medication(s), and to provide a link to the definition for high risk of exposure to TB. | Clarification |
| | Exclusion criterion 20 been renumbered as 20a. It has been modified to specify conditions for administration of other vaccines. | Clarification |
| | Exclusion criterion 28 has been deleted. | Correction |

| | | |
|---|---|---|
| 5.4 Screen failures | First bullet has been changed to allow rescreening after completion of 8 weeks of prophylaxis and to delete the requirement for a washout period for prophylactic medication(s). | Clarification |
| 6.1 Treatments administered | Dose presentation row has been updated to reflect vial sizes and extractable volumes. | Correction |
| 6.5 Concomitant medications/treatments | A statement has been added that all concomitant medications will be recorded in the eCRF. | Clarification |
| 6.5.3 | New section specifying allowed and prohibited vaccines has been added. | Addition |
| 7.2 Participant discontinuation/withdrawal from study | A statement has been added for Investigator determination of balance of burden for each participant against the observed and anticipated clinical benefit, and to recommend study withdrawal if the benefit-risk balance is not favorable. | Addition |
| | Withdrawal criteria have been renumbered and clarified to specify those which require withdrawal of the study participant and those which may result in withdrawal of the study participant. | Clarification |
| | Withdrawal criteria have been updated to incorporate SIB and depression scale scores which may result or require withdrawal of the study participant. | Addition |
| 8.2.2, Vital signs | Pulse rate added as descriptor for heart rate. | Clarification |
| 8.2.4 Neuropsychiatric AE monitoring/suicidal risk monitoring | Text has been added to provide for a mental health professional (ie, licensed psychiatrist or clinical psychologist) to determine at Screening whether participants meeting certain thresholds on the C-SSRS or PHQ-9 assessments are eligible for participation. | Addition |
| | Text has been added to provide for referral to a mental health professional during the conduct of the study. | Addition |
| | Removed statement pertaining to external neuropsychiatric expert review of neurospychiatric AEs. | Clarification |
| 8.2.4.1 C-SSRS | Description of C-SSRS assessment has been added. | Addition |

| | | |
|---|---|---|
| Section 8.2.4.2 PHQ-9 | Description of PHQ-9 assessment has been added. | Addition |
| 8.2.5.2 Assessments at Screening | Specified that study participants will respond to TB questionnaire instead of completing it themselves. | Clarification |
| | Clarified that rescreening will be allowed after completion of 8 weeks of prophylaxis and deleted the requirement for a washout period for prophylactic medication(s). | Clarification |
| | Updated footnote to Table 8-1 to clarify that rescreening will be allowed after completion of 8 weeks of prophylaxis, to delete the requirement for a washout period for prophylactic medication(s), and to specify that the prophylaxis should be completed during the study. | Clarification. |
| 8.2.5.3.2 Chest x-ray for TB | Clarified timing of recent radiograph of the chest prior to Screening. | Clarification |
| 8.2.5.3.3 TB questionnaire | Clarified that Investigator will complete the TB questionnaire. | Clarification |
| 8.2.5.3.5 Latent TB | Clarified that rescreening will be allowed after completion of 8 weeks of prophylaxis and deleted requirement for a washout period for prophylactic medication(s). | Clarification |
| 8.3 Adverse events and serious adverse events | Added statement regarding public disclosure of AE and SAE results. | Addition |
| 8.3.7 Other safety topics of interest | Safety topics of interest updated to reflect monitoring of suicidal ideation/behavior. | Clarification |
| 8.4 Safety signal detection | Removed statement pertaining to external neuropsychiatric expert review of neurospychiatric AEs. | Clarification |
| 9.2.3.1 Efficacy estimands | Modified 4$^{th}$ item under estimand used to define the treatment effect of interest for the secondary efficacy endpoint Change from Baseline in CDLQI response at Week 16: | Clarification |
| 9.4.1.1 Adverse events | Updated MedDRA version number. | Correction |
| 9.4.1.6 C-SSRS | Planned summaries and listings for C-SSRS have been added. | Addition |
| 9.4.1.7 PHQ-9 | Planned analyses for PHQ-9 have been added. | Addition |

| | | |
|---|---|---|
| 10.1.6.2 Apps/Telehealth system | Removed TB questionnaire from electronic PRO bullet | Correction |
| 10.2, Appendix 2: Clinical laboratory tests, Table 10-1 | Removed FSH and estradiol assessment | Correction |
| | Specified collection of plasma sample for HIV antibody assessment at Screening. | Correction |
| 10.1.7 Source documents | Removed TB questionnaire from electronic PRO measures statements | Correction |
| Global | Weight-based changed to weight-categorized. | Clarification of terminology |
| Global | Correction of spelling, grammar, or typographical errors. | Correction |

# SERIOUS ADVERSE EVENT REPORTING

| Serious adverse event reporting (24h) | |
|---|---|
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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

**Protocol title:** A multicenter, open-label, randomized study to assess the pharmacokinetics, safety, and efficacy of two doses of bimekizumab in adolescent study participants with moderate to severe plaque psoriasis

**Short Title:** An open-label, randomized study to evaluate the pharmacokinetics, safety, and efficacy of 2 doses of bimekizumab in adolescent study participants with moderate to severe plaque psoriasis

**Rationale:** The purpose of the study is to evaluate the pharmacokinetics (PK), safety, and efficacy of bimekizumab in adolescent participants (from 12 to <18 years of age) and compare the exposure-response (E-R) relationship to the adult psoriasis (PSO) population. The results will be used to determine the optimal dosing of bimekizumab to be tested in pediatric participants from 6 to <18 years of age with moderate to severe plaque PSO in the subsequent Phase 3 efficacy and safety study (PS0021).

**Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the PK of bimekizumab administered subcutaneously (sc) in adolescents with moderate to severe plaque PSO | • Bimekizumab plasma concentrations |

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| • To evaluate the safety of bimekizumab in adolescents with moderate to severe plaque PSO | • Treatment-emergent adverse events (TEAEs)<br>• Serious TEAEs<br>• TEAEs leading to discontinuation of investigational medicinal product (IMP)<br>• TEAEs leading to withdrawal from the study<br>• Selected safety topics of interest (including infection [serious, opportunistic, fungal, and tuberculosis (TB)], inflammatory bowel disease [IBD], and injection site reactions) with onset occurring from day of first dose through 20 weeks after final dose of IMP adjusted by duration of participant exposure to IMP<br>• Change from Baseline in vital signs (systolic and diastolic blood pressure) at Week 16<br>• Change from Baseline in vital signs (heart rate) at Week 16<br>• Change from Baseline in physical examination findings reported as TEAEs with onset occurring from day of first dose through 20 weeks after final dose of IMP<br>• Change from Baseline in laboratory analyses (chemistry) at Week 16<br>• Change from Baseline in laboratory analyses (hematology) at Week 16<br>• Growth assessment, as assessed by the change in height from Baseline to Week 16<br>• Growth assessment, as assessed by the change in weight from Baseline to Week 16 |
| • To evaluate the efficacy of bimekizumab in adolescents with moderate to severe plaque PSO | • Psoriasis Area and Severity Index (PASI) 90 response at Week 16<br>• Investigator's Global Assessment (IGA) 0/1 response (Clear [0]/Almost Clear [1] with at least 2-category improvement from Baseline) at Week 16<br>• PASI75 response at Week 4 |
| • To evaluate the immunogenicity of bimekizumab in adolescents with moderate to severe plaque PSO | • Anti-bimekizumab antibody detection prior to and following IMP administration |

| Objectives | Endpoints |
|---|---|
| • To evaluate the change in quality of life in adolescents with moderate to severe plaque PSO | • Change from Baseline in Children's Dermatology Life Quality Index (CDLQI) response at Week 16 |
| **Other** | |
| • To assess the efficacy of bimekizumab over time in adolescents with moderate to severe plaque PSO | • PASI50 response over time<br>• PASI75 response over time<br>• PASI90 response over time<br>• PASI100 response over time<br>• Absolute and percent change from Baseline in PASI score over time<br>• IGA 0/1 response (with at least 2-category improvement from Baseline) over time<br>• IGA 0 response (with at least 2-category improvement from Baseline) over time<br>• Scalp-specific IGA (scalp IGA) response (Clear or Almost Clear with at least 2-category improvement from Baseline for participants with scalp PSO at Baseline) over time |
| • To assess the exposure (PK)-response relationship with selected clinical outcomes in adolescents with moderate to severe plaque PSO | • The relationship between plasma bimekizumab exposure and, though not limited to, the following clinical outcomes: PASI score over time, PASI change from Baseline, IGA score over time, IGA change from Baseline |
| • To assess the change in quality of life over time in adolescents with moderate to severe plaque PSO | • Change from Baseline in CDLQI response over time<br>• CDLQI 0/1 response over time |

## Overall Design

In this Phase 2, multicenter, randomized, open-label study, the PK, safety, and efficacy of bimekizumab in male and female adolescents (from 12 to <18 years of age) with moderate to severe plaque PSO will be assessed.

The PK, safety, and efficacy of bimekizumab will be evaluated by treating at least 20 participants in each of 2 dose groups (for a total of at least 40 participants evaluable for PK). Both doses are expected to be efficacious based on E-R predictions. Dose A (320mg every 4 weeks [Q4W] in participants ≥65kg and 160mg Q4W in participants <65kg) is predicted to provide the same systemic bimekizumab exposure as the 320mg Q4W adult dose, and Dose B (64mg Q4W in participants ≥65kg and 32mg Q4W in participants <65kg) is aimed at providing a

lower systemic bimekizumab exposure. Weight-categorized dosing during the Initial Treatment Period will be based on the participant's weight at Baseline.

This study will consist of the following periods (as shown in the study schematic in Section 1.2):

- Screening Period: up to 5 weeks
- Initial Treatment Period: 20 weeks (5 doses of bimekizumab; administered sc at Weeks 0 [Baseline], 4, 8, 12, and 16 followed by 4 weeks of observation)
- Open-label Extension (OLE) Period: 104 weeks (bimekizumab administration starts at Week 20 if participant is eligible, as defined below)
- Safety Follow-up (SFU) Period: 20 weeks after the final dose of bimekizumab

After the Screening Period of up to 5 weeks, eligible participants will be randomized to 1 of the 2 dose groups. The randomization will be stratified by weight category. During the Initial Treatment Period, participants will receive 5 doses of open-label bimekizumab (at Weeks 0 [Baseline], 4, 8, 12, and 16). Participants who complete the Initial Treatment Period, tolerate the treatment, and achieve an IGA response ≤2 at Week 20 may continue bimekizumab treatment at the same dose level in the OLE Period. All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information. Upon identification of the PS0021 dose, study participants in PS0020 may switch to the PS0021 dose at the Investigator's discretion during the 104-week OLE Period. Participants who have an IGA response ≥3 (on a scale from 0 to 4) at Week 20 will be withdrawn from the study. Each participant will complete the SFU Period of 20 weeks following his/her final dose of bimekizumab (see study schematic in Section 1.2).

During the Initial Treatment Period, IMP will be administered by a health care professional at the study site. In the OLE Period, Dose A and Dose B may be administered at the study site or at home, as indicated in the Schedule of Activities (Table 1-2). Home visits are encouraged during the OLE Period upon agreement of the Investigator, study participant, and his/her caregiver. Dose A of the IMP may be administered by a health care professional, caregiver, or the study participant (once he/she becomes 18 years of age). Administration of Dose A by the caregiver or study participant is optional and requires training, as discussed in Section 6.2. If Dose A is administered by a caregiver or a participant at home, the visit will be conducted via a telehealth system, as described in Section 10.1.6.2. Dose B will be administered by a health care professional, whether at home or at the study site, to ensure accurate dosing of the lower volume of IMP.

The end of the study is defined as the date of the last participant's last visit. The study design of PS0020 provides participants who are receiving benefit from bimekizumab therapy with the opportunity to receive active treatment for a total of 120 weeks.

Safety assessments will be made by ongoing monitoring and evaluation of adverse events (AEs), including safety topics of interest specific to bimekizumab. Safety topics of interest for this study include infections (serious, opportunistic, fungal, and TB), IBD, and injection site reactions. Additionally, in keeping with the conduct of the adult bimekizumab program, the following topics will also be closely monitored: neutropenia, hypersensitivity (including anaphylaxis),

major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and suicidal ideation/behavior [SIB]. Additional safety assessments will include physical examinations (including growth assessments), pregnancy testing for female participants of childbearing potential, and screening for neuropsychiatric AEs.

An independent external Data Monitoring Committee (DMC) will periodically review and monitor safety data from this study, as described in Section 8.4. An IBD Adjudication Committee will also periodically review data from this study. Details will be provided in the IBD Adjudication Committee charter.

**Number of Participants**

Approximately 58 participants will be screened to achieve at least 40 participants randomly assigned to IMP for an estimated total of 20 evaluable participants per dose group. A participant will be considered evaluable if he/she receives IMP and provides at least 1 sample for PK analyses.

**Treatment Groups and Duration**

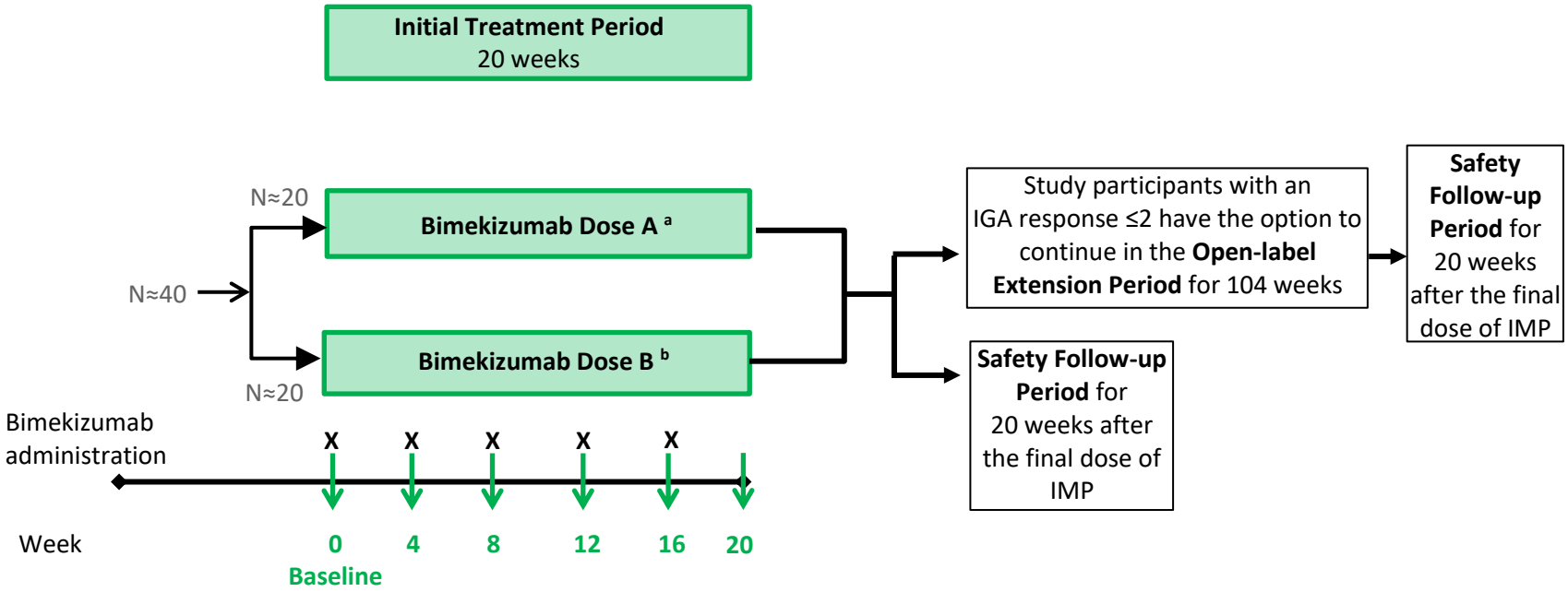
Participants will be randomized 1:1 to 2 dose groups; both doses are expected to be efficacious based on E-R predictions. Dose A (320mg Q4W in participants ≥65kg and 160mg Q4W in participants <65kg) is predicted to provide the same systemic bimekizumab exposure as the 320mg Q4W adult dose, and Dose B (64mg Q4W in participants ≥65kg and 32mg Q4W in participants <65kg) is aimed at providing a lower systemic bimekizumab exposure based on E-R predictions. Weight-categorized dosing during the Initial Treatment Period will be based on the participant's weight at Baseline.

The randomization will be stratified by weight category.

For each participant, the total duration of the study (including the Screening, Initial Treatment, OLE, and SFU Periods) will be up to 145 weeks.

## 1.2 Schema

### Figure 1-1: Study schematic




**Dose A:** 320mg Q4W in participants ≥65kg and 160mg Q4W in participants <65kg
**Dose B:** 64mg Q4W in participants ≥65kg and 32mg Q4W in participants <65kg
Weight-categorized dosing during the Initial Treatment Period will be based on the participant's weight at Baseline.

IGA=Investigator's Global Assessment; IMP=investigational medicinal product; OLE=Open-label Extension; PK=pharmacokinetics; Q4W=every 4 weeks
Note: All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information. Upon identification of the PS0021 dose, study participants in PS0020 may switch to the PS0021 dose at the Investigator's discretion during the 104-week OLE Period.
Note: Participants who do not tolerate the IMP or who have an IGA response ≥3 (on a scale from 0 to 4) at Week 20 will be withdrawn from the study.
[a] Dose A is predicted to provide the same systemic bimekizumab exposure as the 320mg Q4W adult dose.
[b] Dose B is aimed at providing a lower systemic bimekizumab exposure than Dose A.

## 1.3 Schedule of Activities

### Table 1-1: Schedule of study assessments – Initial Treatment Period

| Visit [a]/ Week / Protocol activity | Screening (Day -35 to -10)[m] | Initial Treatment Period | | | | | | | SFU W36[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline W0 | W1 | W4 | W8 | W12 | W16 | W20/ EDV[c] | |
| Written informed consent/assent | X | | | | | | | | |
| Inclusion/exclusion criteria | X | X | | | | | | | |
| Demographic data | X | | | | | | | | |
| Psoriasis history | X | | | | | | | | |
| Significant past medical history and concomitant diseases | X | | | | | | | | |
| Physical examination [d] | X | X | | | | | X | X | X |
| Weight | X | X | | X | | X | X | X | X |
| Height | X | X | | | | | X | X | X |
| Vital signs (heart rate/blood pressure/temperature) [e] | X | X | | X | X | X | X | X | X |
| Hematology/chemistry/urine [f] | X | X[l] | X | | | X | X | X | X |
| Plasma for BKZ concentration and anti-BKZ antibodies | | X | X | X | X | X | X | X | X |
| Hepatitis B and C and HIV testing [g] | X | | | | | | | | |
| Pregnancy testing [h] | X | X | | X | X | X | X | X | X |
| Chest X-ray [i] | X | | | | | | | | |
| Tuberculosis test (IGRA) [j] | X | | | | | | | | |
| Tuberculosis questionnaire | X | X | | | | | X | | X |
| BSA | X | X | X | X | X | X | X | X | X |

## Table 1-1: Schedule of study assessments – Initial Treatment Period

| Visit [a]/ Week / Protocol activity | Screening (Day -35 to -10)[m] | Initial Treatment Period | | | | | | | SFU W36[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline W0 | W1 | W4 | W8 | W12 | W16 | W20/ EDV[c] | |
| PASI | X | X | X | X | X | X | X | X | X |
| IGA | X | X | X | X | X | X | X | X | X |
| CDLQI | | X | | X | X | X | X | X | |
| Scalp IGA [k] | | X | | X | X | X | X | X | |
| C-SSRS | X | X | | X | X | X | X | X | X |
| PHQ-9 | X | X | | X | X | X | X | X | |
| Adverse events | X | X | X | X | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X | X | X | X | X |
| IVRS/IWRS | X | X | X | X | X | X | X | X | X |
| IMP administration | | X | | X | X | X | X | | |

AE=adverse event; BSA=body surface area; BKZ=bimekizumab; CDLQI=Children's Dermatology Life Quality Index; eCRF=electronic Case Report Form; C-SSRS=electronic Columbia Suicide Severity Rating Scale; EDV=Early Discontinuation Visit; HIV =human immunodeficiency virus; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IVRS=interactive voice response system; IWRS=interactive web response system; OLE=Open-label Extension; PASI=Psoriasis Area and Severity Index; PHQ-9=Patient Health Questionnaire 9; scalp IGA=scalp-specific Investigator's Global Assessment; SFU=safety follow up; W=week

[a] Visit windows of ±3 days.

[b] If participant is not eligible for the OLE Period at Week 20 or does not wish to continue into the OLE Period.

[c] The EDV is only needed if the participant is not entering the OLE Period.

[d] Physical examination findings (Week 0 to Week 20) that are clinically significant will be recorded as AEs.

[e] Pulse, systolic/diastolic blood pressure, and temperature are to be measured prior to IMP administration and prior to any blood collection.

[f] Analyses will be performed by a central laboratory, except urine dipsticks, which will be assessed locally at the site. Participants do not have to be fasting.

[g] Serum samples will be obtained for the hepatitis B and hepatitis C assessment. A plasma sample will be obtained for the HIV assessment. The HIV test results will not be recorded in the eCRF.

[h] Pregnancy testing for postmenarchal female participants. Serum testing by central laboratory at Screening and urine testing locally at the site for all other time points.

## Table 1-1: Schedule of study assessments – Initial Treatment Period

| Visit [a]/ Week / Protocol activity | Screening (Day -35 to -1)[m] | Initial Treatment Period | | | | | | | SFU W36[b] |
|---|---|---|---|---|---|---|---|---|---|
| | | Baseline W0 | W1 | W4 | W8 | W12 | W16 | W20/ EDV[c] | |

[i] If a participant has had a recent radiograph of the chest within approximately 6 months prior to Screening, this may be used in lieu of the protocol-required radiograph.

[j] The IGRA testing is required to be performed by the central laboratory.

[k] Scalp IGA to be completed for all participants at Baseline. Post-Baseline scalp IGA will only be completed for participants with a scalp IGA score >0 at Baseline.

[l] Hematology, chemistry, and urinalysis will only be performed at Baseline if, in the Investigator's opinion, there is a change in the study participant's status compared with the Screening Visit.

[m] Screening must be completed 10 days prior to the Baseline Visit to allow time for shipping of IMP to the site.

## Table 1-2: Schedule of study assessments – Open-label Extension Period

| Week [a] / Protocol activity | OLE Period | | | | | | | | | | | | | | | | | | | | | | | | | SFU [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | W20 | W24 [c] | W28 | W32 [c] | W36 [c] | W40 | W44 [c] | W48 [c] | W52 | W56 [c] | W60 [c] | W64 | W68 [c] | W72 [c] | W76 | W80 [c] | W84 [c] | W88 | W92 [c] | W96 [c] | W100 | W104 [c] | W108 [c] | W112 | W116 [c] | W120 [c] | W124/EDV | |
| Physical examination [d] | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| Weight | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| Height | X | | | | | | | | | | | X | | | | | | | | | | | | | | | X | X |
| Vital signs (heart rate/blood pressure/ temperature) [e] | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| Hematology/ chemistry/urine [f] | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |

## Table 1-2: Schedule of study assessments – Open-label Extension Period

| Week [a] / Protocol activity | OLE Period | | | | | | | | | | | | | | | | | | | | | | | | | | | SFU [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | W20 | W24 [c] | W28 | W32 [c] | W36 [c] | W40 | W44 [c] | W48 [c] | W52 | W56 [c] | W60 [c] | W64 | W68 [c] | W72 [c] | W76 | W80 [c] | W84 [c] | W88 | W92 [c] | W96 [c] | W100 | W104 [c] | W108 [c] | W112 | W116 [c] | W120 [c] | W124/EDV | |
| Plasma for BKZ concentration and anti-BKZ antibodies | X | | | | | X | | | | | | X | | | | | | X | | | | | | X | | | X | X |
| Pregnancy testing [g] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Tuberculosis test (IGRA) [h] | | | X | | | | | | | | | | | | X | | | | | | | | | | | | X | |
| Tuberculosis questionnaire | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| BSA | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| PASI | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| IGA | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| CDLQI | X | | X | | | | | | X | | | | | | X | | | | | | X | | | | | | X | |
| Scalp IGA [i] | X | | X | | | | | | X | | | | | | X | | | | | | X | | | | | | X | |
| C-SSRS | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| PHQ-9 | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| IVRS/IWRS | X | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | | | X | X |
| IMP administration [j] | X [k] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |

AE=adverse event; BKZ=bimekizumab; BSA=body surface area; CDLQI=Children's Dermatology Life Quality Index; C-SSRS=electronic Columbia Suicide Severity Rating Scale; EDV=Early Discontinuation Visit; IGA=Investigator's Global Assessment; IGRA=interferon-gamma release assay;

## Table 1-2: Schedule of study assessments – Open-label Extension Period

| Protocol activity \ Week [a] | OLE Period | | | | | | | | | | | | | | | | | | | | | | | | | | SFU [b] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | W20 | W24 [c] | W28 | W32 [c] | W36 [c] | W40 | W44 [c] | W48 [c] | W52 | W56 [c] | W60 [c] | W64 | W68 [c] | W72 [c] | W76 | W80 [c] | W84 [c] | W88 | W92 [c] | W96 [c] | W100 | W104 [c] | W108 [c] | W112 | W116 [c] | W120 [c] | W124/EDV | |

IMP=investigational medicinal product; IVRS=interactive voice response system; IWRS=interactive web response system; OLE=Open-label Extension; PASI=Psoriasis Area and Severity Index; PHQ-9=Patient Health Questionnaire 9; PK=pharmacokinetics; scalp IGA=scalp-specific Investigator's Global Assessment; SFU=safety follow up; W=week

Note: All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information. Upon identification of the PS0021 dose, study participants in PS0020 may switch to the PS0021 dose at the Investigator's discretion during the 104-week OLE Period.

Note: A participant's weight-categorized dose may only be changed during the OLE Period after assessment of weight change by the Investigator at a scheduled clinic visit and if the participant's weight crosses the 65kg boundary at 2 consecutive weight assessments. If a participant's body weight decreases from the ≥65kg to <65kg group during the OLE Period, the participant should be discussed with the Medical Monitor to determine whether a dose adjustment is needed.

[a] Visit windows of ±5 days.

[b] Safety Follow-up Visit should occur 20 weeks after the final dose of IMP.

[c] This visit may be conducted at home. Home visits are encouraged during the OLE Period upon agreement of the Investigator, study participant, and his/her caregiver and may be conducted by a health care professional or via a telehealth system. For IMP administration at home, see footnote j.

[d] Physical examination findings that are clinically significant will be recorded as AEs.

[e] Pulse, systolic/diastolic blood pressure, and temperature are to be measured prior to IMP administration and any blood collection.

[f] Analyses will be performed by a central laboratory, except urine dipsticks, which will be assessed locally at the site. Participants do not have to be fasting.

[g] Pregnancy testing for postmenarchal female participants via urine testing locally (or at home). Pregnancy test results at home will be monitored via a telehealth system or, if present, by the visiting health care professional.

[h] IGRA testing is required to be performed by the central laboratory.

[i] Post-Baseline scalp IGA will only be completed for participants with a scalp IGA score >0 at Baseline.

[j] Dose A and Dose B may be administered at the study site or at home. If the Investigator deems it appropriate, a participant receiving Dose A may self-administer IMP (once he/she has become 18 years of age) or have a caregiver administer IMP at home visits during the OLE Period. Administration of Dose A by the participant or caregiver is optional; a health care professional will also be available to administer IMP at the participant's home, as needed. Caregivers and study participants must undergo appropriate training prior to administering Dose A, as described in Section 6.2. If Dose A is administered by a caregiver or a participant at home, the visit will be monitored via a telehealth system. Dose B must be administered by a health care professional, whether at home or at the study site, to ensure accurate administration of the lower volume of IMP. If IMP is administered at home, the administration will be documented as described in Section 6.2.1.

[k] Investigational medicinal product will only be administered at Week 20 if the participant continues into the OLE Period.

# 2 INTRODUCTION

## 2.1 Study rationale

Psoriasis is a common, chronic inflammatory disease characterized by a series of linked cellular changes in the skin. Though the pathophysiology of PSO is not fully understood, the importance of T-cells and inflammatory cytokines has been demonstrated by the clinical benefit provided by therapies directed at these targets (Krueger and Ellis, 2005). While antibodies targeting interleukin (IL)-17A cytokines have demonstrated efficacy in patients with PSO, psoriatic arthritis (PsA), and ankylosing spondylitis, as yet, no approved therapeutic approach selectively and potently inhibits the activity of both IL-17A and IL-17F. Bimekizumab, a monoclonal antibody (mAb) of immunoglobulin G1 (IgG1), potently and selectively binds and neutralizes IL-17A (IL-17A), IL-17F, and IL-17AF cytokines. Bimekizumab is being developed for the treatment of adults with moderate to severe plaque PSO. Parallel programs in the inflammatory diseases of PsA, axial spondyloarthritis, and hidradenitis suppurativa are ongoing.

The purpose of the study is to evaluate the PK, safety, and efficacy of bimekizumab in adolescent (from 12 to <18 years of age) participants and to assess the E-R/efficacy relationship relative to the adult PSO population. Data from this study will be used to determine the bimekizumab dosing regimen to be assessed in pediatric participants from 6 to <18 years of age with moderate to severe plaque PSO in the subsequent Phase 3 efficacy and safety study (PS0021).

## 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. Plaque PSO can affect people of any age, and the pathophysiology and presentation are essentially similar in adult and pediatric patients (Raychaudhuri and Gross, 2000). However, lesions are often smaller, less scaly, and thinner in pediatric patients than in the adult population, and scalp and facial involvement may be more common in pediatric patients (Feldman, 2015). Pediatric patients may also have impaired health-related quality of life from their PSO, particularly with respect to emotional, social, and school functioning (Varni et al, 2012).

Psoriasis affects approximately 3% of the adult US population (Rachakonda et al, 2014; Kurd and Gelfand, 2009). Although it can begin at any age, incidence rates peak in the third decade, and again around the fifth to sixth decade of life (Parisi et al, 2013; Icen et al, 2009; Farber and Nall, 1974). Plaque PSO comprises approximately 80% to 90% of all cases. Approximately 17% of patients with plaque-type PSO have moderate to severe disease (Kurd et al, 2008).

There is a paucity of data on the epidemiology of PSO in the pediatric population (18 years of age and younger) and much of the epidemiology of PSO in pediatric patients references all variants of the disease (plaque, guttate, pustular, inverse, and erythrodermic PSO). Psoriasis represents approximately 4% of all dermatoses in the pediatric population, and the US prevalence of pediatric PSO is estimated at 0.3% (Parisi et al, 2013; Wu et al, 2011). The most common type of pediatric PSO is plaque PSO, and approximately 68% to 75% of pediatric patients have this form of the disease (Lara-Corrales et al, 2011; Tollefson et al, 2010).

Because there are few studies that delineate between the types of pediatric PSO, estimates include all variants of PSO in this population, unless otherwise noted. The most cited study of the incidence of PSO in pediatric patients was a population-based study in Olmsted County, Minnesota covering the period from 1970 to 1999. The age- and sex-adjusted annual incidence of PSO in the pediatric population was 40.8 per 100,000, and most incident patients (74%) had plaque PSO (Tollefson et al, 2010). When the diagnosis was restricted to dermatologist-confirmed PSO only, the annual incidence was found to be 33.2 per 100,000 (95% confidence interval [CI]: 29.3, 37.0) (Tollefson et al, 2010). The age- and sex-specific incidence did not appear to increase rapidly before age 7 in either boys or girls and appeared to plateau after age 7. In this study, the annual incidence of PSO in the pediatric population increased over time (29.6/100,000 pediatric patients from 1970 to 1974 compared with 62.7/100,000 pediatric patients from 1995 to 1999).

Overall and age-specific prevalence of pediatric PSO were analyzed using insurer provider data in Germany (Augustin et al, 2010). The prevalence identified was 0.71% among covered participants aged 0 to 18 years. Age-specific prevalence rates revealed a linear increasing prevalence of PSO from the age of 1 year (0.12%) to the age of 18 years (1.24%) (Augustin et al, 2010). Comparatively, Wu et al, 2011 examined electronic medical records among the US population of Southern California and identified a prevalence rate of 0.3% for potential PSO cases; however, that declined to 0.19% once cases were confirmed through medical record review (Wu et al, 2011). Calculations utilizing data obtained in Wu et al, 2011 estimate the prevalence of PSO among patients age 2 to 5 years old to be 0.034%.

Studies debate the existence of "two incidence peaks" or bimodal age of onset. The proposed first peak is in late adolescence, before 20 years of age, and the other peak is in adulthood (Shah, 2013; Tollefson et al, 2010). The exact time of this early "incidence peak" is not very well documented, but the mean age of onset of pediatric patients with PSO varies from 8 to 11 years of age (Shah, 2013; Lara-Corrales et al, 2011; Tollefson et al, 2010). In the population-based study of pediatric patients in Olmsted County, the median age of diagnosis was 10.6 years (Tollefson et al, 2010).

Bimekizumab is a humanized, full-length mAb of 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 distinctly different 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). 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).

## 2.3 Benefit/risk assessment

The benefits and risks of bimekizumab administration in pediatric study participants are expected to be similar to adult study participants, given that the pathophysiology and presentation are essentially similar in adult and pediatric patients (Raychaudhuri and Gross, 2000).

In studies of bimekizumab in adults with PSO, study participants achieved and maintained skin clearance across multiple efficacy variables, as assessed by PASI (change from Baseline and by various levels of response) and IGA responses, after up to 60 weeks of treatment across a range of doses administered Q4W and every 8 weeks (Q8W) sc. The observed safety data in adults

with PSO were as expected considering the mechanism of action of bimekizumab and the population under investigation. The vast majority of AEs were nonserious, mild to moderate, and did not lead to IMP discontinuation. The most commonly reported TEAEs in bimekizumab-treated study participants were nasopharyngitis, oral candidiasis, and upper respiratory tract infection.

Safety topics of interest for this study include infections (serious, opportunistic, fungal, and TB), IBD, and injection site reactions. Additionally, in keeping with the conduct of the adult bimekizumab program, the following topics will also be closely monitored: neutropenia, hypersensitivity (including anaphylaxis), major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and SIB. Safety topics of interest are defined as events for which special monitoring, additional data collection activities, and/or enhanced signal detection activities (within UCB) are applied. Safety topics of interest are based on findings from the clinical program with bimekizumab or molecules with a related mechanism of action, potential risks generally associated with biologic immunomodulators, or comorbidities and risk factors prevalent in the study population. Additional safety assessment will include physical examinations (including growth assessments), pregnancy testing for female participants of childbearing potential, and screening for neuropsychiatric AEs.

The potential risks to adolescent participants in this study include exposure to bimekizumab, with the potential for AEs. The 2 selected dosing regimens have been well-tolerated by adult study participants with PSO, and permit quantification of plasma concentrations. Additional design measures to minimize the burden of participating in this clinical study include: no exposure to placebo, both dose regimens anticipated to provide efficacy that is equivalent to or better than standard of care, and the allowance of permitted concomitant treatment options. The PS0020 study design further ensures that adolescents not benefitting from study participation are withdrawn quickly (ie, if IGA is ≥3 at Week 20) so that they can receive the appropriate alternate therapy outside of the study. A DMC will monitor safety and assess the benefit-risk balance throughout the conduct of the study.

Subcutaneous injection and blood collection may cause distress, pose risks, and are a potential burden to participants. The collection of blood samples and volumes has been minimized to alleviate distress, burden, and risks to participants as much as possible (eg, butterfly needles), and by allowing Screening safety laboratory assessments to be used as Baseline assessments. The blood sampling scheme was designed to collect the minimum number of blood samples needed to accurately and completely describe the PK of bimekizumab. This minimizes the number of venipunctures and the total volume of blood collected from each participant during the study. The planned total blood volumes collected for this study will not exceed the limits recommended in the Ethical Considerations for Clinical Trials on Medicinal Products conducted with the Paediatric Population (European Union, 2008).

Investigational sites selected for participation in PS0020 will employ Investigators and personnel who are experienced and well-trained to conduct research studies. Furthermore, they will be experienced in dermatology and in International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulated clinical research.

Investigators are expected to continually assess the balance of burden to each participant against the observed and anticipated clinical benefit, and to recommend study withdrawal if the benefit-risk balance is not favorable.

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

# 3 OBJECTIVES AND ENDPOINTS

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To assess the PK of bimekizumab administered subcutaneously (sc) in adolescents with moderate to severe plaque PSO | • Bimekizumab plasma concentrations |
| **Secondary** | |
| • To evaluate the safety of bimekizumab in adolescents with moderate to severe plaque PSO | • Treatment-emergent adverse events (TEAEs)<br>• Serious TEAEs<br>• TEAEs leading to discontinuation of investigational medicinal product (IMP)<br>• TEAEs leading to withdrawal from the study<br>• Selected safety topics of interest (including infection [serious, opportunistic, fungal, and tuberculosis (TB)], inflammatory bowel disease [IBD], and injection site reactions) with onset occurring from day of first dose through 20 weeks after final dose of IMP adjusted by duration of participant exposure to IMP<br>• Change from Baseline in vital signs (systolic and diastolic blood pressure) at Week 16<br>• Change from Baseline in vital signs (heart rate) at Week 16<br>• Change from Baseline in physical examination findings reported as TEAEs with onset occurring from day of first dose through 20 weeks after final dose of IMP<br>• Change from Baseline in laboratory analyses (chemistry) at Week 16<br>• Change from Baseline in laboratory analyses (hematology) at Week 16<br>• Growth assessment, as assessed by the change in height from Baseline to Week 16<br>• Growth assessment, as assessed by the change in weight from Baseline to Week 16 |

| Objectives | Endpoints |
|---|---|
| • To evaluate the efficacy of bimekizumab in adolescents with moderate to severe plaque PSO | • Psoriasis Area and Severity Index (PASI) 90 response at Week 16<br>• Investigator's Global Assessment (IGA) 0/1 response (Clear [0]/Almost Clear [1] with at least 2-category improvement from Baseline) at Week 16<br>• PASI75 response at Week 4 |
| • To evaluate the immunogenicity of bimekizumab in adolescents with moderate to severe plaque PSO | • Anti-bimekizumab antibody detection prior to and following IMP administration |
| • To evaluate the change in quality of life in adolescents with moderate to severe plaque PSO | • Change from Baseline in Children's Dermatology Life Quality Index (CDLQI) response at Week 16 |
| **Other** | |
| • To assess the efficacy of bimekizumab over time in adolescents with moderate to severe plaque PSO | • PASI50 response over time<br>• PASI75 response over time<br>• PASI90 response over time<br>• PASI100 response over time<br>• Absolute and percent change from Baseline in PASI score over time<br>• IGA 0/1 response (with at least 2-category improvement from Baseline) over time<br>• IGA 0 response (with at least 2-category improvement from Baseline) over time<br>• Scalp-specific IGA (scalp IGA) response (Clear or Almost Clear with at least 2-category improvement from Baseline for participants with scalp PSO at Baseline) over time |
| • To assess the exposure (PK)-response relationship with selected clinical outcomes in adolescents with moderate to severe plaque PSO | • The relationship between plasma bimekizumab exposure and, though not limited to, the following clinical outcomes: PASI score over time, PASI change from Baseline, IGA score over time, IGA change from Baseline |
| • To assess the change in quality of life over time in adolescents with moderate to severe plaque PSO | • Change from Baseline in CDLQI response over time<br>• CDLQI 0/1 response over time |

# 4 STUDY DESIGN

## 4.1 Overall design

In this Phase 2, multicenter, randomized, open-label study, the PK, safety, and efficacy of bimekizumab in male and female adolescents (from 12 to <18 years of age) with moderate to severe plaque PSO will be assessed.

The purpose of the study is to evaluate the PK, safety, and efficacy of bimekizumab in adolescent participants and compare the PK and E-R relationship to the adult PSO population. The results will be used to determine the optimal dosing of bimekizumab to be tested in pediatric participants from 6 to <18 years of age with moderate to severe plaque PSO in the Phase 3 efficacy and safety study (PS0021).

The PK, safety, and efficacy of bimekizumab will be evaluated by treating at least 20 participants in each of 2 dose groups (for a total of at least 40 participants evaluable for PK). A participant will be considered evaluable if he/she receives IMP and provides at least 1 sample for PK analysis. Two doses were selected and both are expected to be efficacious based on E-R predictions. Dose A (320mg Q4W in participants ≥65kg and 160mg Q4W in participants <65kg) is predicted to provide the same systemic bimekizumab exposure as the 320mg Q4W adult dose, and Dose B (64mg Q4W in participants ≥65kg and 32mg Q4W in participants <65kg) is aimed at providing a lower systemic bimekizumab exposure. Weight-categorized dosing during the Initial Treatment Period will be based on the participant's weight at Baseline.

This study will consist of the following periods (as shown in the study schematic in Section 1.2):

- Screening Period: up to 5 weeks
- Initial Treatment Period: 20 weeks (5 doses of bimekizumab; administered sc at Weeks 0 [Baseline], 4, 8, 12, and 16 followed by 4 weeks of observation)
- Open-label Extension Period: 104 weeks (bimekizumab administration starts at Week 20 if participant is eligible, as defined below)
- Safety Follow-up Period: 20 weeks after the final dose of bimekizumab

After the Screening Period of up to 5 weeks, eligible participants will be randomized to 1 of the 2 dose groups. The randomization will be stratified by weight category. During the Initial Treatment Period, participants will receive 5 doses of open-label bimekizumab (at Weeks 0 [Baseline], 4, 8, 12, and 16). Participants who complete the Initial Treatment Period, tolerate the treatment, and achieve an IGA response ≤2 at Week 20 may continue bimekizumab treatment at the same dose level in the OLE Period. All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information. Upon identification of the PS0021 dose, study participants in PS0020 may switch to the PS0021 dose at the Investigator's discretion during the 104-week OLE Period. Participants who do not tolerate the IMP or who have an IGA response ≥3 (on a scale from 0 to 4) at Week 20 will be withdrawn from the study. Each participant will complete the SFU Period of 20 weeks following his/her final dose of bimekizumab (see study schematic in Section 1.2).

During the Initial Treatment Period, IMP will be administered by a health care professional at the study site. In the OLE Period, Dose A and Dose B may be administered at the study site or at home. Home visits are encouraged during the OLE Period upon agreement of the Investigator, study participant, and his/her caregiver. Dose A of the IMP may be administered by a health care professional, caregiver, or study participant (once he/she becomes 18 years of age). Administration of Dose A by the caregiver or study participant is optional and requires training, as discussed in Section 6.2. If Dose A is administered by a caregiver or a participant at home, the visit will be conducted via a telehealth system, as described in Section 10.1.6.2. Dose B will be administered by a health care professional, whether at home or at the study site, to ensure accurate dosing of the lower volume of IMP. Planned IMP administration is described in the Schedule of Activities (Table 1-1 and Table 1-2) and in Section 6.2.

The end of the study is defined as the date of the last participant's last visit. The study design of PS0020 provides participants who are receiving benefit from bimekizumab therapy with the opportunity to receive active treatment for a total of 120 weeks.

Safety assessments will be made by ongoing monitoring and evaluation of adverse events (AEs), including safety topics of interest specific to bimekizumab. Safety topics of interest for this study include infections (serious, opportunistic, fungal, and TB), IBD, and injection site reactions. Additionally, in keeping with the conduct of the adult bimekizumab program, the following topics will also be closely monitored: neutropenia, hypersensitivity (including anaphylaxis), major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and SIB. Additional safety assessments will include physical examinations (including growth assessments), pregnancy testing for female participants of childbearing potential, and screening for neuropsychiatric AEs.

Selected data from this study will be reviewed periodically to detect as early as possible any safety concern(s) related to the IMP (see Section 8.4). An independent external DMC will also periodically review and monitor safety data from this study. The membership of the DMC is discussed in Section 9.7.2 and details will be provided in a separate DMC charter. An IBD Adjudication Committee will also periodically review data from this study. Details will be provided in the IBD Adjudication Committee charter.

## 4.2 Scientific rationale for study design

The bimekizumab pediatric PSO program is based on a clinical development principle of partial extrapolation, whereby an initial extrapolation of efficacy in adults is made to efficacy in a pediatric population based on matching PK exposures. The extrapolation is then confirmed in a clinical efficacy study in pediatric participants. During discussions of this program, the Paediatric Committee of the European Medicines Agency recommended that adolescents be studied first to establish safety before evaluating younger patients. PS0020 will therefore be conducted in adolescent participants (from 12 to <18 years of age), and the study will be used to inform the data required in younger participants and to further support an extrapolation approach. Consequently, data from PS0020 will be used to confirm the dosing regimen for the Phase 3 efficacy and safety study (PS0021).

PS0021 will be the pivotal study of bimekizumab in the pediatric PSO population (participants aged from 6 to <18 years). Since the purpose of PS0020 is to derive PK data in the pediatric

population prior to conducting PS0021, administration of placebo and treatment blinding of PS0020 is not deemed necessary.

Male and female adolescents with moderate to severe plaque PSO who meet all inclusion criteria and who do not meet any of the exclusion criteria will be eligible for this study. The inclusion and exclusion criteria are designed to ensure the safety of study participants and to enroll a broad adolescent population able to provide adequate PK data for understanding bimekizumab dosing requirements in pediatric PSO, as well as to gain insight into clinical response to bimekizumab in this population.

## 4.3 Justification for dose

Two sc bimekizumab dosing regimens will be evaluated in PS0020 and both are expected to be efficacious based on E-R predictions. Participants in the Dose A group will receive 320mg Q4W for body weight ≥65kg and 160mg Q4W for body weight <65kg. Participants in the Dose B group will receive 64mg Q4W for body weight ≥65kg and 32mg Q4W for body weight <65kg. Dose A is predicted to provide the same systemic bimekizumab exposure as the 320mg Q4W adult dose, and Dose B is aimed at providing a lower systemic bimekizumab exposure.

Bimekizumab doses for PS0020 have been selected using PK and E-R modeling of adult PSO data, with the aim of matching systemic bimekizumab exposures in adolescents with that in adults. Population models developed based on data from adult study participants with PSO in Phase 2 and Phase 3 studies were used for this purpose. Simulations of a realistic adolescent population (with real age-body weight-height distributions based on the National Health and Nutrition Examination Survey database) were performed from the allometrically scaled PK model. The PS0020 regimens were also supported by predicted efficacy outcomes (PASI75/90/100 [ie, at least 75%, 90%, or 100% improvement from Baseline in PASI] and IGA 0/1) from the adult E-R models, premised on the assumption that a similar level of bimekizumab exposure will result in similar response rates across both age populations.

Given the range of adolescent body sizes to be recruited in PS0020, PK simulations demonstrated that, within each dose group (Dose A or B), separate bimekizumab doses for a specified body weight cutoff would result in a lower variation of predicted bimekizumab concentrations relative to the targeted geometric mean concentrations for the adult bimekizumab dose in PSO (320mg Q4W). Thus, each PS0020 dose group will have separate doses based on 2 body weight categories. The derived body weight cutoff for the 2 body weight categories was found to be 65kg. The simulations also found that additional body weight cutoffs within each PS0020 dose group did not improve the variability of predicted adolescent exposures relative to the targeted exposure.

A participant’s weight-categorized dose may only be changed during the OLE Period after assessment of weight change by the Investigator at a scheduled clinic visit and if the participant's weight crosses the 65kg boundary at 2 consecutive weight assessments. If a participant’s body weight decreases from the ≥65kg to <65kg group during the OLE Period, the participant should be discussed with the Medical Monitor to determine whether a dose adjustment is needed. See Section 6.6 for dose modification details.

## 4.4 End of study definition

A participant will be considered to have completed the study as follows:

- For participants who do not enter the OLE: Completion is defined as completion of the Screening Period, the Initial Treatment Period, and the SFU Visit.
- For participants who enter the OLE: Completion is defined as completion of all periods of the study (ie, Screening Period, Initial Treatment Period, OLE Period, and the SFU Visit).

The end of the study is defined as the date of the last participant's last 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

Participants will be eligible to be included in the study only if all of the following criteria apply:

### Age

1. Participant must be ≥12 to <18 years of age at the time of signing the informed consent/assent according to local regulation.

### Type of participant and disease characteristics

2. Participant has had a diagnosis of moderate to severe plaque PSO for at least 3 months prior to the Screening Visit and:
    - Body surface area (BSA) affected by PSO ≥10%
    - IGA score ≥3 (on a scale from 0 to 4)
    - PASI score ≥12 OR
    - PASI score ≥10 plus at least 1 of the following:
        i. Clinically relevant facial involvement
        ii. Clinically relevant genital involvement
        iii. Clinically relevant hand and foot involvement
3. Participant must be candidate for systemic PSO therapy and/or photo/chemotherapy.
4. Participant has no other medical condition (including other dermatological conditions) that would preclude participation/assessment in the study, as determined by medical evaluation including medical history, physical examination, chest X-ray, and laboratory tests during the Screening Period.

### Weight

5. Body weight ≥30kg and body mass index for age percentile of ≥5 at Baseline.

### Sex

6. Male or female

   - A female participant will be eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least 1 of the following conditions applies:

     – Not a woman of childbearing potential (WOCBP) as defined in Appendix 4.

     OR

     – A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 during the Initial Treatment Period, the OLE Period, and for at least 20 weeks after the final dose of IMP.

     Note: A female participant who becomes menarchal during the study must also agree to follow the contraceptive guidance in Appendix 4 during the Initial Treatment Period, the OLE Period, and for at least 20 weeks after the final dose of IMP.

### Informed consent

7. Capable of giving/having parent(s) or legal representative provide signed informed consent/assent (where appropriate) as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the Informed Consent Form (ICF) and assent and in this protocol.

## 5.2 Exclusion criteria

Participants will be excluded from the study if any of the following criteria apply:

**Medical conditions**

1. Participant or his/her parent(s)/legal representative has any medical or psychiatric condition, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study.
2. Participant has a history of alcohol or drug abuse within the previous 6 months.
3. Criterion deleted.
4. Participant has a known hypersensitivity to any components of the IMP as stated in this protocol.
5. Participant has clinically significant multiple or severe drug allergies (including to other humanized mAbs) or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis).
6. Participant has a presence of guttate, inverse, pustular, or erythrodermic PSO or other dermatological condition that may impact the clinical assessment of PSO.
7. Participant has a history of IBD or symptoms suggestive of IBD.

8a. Participant has any of the following:

   - Known active TB disease.

- History of active TB involving any organ system unless adequately treated according to World Health Organization/Centers for Disease Control therapeutic guidance and proven to be fully recovered upon consult with a TB specialist.
- Latent TB infection (LTBI). Participants with LTBI diagnosed during Screening must have completed 8 weeks of prophylaxis prior to rescreening. Prophylaxis should be in accordance with applicable clinical guidelines and TB specialist judgment based on the origin of infection.
- High risk of exposure to TB infection (refer to Section 8.2.5.1 for definition of high risk of exposure to TB infection).
- Current pulmonary nontuberculous mycobacterial (NTMB) infection, or history of pulmonary NTMB unless proven to be fully recovered.

  Note: For further information relating to definitions of known active TB, past history of TB, LTBI, high risk of acquiring TB infection, and NTMB infection refer to Section 8.2.5.

9. Participant has an active infection or history of infections as follows:
   - Any active 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 Baseline visit.
   - A history of opportunistic, recurrent, or chronic infections that, in the opinion of the Investigator, might cause this study to be detrimental to the participant. Opportunistic infections are infections caused by uncommon pathogens (eg, *Pneumocystis jirovicii*, cryptococcosis) or unusually severe infections caused by common pathogens (eg, cytomegalovirus, herpes zoster).
10. Participant has any congenital or hereditary immunodeficiency syndrome (eg, severe combined immunodeficiency, Job's syndrome).
11. Participant has had major surgery (including joint surgery) within the 3 months prior to the Baseline Visit or has planned major surgery within 6 months after entering the study.
12. Participant has a history of, or suspected, lymphoproliferative disease or history of, or suspected, malignancy of any organ system within the past 5 years.
13. Participant has alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) >2.0x upper limit of normal (ULN).
14. Participant has bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
15. Participant has current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

    For randomized 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 participant has ALT, AST, or ALP values that are >ULN but do 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 participant must be discussed with the Medical Monitor.

Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. The results should be discussed with the Medical Monitor and, provided the Investigator has an understanding of the temporary elevation, the participant may be enrolled. This includes rescreening.

16. Participant has laboratory abnormalities at Screening, including any of the following:
    - White blood cell (WBC) count <$3.00x10^3/\mu L$.
    - Absolute neutrophil count <$1.5x10^3/\mu L$.
    - Lymphocyte count <500 cells/μL.
    - Hemoglobin <8.5g/dL.
    - Any other laboratory abnormality, which, in the opinion of the Investigator, will prevent the 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 for confirmation during the Screening Period. Upon retesting, participants whose results remain outside this threshold should not be randomized.

**Prior/Concomitant therapy**

17. Participant has previously participated in this study or has received bimekizumab in another study.
18. Participant has received drugs listed in Table 5-1 outside the specified timeframes relative to the Baseline Visit or receives prohibited concomitant treatments (see Section 6.5.2).

### Table 5-1: Exclusions for prior treatments

| Drug class | Dose | Washout period relative to Baseline Visit |
|---|---|---|
| Systemic retinoids | Any dose | 4 weeks |
| Systemic treatment (non-biological)<br>Systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)<br>Systemic fumarate/fumaric esters specifically used for treatment of PSO<br>Systemic corticosteroids<br>Photo/chemotherapy | Any dose | 4 weeks |
| Anti-TNFs<br>Adalimumab | Any dose | |

**Table 5-1: Exclusions for prior treatments**

| Drug class | Dose | Washout period relative to Baseline Visit |
|---|---|---|
| Infliximab, golimumab, certolizumab pegol (including biosimilars for any of these anti-TNFs)<br>Etanercept (including biosimilar) | | 12 weeks for infliximab, golimumab, adalimumab, certolizumab pegol<br>4 weeks for etanercept |
| Other biologics and other systemic therapies:<br>Ustekinumab<br>Briakinumab<br>Apremilast, tofacitinib<br>Alefacept, efalizumab, guselkumab<br>Rituximab | Any dose | <br>24 weeks for ustekinumab and briakinumab<br>2 weeks for apremilast/tofacitinib<br>12 weeks for alefacept, efalizumab, and guselkumab<br>52 weeks for rituximab |
| Anti-IL-17 therapy (including ixekizumab and secukinumab) | Any dose | 12 weeks (any prior use of bimekizumab is excluded) |
| Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved) | Any dose | 12 weeks (or 5 half-lives, whichever is longer) |
| Topical agents (except as outlined in Section 6.5.1)<br>Topical corticosteroids for dermatological use<br>Vitamin D analogs, topical retinoids, and topical calcineurin inhibitors<br>Keratolytics and coal tar | Any dose | 2 weeks |
| Any other topical antipsoriatic agent under investigation | Any dose | 4 weeks |

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

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

20a. Participant has received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline Visit (eg, inactivated vaccines such as influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted). Live vaccines are not allowed during the study, including the SFU Period (20 weeks after the final dose of IMP). Administration of any other vaccine not mentioned above may be allowed following discussion with the Medical Monitor.

21. Participant has received Bacillus Calmette-Guerin vaccination within 1 year prior to IMP administration.

**Prior/Concurrent clinical study experience**

22. Participant has participated in another study of an IMP (and/or an investigational device) within the previous 3 months or 5 half-lives (whichever is longer) prior to the Baseline Visit, or is currently participating in another study of an IMP (and/or an investigational device).

**Diagnostic assessments**

23. Participant has positive human immunodeficiency virus antibody test.
24. Participant has presence of hepatitis B surface antigen or hepatitis B core antibody at Screening.
25. Participant has positive hepatitis C antibody test result at Screening or within 3 months prior to starting IMP. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C ribonucleic acid (RNA) test is obtained.
26. Participant has positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of IMP. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.
    - Participants with chronic stable hepatitis C (eg, presence of positive hepatitis C RNA test result at Screening or within 3 months prior to first dose of IMP) should generally be excluded. Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled only if a confirmatory negative hepatitis C RNA test is obtained.
    - NOTE: The hepatitis C antibody test is a standard test used at screening to determine eligibility, and hepatitis C RNA testing is optional and only performed when the antibody test is positive in order to consider participants with positive hepatitis C antibody test for enrollment into the study. Where hepatitis C RNA testing is unavailable, a positive hepatitis C antibody test will be used for exclusion.

**Other exclusions**

27. Participant is part of the 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.
28. Criterion deleted
29. Participant has sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study.
30. Presence of active suicidal ideation, or positive suicide behavior as evidenced by any of the following criteria:
    - Participant has been diagnosed with suicidal behavior within the previous 6 months

- Suicidal ideation in the past 6 months prior to the Screening Visit as indicated by a positive response ("Yes") to either Question 4 or Question 5 of the “Baseline/Screening” version of the C-SSRS.
  - Participants with a lifetime history of suicidal ideation or behavior (more than 6 months prior to the Screening Visit) will be evaluated by a mental healthcare practitioner (ie, licensed psychiatrist or clinical psychologist) to determine whether they are eligible for participation.

31. Participant has been diagnosed with severe depression in the past 6 months, or has presence of moderately severe major depression or severe major depression as indicated by a score ≥15 using the Patient Health Questionnaire 9 (PHQ-9).
    - Participants with a screening PHQ-9 score of 10 to 14, will be referred to a mental healthcare practitioner (ie, licensed psychiatrist or clinical psychologist) to determine whether they are eligible for participation.
32. History of psychiatric inpatient hospitalization within the past year before enrolling into the study.

## 5.3 Lifestyle restrictions

No lifestyle restrictions are required.

## 5.4 Screen failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently randomized to IMP. A minimal set of screen failure information is required to ensure transparent reporting of screen failure 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 serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after consultation with the Medical Monitor. Rescreened participants should be assigned a new participant number. Reasons for rescreening include, but are not limited to, the following:

- Study participant needs to complete 8 weeks of prophylaxis for LTBI prior to rescreening described in the exclusion criteria (Section 5.2).
- Individual laboratory screening tests for which the results are exclusionary can be retested. For example, tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation; however, the Investigator will need to discuss with the Medical Monitor to help understand the elevation before the participant can be enrolled. Test can also be repeated during rescreening. Repetition of laboratory screening tests within the Screening Period for other than technical reasons (eg, frozen sample, expired laboratory kit) may not be performed without approval by Medical Monitor.
- Eligibility assessments could not be completed as planned (eg, for technical reasons) within the defined Screening Period of 5 weeks without approval by Medical Monitor.

- Participant does not meet the required washout period for concomitant medications.

# 6 STUDY TREATMENTS

Study treatment 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

| **ARM Name** | Dose A | Dose B |
|---|---|---|
| **Intervention name** | Bimekizumab | Bimekizumab |
| **Type** | Biologic | Biologic |
| **Dose presentation** | 1mL PFS (not less than 1.0mL extractable volume) | 2mL vial (not less than 1.0mL extractable volume) |
| **Unit dose strength(s)** | 160mg/mL | 160mg/mL |
| **Dosage level(s)** [a] | Dose A, administered Q4W, will be based on weight at Baseline<br>320mg in participants ≥65kg and 160mg in participants <65kg | Dose B, administered Q4W, will be based on weight at Baseline<br>64mg in participants ≥65kg and 32mg in participants <65kg |
| **Dose administration performed by** | Health care professional,<br>caregiver (once training is received), or<br>study participant (once he/she becomes 18 years of age and training is received) | Health care professional (in order to ensure accuracy as this dose is drawn up from a vial) |
| **Route of administration** | sc injection | sc injection |
| **Use** | Open-label | Open-label |
| **IMP and NIMP** | IMP | IMP |
| **Sourcing** | Provided centrally by the Sponsor | Provided centrally by the Sponsor |
| **Packaging and labeling** | Study intervention will be provided in PFS. Each PFS will be labeled as required per country requirement. | Study intervention will be provided in vials. Each vial will be labeled as required per country requirement. |

IMP=investigational medicinal product; NIMP=non-investigational medicinal product; OLE=Open-label Extension; PFS=prefilled syringe; Q4W=every 4 weeks; sc=subcutaneous

NOTE: For both Dose A and Dose B, IMP administration is to occur at the site in the Initial Treatment Period and may occur at home or at the site in the OLE Period.

[a] Dose modifications are allowed, as described in Section 6.6.

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

For the first 5 doses of IMP (during the Initial Treatment Period), a health care professional at the study site 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. In the OLE Period, Dose A and Dose B may be administered at the study site or at home, as indicated in the Schedule of Activities (Table 1-2). Home visits are encouraged during the OLE Period upon agreement of the Investigator, study participant, and his/her caregiver. Dose A of the IMP may be administered by a health care professional or caregiver or self-administered by the study participant (once he/she becomes 18 years of age). Dose B will be administered by a health care professional, whether at home or at the study site, to ensure accurate dosing of the lower volume of IMP (Table 1-1 and Table 1-2). Training to administer Dose A of the IMP will be provided by qualified study personnel at least 2 visits prior to the first visit at which IMP is planned to be administered by the caregiver or study participant (once ≥18 years of age). During the next visit, the caregiver/study participant will perform administration under the supervision of a health care professional to ensure that IMP is being properly and safely injected.

Once study participants/caregivers are determined by the Investigator (or designee) to be trained, they will receive the required number of syringes to perform administration of Dose A at home. Study participants who are unable or unwilling to self-administer (once he/she becomes 18 years of age) or who do not have a caregiver to administer IMP will not be discontinued; such study participants may have IMP administered by a health care professional at the site or at home. In the case of home administration, dates, body locations, kit numbers, and time of administration will be documented, and IMP administration by a caregiver or participant will be monitored via a telehealth system.

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

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

Only participants enrolled in the study may receive IMP and only authorized site staff/health care professional may supply 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.

In addition, the Investigator (or designee) will instruct the health care professional, caregiver, or study participant on how to handle the IMP during transport and how to store the IMP following the instruction guide. Cooler bags with freezer packs will be provided. Additional information will be provided in the IMP Handling Manual.

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).

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

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.

The date, body location, kit number, and time of administration of IMP will be documented. All used syringes (Dose A and B) and vials (Dose B only) will be disposed of by the health care professional, caregiver, or study participant in a disposal (sharps) container directly after the administration. The Investigator (or designee) is responsible for retaining all used, unused, and partially used containers of IMP until returned or destroyed.

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

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

Periodically, and/or after completion of the clinical phase of the study, all used (including empty containers)/partially used, unused, damaged, and/or expired IMP must be reconciled and either destroyed at the site according to local laws, regulations, and UCB Standard Operating Procedures 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

This is an open-label study; however, the specific intervention to be taken by a participant will be randomly assigned using an interactive voice response system (IVRS)/interactive web response system (IWRS). The site will contact the IVRS/IWRS prior to the start of IMP administration for each participant. The site will record the intervention assignment on the applicable eCRF, if required. Participant randomization will be produced by the IVRS/IWRS vendor. The randomization will be stratified by weight category.

Investigational medicinal product will be dispensed at the study visits summarized in the Schedule of Activities (Table 1-1 and Table 1-2).

Returned IMP should not be re-dispensed to the participants.

## 6.4 Treatment compliance

During the Initial Treatment Period, IMP will be administered by a health care professional and compliance will be determined at the visit by the health care professional. Drug accountability must be recorded on the Drug Accountability Form.

During the OLE Period (ie, after Week 20), at-home injections of Dose A may be possible and can be administered by a health care professional or caregiver or self-administered by the study participant (once ≥18 years of age), as detailed in Section 6.2. Dates, body locations, kit numbers, and time of administration will be documented, and IMP administration by a caregiver

or participant will be monitored via a telehealth system. Dose B will be administered by a health care professional, to ensure accurate dosing of the lower volume of IMP, at home or at the study site. All used syringes (Dose A and Dose B) and vials (Dose B only) will be disposed of as detailed in Section 6.2.1. Home administration documentation should be reviewed by the Investigator.

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

## 6.5 Concomitant medications/treatments

All concomitant medications and interventions administered during the study will be recorded on the appropriate eCRF pages.

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

The use of concomitant medications for medical conditions (eg, diabetes, acute infections) or treatment of an AE is permitted during this study as long as medications are not explicitly prohibited by the protocol.

The following concomitant medications are permitted during the study:

- Nonsteroidal anti-inflammatory drugs, acetaminophen, paracetamol, and opioids, as appropriate for the study participant.
- Keratolytics and coal tar for PSO in the OLE Period (ie, from Week 20 onwards).
- Study participants may continue to use topical moisturizers or emollients, bath oils, or oatmeal bath preparations for skin conditions during the study, as needed.
- As needed (PRN) use of mild (Class VII) to moderate (Class IV) potency topical corticosteroids for PSO is permitted in the OLE Period (ie, from Week 20 onwards) at the Investigator's discretion.
- As needed (PRN) use of treatment for scalp PSO, such as shampoo. If this treatment contains a corticosteroid, it must adhere to the guidance for topical corticosteroids outlined in the above bullet.
- Vitamin D analogs, topical retinoids, and topical calcineurin inhibitors (if appropriate for the participant) for PSO during the OLE Period (ie, from Week 20 onwards).

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

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

The following concomitant medications and therapies are prohibited during the study:

- Systemic agents:
  - Systemic retinoids
  - Systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine)
  - Systemic fumarate

  - Systemic corticosteroids
  - Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol is approved)
- Photo/chemotherapy
- Biologic therapies (other than bimekizumab)
- Topical agents for dermatologic use:
  - High potency topical corticosteroids (Class I, II, and III)
  - Any other antipsoriatic agent (topical) under investigation
  - Mild (Class VII) to moderate (Class IV) potency topical corticosteroids before Week 20
  - Keratolytics and coal tar for PSO before Week 20
  - Vitamin D analogs, topical calcineurin inhibitors, and topical retinoids for PSO before Week 20

### 6.5.3 Vaccines

Administration of live (including attenuated) vaccines is not allowed during the conduct of the study and for 20 weeks after the final dose of IMP.

Administration of inactivated vaccines is allowed during the study at the discretion of the Investigator.

Administration of any other vaccine not mentioned above may be allowed following discussion with the Medical Monitor.

## 6.6 Dose modification

Dose modification during the study may occur under restricted circumstances.

No dose modifications are allowed during the Initial Treatment Period.

In the OLE Period (at Week 20 or later), participants whose weight increases to the next body weight category (ie, from <65kg to ≥65kg) will be administered the corresponding dose for ≥65kg body weight regardless of weight at Baseline. To prevent unnecessary switching of participants between weight categories, this change may only occur during the OLE Period after assessment of weight change by the Investigator at a scheduled clinic visit that is maintained for 2 consecutive weight assessments.

In the OLE Period, if a participant's body weight decreases from the ≥65kg to <65kg group, the participant should be discussed with the Medical Monitor to determine whether a dose adjustment is needed.

Once a study participant enters the OLE Period, and once the bimekizumab dose for PS0021 (the Phase 3 efficacy and safety study) has been selected, a study participant may switch to the selected PS0021 dose at the Investigator's discretion.

## 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 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

Study participants will be scheduled to have the SFU Visit 20 weeks after the final injection of IMP (the final dose of IMP may be administered in the Initial Treatment Period or in the OLE Period). During the SFU, if study participants' PSO deteriorates, the Investigator may consider standard of care for PSO treatment after discussion with the Medical Monitor or UCB Study Physician. Note that the half-life of bimekizumab must be considered in selection of appropriate PSO treatments during the SFU Period. All concomitant medications and PSO interventions administered during the SFU will be recorded on the appropriate eCRF pages.

# 7 DISCONTINUATION OF STUDY MEDICATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of study medication

Investigational medicinal product should be stopped if the study participant develops a medical condition, AE, or laboratory abnormality that, in the opinion of the Investigator, compromises the safety of the study participant or his/her ability to continue participation in the study.

In particular, IMP must be stopped if the study participant meets a laboratory value meeting stopping criteria (Section 7.1.1 and Section 7.1.2) or in situations described in Section 7.2.

Study participants who are permanently discontinued from IMP should be encouraged by the Investigator to return for all scheduled visits through Week 20 and should be asked to return for a SFU Visit 20 weeks after the final dose of IMP. Any study participant who discontinues IMP but continues in the study should be discussed with the Medical Monitor or UCB Study Physician.

In all cases, the study participant should be followed until the condition has resolved, and the Investigator should make an effort to reach the participant, as described in Section 7.3. Investigators should contact the Medical Monitor and/or UCB Study Physician, in advance whenever possible, to discuss potential withdrawal of a study participant.

### 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.

#### 7.1.1.1 PDILI discontinuation criteria

The PDILI criteria below require immediate and permanent discontinuation of IMP for study participants with either of the following:

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

The PDILI criterion below requires immediate discontinuation of IMP for:

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

If a nondrug-related cause for the symptoms can be confirmed, these study participants may resume IMP administration after discussion with the Medical Monitor and/or UCB Study Physician, but only when the requirements for rechallenge with IMP as provided in Section 10.6.2 are followed.

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

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

Evaluation of PDILI must be initiated as described in Appendix 6 (Section 10.6) with repeat tests performed in 2 weeks. Upon re-test, if ALT or AST values have reduced to <5xULN, the study participant can continue with the study. However, if ALT or AST remains ≥5xULN and <8xULN after re-test, IMP should be temporarily withheld and study participant should undergo a repeat test in 2 weeks. If ALT or AST values remain ≥5xULN even after the second re-test, then the study participant should be permanently withdrawn from IMP and should be followed for possible PDILI.

If study participants are 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.

#### 7.1.1.1.1 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10-2. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB Study Physician, as needed.

### 7.1.2 Clinical laboratory criteria

Study participants should be monitored for absolute neutrophil count $<1.0x10^3/\mu L$ and/or absolute lymphocyte count $<0.2x10^3/\mu L$.

Participants 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 participant must be withdrawn. If the repeat absolute neutrophil count or absolute lymphocyte count is above the allowable values, the participant may continue in the study.

### 7.1.3 Treatment interruptions/temporary discontinuation of study medication

Doses of IMP that were missed due to a reasonable interfering AE or exceptional circumstance, which does not allow administration of IMP due to safety reasons, will not result in the study participant being considered noncompliant. The AE or exceptional circumstance should be discussed immediately with the Medical Monitor.

Any considerations related to restarting IMP should be discussed with the Medical Monitor.

## 7.2 Participant discontinuation/withdrawal from the study

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

A 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.

Investigators are expected to continually assess the balance of burden to each participant against the observed and anticipated clinical benefit, and to recommend study withdrawal if the benefit-risk balance is not favorable.

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

If a 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 Schedule of Activities (Table 1-1 and Table 1-2) for data to be collected at the time of early discontinuation (Early Discontinuation Visit [EDV]) and follow up (SFU) and for any further evaluations that need to be completed.

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

Participants must be withdrawn from the study if any of the following events occur:

1. Participants **must be referred** immediately to a mental healthcare practitioner (ie, licensed psychiatrist or clinical psychologist) for further assessment of any SIB and/or any evidence of major depression, if any of the following events occur:
   - Active suicidal ideation as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the C-SSRS
   - Any suicidal behavior since last visit
   - Severe depression as indicated by a PHQ-9 score ≥20

   The mental health consultation will be documented in source documentation.
2. Participant or legal representative withdraws consent/assent to participate in the study.
3. There is confirmation of a pregnancy in a female study participant, as evidenced by a positive pregnancy test during the study. (For further information see Section 8.3.5.)
4. The Sponsor or a regulatory agency requests withdrawal of the participant.
5. Participant has a diagnosis of active TB, an NTMB infection, or LTBI during the study. (For further information see Section 8.2.5.3.7.)
6. Participant has an IGA response ≥3 (on a scale from 0 to 4) at Week 20.

Investigators should contact the Medical Monitor to discuss whether a participant is to be withdrawn from the study if any of the following events occur:

7. Participant develops an illness that would interfere with his/her continued participation.
8. Participant or caregiver is noncompliant with the study procedures or medications in the opinion of the Investigator.
9. Participant takes prohibited concomitant medications as defined in this protocol (Section 6.5.2).
10. Participant does not tolerate the IMP.
11. Study participants **must be referred** immediately to a mental healthcare practitioner (ie, licensed psychiatrist or clinical psychologist) and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk for either of the following:
    - Active suicidal ideation as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the C-SSRS.
    - Moderately severe major depression as indicated by a PHQ-9 score of 15 to 19 if this represents an increase of 3 points compared to last visit.

    The mental health consultation will be documented in source documentation.

## 7.3 Lost to follow up

A participant will be considered lost to follow up if he or 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 participant fails to return to the clinic for a required study visit:

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

Should the 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 Schedule of Activities (Table 1-1 and Table 1-2). An unscheduled visit(s) can be conducted if necessary.

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 participant should continue or discontinue IMP.

Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.

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

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or Baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed the maximum volume of blood as specified by IRB/IEC requirements. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## 8.1 Efficacy assessments

All efficacy assessments are considered appropriate for, and applicable to, adolescents.

### 8.1.1 Psoriasis Area and Severity Index

The PASI is the most commonly used and validated assessment for grading the severity of PSO in clinical studies (Feldman, 2004). The PASI quantifies the severity and extent of the disease and weighs these with the percentage of BSA involvement. The PASI will be completed as specified in Table 1-1 and Table 1-2. The PASI will be completed by the Investigator electronically.

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

The Investigator assesses the average redness, thickness, and scaliness of lesions in each body area (each on a 5-point scale); 0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked.

The PASI score ranges from 0 to 72 with a higher score indicating increased disease severity.

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

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

### 8.1.2 Investigator's Global Assessment

A static IGA for PSO will be used to assess disease severity in all participants during the study. The IGA will be completed as specified in Table 1-1 and Table 1-2. The IGA will be completed by the Investigator electronically.

The Investigator will assess the overall severity of PSO using the following 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 Children's Dermatology Life Quality Index

The CDLQI is a questionnaire designed to measure the impact of skin diseases on the lives of children. The questionnaire consists of 10 questions that are based on the experiences of children with skin disease. The instrument asks participants about symptoms and feelings, leisure, school or holidays, personal relationships, sleep, and treatment. The questions relate to the impact of the skin disease on the child over the last week, (ie, over the last 7 days). The CDLQI score ranges from 0 to 30 with higher scores indicating lower health related QOL. Participants will be asked to complete the CDLQI as outlined in the Schedule of Activities (Table 1-1 and Table 1-2). The CDLQI will be completed via an app, as discussed in Section 10.1.6.2.

The CDLQI has been validated from the age of 4 years to 16 years. It is possible that the Dermatology Life Quality Index (DLQI) could be used for participants ≥17 years of age. However, using 2 assessments (CDLQI and DLQI) would generate data that could not be pooled across all participants when assessing changes from Baseline. Additionally, studies have indicated that although the CDLQI is not validated in adolescents ≥17 years of age, the CDLQI scores and associated meaning bands have been shown appropriate in the context of parallel use of DLQI and may actually be more sensitive in detecting low levels of impact (van Geel et al, 2016). These findings, coupled with the small number of participants in the study and potential data analysis complications that would be introduced by the use of 2 patient-reported outcome (PRO) instruments, indicates that the use of a single tool (CDLQI) for all study participants is the most appropriate, and as a result only the CDLQI will be used in this study.

The change from Baseline in CDLQI response and the proportion of study participants having a CDLQI total score of 0 or 1 will be assessed.

### 8.1.4 Scalp IGA

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

The scalp IGA will be assessed for all participants at Baseline. The scalp IGA will be completed by the Investigator electronically. Only participants with a scalp IGA score >0 at Baseline will have the scalp IGA assessed as specified in Table 1-1 and Table 1-2.

Scalp lesions will be assessed in terms of clinical signs of redness, thickness, and scaliness using a 5-point scale (Table 8-3).

**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 |

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

## 8.2 Safety assessments

Planned time points for all safety assessments are provided in the Schedule of Activities.

### 8.2.1 Physical examination

A physical examination will be performed at the visits specified in the Schedule of Activities (Table 1-1 and Table 1-2). A complete physical examination will include, at a minimum, general appearance; ears, nose, and throat; eyes, hair, and skin; and assessments of the respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, and neurological (including limb reflexes) systems, as well as mental status. All physical examinations will also include evaluation of signs and symptoms of active TB and risk for exposure to TB (see Section 8.2.5.3.1). Height and weight will also be measured and recorded as per the Schedule of Activities.

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

Clinically significant findings or worsening of previous findings since the physical examination at Baseline will be recorded as AEs.

### 8.2.2 Vital signs

Vital signs, including temperature (oral, axillary, or otic), heart rate (or pulse rate), and blood pressure, will be assessed as specified in Table 1-1 and Table 1-2.

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 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the Schedule of Activities for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant 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 participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 20 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.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the Laboratory Manual and the Schedule of Activities.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in 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.

### 8.2.4 Neuropsychiatric AE monitoring/suicidal risk monitoring

At Screening, participants who meet specified thresholds on the C-SSRS or PHQ-9 assessments, as noted in exclusion criteria 30 and 31, will be evaluated by a mental health professional (ie, licensed psychiatrist or clinical psychologist) to determine whether they eligible for participation. In addition, participants may be referred to a mental health professional during the conduct of the study as outlined in Section 8.2.4.1 and Section 8.2.4.2.

The Medical Monitor will review AEs every 2 weeks for any potential neuropsychiatric AEs (including SIB) and will discuss such AEs with the Investigator. Additionally, neuropsychiatric AEs will be reviewed at periodic DMC meetings.

#### 8.2.4.1 C-SSRS

Suicidal ideation and behavior will be assessed by trained study personnel using the C-SSRS. This scale will be used for screening as well as to assess suicidal ideation and behavior that may occur during the study. The visits at which the C-SSRS assessments will be performed are specified in the Schedule of Activities (Section 1.3).

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

Refer to Section 7.2 for C-SSRS-related withdrawal criteria.

#### 8.2.4.2 PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression (Kroenke et al, 2001). A validation study has been conducted in adolescents to assess the psychometric properties of the PHQ-9 (Richardson, 2010). The PHQ-9 scores for depression range from 0 to 27, with higher scores indicating worse state. A score of 5 to 9 is considered to be minimal symptoms of depression. A score of 10 to 14 is considered to be minor depression, dysthymia, or mild major depression. A score of 15 to 19 is considered to indicate moderately severe major depression, and a score ≥20 is considered to be severe major depression.

The PHQ-9 will be self-administered by the study participant and will be assessed by the study personnel at the visits specified in the Schedule of Activities (Section 1.3).

Refer to Section 7.2 for PHQ-9-related withdrawal criteria.

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

All participants will be assessed for TB through physical examination for signs and symptoms of TB (Section 8.2.5.3.1), laboratory testing (Section 8.2.3), chest x-ray (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 extra pulmonary)
   - 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 interferon-gamma release assay (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 *M. tuberculosis* infections.

#### 8.2.5.2 Assessments at Screening

At Screening, all participants will have an IGRA test (QuantiFERON Gold Plus TB test is recommended), a chest x-ray (unless already performed within 6 months of Screening; a computed axial tomography [CAT] scan of the chest at Screening or within 6 months prior to Screening is acceptable, if available), and examination for signs and symptoms of TB. In addition, each participant (or parent or caregiver) will be asked to respond to 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 8 weeks of prophylaxis prior to Baseline.

Study participant eligibility, retesting requirements, and treatment requirements are shown in Figure 8-1 (screening).

**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] IGRA retest must be done during the protocol-defined Screening window

[b] Study participants with LTBI diagnosed during Screening can be rescreened after completion of 8 weeks of TB prophylaxis. Participants must agree to continue the full course of TB prophylaxis during the study.

#### 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 gastrointestinal system, bone/joints, lymph glands and meninges, etc. However, in immune-compromised patients, study participants, and/or patients treated with biologics, especially tumor necrosis factors inhibitors, extra-pulmonary manifestations of TB is common compared to 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, abdominal pain (mimicking IBD), etc. Unusual presentations should always be considered.

##### 8.2.5.3.2 Chest x-ray 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 CAT scan is available within 6 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 TB questionnaire

A questionnaire entitled "Evaluation of Signs and Symptoms of Tuberculosis" has been developed by UCB (document mod-000582) to help in identifying TB risk factors in study participants. For the purpose of case reporting, this questionnaire also ensures appropriate follow up with reporters when a case of either latent TB or active TB is diagnosed. Moreover, it ensures proactive and appropriate follow up with Investigators and study participants on treatment course.

The TB questionnaire will be completed by the Investigator during an interview with the study participant.

##### 8.2.5.3.4 IGRA test conversion

The IGRA is a whole blood testing methodology for diagnosing *M. tuberculosis* infection. It has become the gold standard but 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. Additional assessments (eg, blood tests or IGRA, chest X-rays, or other

imaging) should be performed where medically relevant and documented. Such conversions should be reported as AEs as described in the protocol. The AE term would need to be updated with final diagnosis once available.

#### 8.2.5.3.5 Latent TB

In case the 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. Participants can be rescreened after completion of 8 weeks of prophylaxis.

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 immediately be withdrawn from the study. Once withdrawn, the EDV 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 per protocol requirement until such time as the LTBI resolves.

#### 8.2.5.3.6 Active TB or non-tuberculosis mycobacterium 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 an EDV 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. Follow-up reports should be completed as per protocol requirement until such time as 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 or LTBI during the study must be withdrawn and scheduled to return for the EDV as soon as possible but no later than the next scheduled study visit and complete all EDV 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 serious adverse events

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, or the participant's legally authorized representative).

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, including those that are serious, considered related to the IMP or study procedures, or that caused the participant to discontinue IMP or the study (see Section 7).

For results disclosure on public registries (eg, ClinicalTrials.gov), treatment-emergent AEs and treatment-emergent SAEs will be published.

### 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 time points specified in the Schedule of Activities (Section 1.3).

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

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 3 (Section 10.3). 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 20 weeks from the final dose of IMP for each participant, and to also inform 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 AE and SAE and the procedures for completing and transmitting SAE reports are provided in 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 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 participant at subsequent visits/contacts. All will be followed until resolution, stabilization, the

Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the participant is lost to follow up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

### 8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of 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 an IMP under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

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 participants and, if indicated, female partners of male participants will be collected after the start of IMP and through the SFU Visit (ie, 20 weeks after the final dose of IMP).

If a pregnancy is reported, the Investigator must immediately inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4). Pregnancy test results at home will be monitored via a telehealth system or, if present, by the visiting health care professional.

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

- The participant should return for an EDV
- The participant should immediately stop the intake of the IMP
- An SFU Visit should be scheduled 20 weeks after the participant has discontinued her IMP

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

### 8.3.6 Adverse events of special interest

An AE of special interest is any AE that a regulatory authority has mandated be reported on an expedited basis, regardless of the seriousness, expectedness, or relatedness of the AE to the administration of a UCB product/compound.For bimekizumab, the following event requires immediate reporting (within 24 hours regardless of seriousness) to UCB:

- Potential Hy's Law, defined as ≥3xULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN ALP, with no alternative explanation for the biochemical

abnormality (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 participant.

### 8.3.7 Other safety topics of interest

Safety topics of interest for this study include infections (serious, opportunistic, fungal, and TB), IBD, and injection site reactions. Additionally, in keeping with the conduct of the adult bimekizumab program, the following topics will also be closely monitored: neutropenia, hypersensitivity (including anaphylaxis), major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and SIB.

These are based on findings from the IMP clinical program to date, potential risks generally associated with biologic immunomodulators, or findings from other medicines with a related mechanism of action. There are no specific AE reporting requirements for these topics, except those listed below for events relating to TB; 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:

- The IGRA test conversions defined as a positive or indeterminate (and confirmed indeterminate on repeat) should be reported as AEs. The AE term would need to be updated with final diagnosis once available.
- Latent TB infection must be reported as an AE. Follow-up reports should be completed as per protocol requirement until the LTBI resolves.
- Confirmed active TB is always considered an SAE and must be reported per SAE reporting instruction in the study protocol. Follow-up reports should be completed as per protocol requirement until TB infection resolves.

### 8.3.8 Anticipated SAEs

The following Anticipated SAEs (Table 8-4) are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 8.3 and Appendix 3 (Section 10.3).

**Table 8-4: Anticipated SAEs for the population of participants with moderate to severe plaque psoriasis**

| 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; 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.

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

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

An independent DMC will periodically review and monitor safety data from this study and advise UCB (see Section 9.7.2 for details). Further details are provided in a separate DMC charter. An IBD Adjudication Committee will also periodically review data from this study. Details will be provided in the IBD Adjudication Committee charter.

The Medical Monitor will review AEs every 2 weeks for any potential neuropsychiatric AEs (including SIB) and will discuss such AEs with the Investigator.

## 8.5 Treatment of overdose

For this study, any dose of bimekizumab greater than that prescribed in the protocol 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 participant for any AE/SAE and laboratory abnormalities until bimekizumab can no longer be detected systemically (at least 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 participant.

## 8.6 Pharmacokinetics

Plasma samples will be collected for measurement of plasma concentrations of bimekizumab as specified in the Schedule of Activities in Table 1-1 and Table 1-2. 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. Each plasma sample will be divided into 6 aliquots (2 each for PK, antidrug antibodies, and neutralizing antibodies; 1 primary and 1 back-up for each category). 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. The procedure for PK sample analysis and the relevant validation results will be described in a separate bioanalytical report.

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained. At weeks during which plasma samples for the determination of multiple aspects of bimekizumab will be taken, 1 sample of sufficient volume can be used.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

## 8.7 Genetics

Genetics are not evaluated in this study.

## 8.8 Pharmacodynamics

Pharmacodynamic (PD) parameters are not evaluated in this study.

## 8.9 Biomarkers

### 8.9.1 Immunogenicity assessments

Antibodies to bimekizumab will be evaluated in plasma samples collected from all participants according to the Schedule of Activities (Table 1-1 and Table 1-2). Additionally, plasma samples should also be collected at the final visit from participants who discontinued IMP or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

A tiered-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 participant’s last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to bimekizumab.

## 8.10 Medical resource utilization and health economics

Medical resource utilization and health economics parameters are not evaluated in this study.

# 9 STATISTICAL CONSIDERATIONS

A description of statistical methods follows and 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 participants who have given informed consent/assent.

The Randomized Set (RS) will consist of all randomized participants. Unless otherwise stated, efficacy analyses will be based on the RS.

The Safety Set (SS) will consist of all participants that receive at least 1 dose of the IMP. Safety and immunogenicity analyses will be based on the SS.

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized participants who receive at least 1 dose of the IMP and provide at least 1 quantifiable plasma concentration post-dose without important protocol deviations that would affect the concentration. Pharmacokinetic variables will be analyzed for all participants in the PK-PPS.

The Open-label Set (OLS) will consist of all study participants who receive at least 1 dose of IMP at or after Week 20 in the OLE Period (including the Week 20 dose).

## 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).

## 9.3 Planned efficacy/outcome analyses

### 9.3.1 Analysis of the primary endpoint

#### 9.3.1.1 Pharmacokinetic analyses

The primary variable of this study is bimekizumab plasma concentrations, which will be summarized by visit and dose group and presented together with descriptive statistics for the PK-PPS. Concentrations will be plotted for the overall population and for each dose group, and by treatment-emergent anti-bimekizumab antibody titer if appropriate. Objectives and endpoints related to PK analyses are described in Section 3.

A population PK analysis will be performed to derive the population estimates of PK parameters such as clearance and volume of distribution. This analysis will be performed by combining the data from the current study with data from relevant adult studies to evaluate the effect of body weight or other body size covariates on PK parameters. The model developed, including covariate effects, will be used to predict the PK and dosing for pediatric participants from 6 to <18 years of age in the Phase 3 study (PS0021). Further details on the modeling can be found in the Modeling and Simulation Plan.

### 9.3.2 Secondary efficacy analyses

The secondary efficacy variables will be analyzed for all study participants in the RS by randomized treatment arm.

No formal statistical testing will be conducted for the secondary efficacy variables. Objectives and endpoints related to secondary efficacy analyses are described in Section 3. The estimands related to secondary efficacy analyses are described in Section 9.3.2.1.

A participant will be classified as a PASI90 responder at Week 16 if the PASI score at Week 16 has improved by at least 90% from Baseline.

A participant will be classified as an IGA 0/1 responder if he/she has at least a 2-category improvement from Baseline at Week 16 and the IGA score is Clear [0] or Almost Clear [1].

A participant will be classified as a PASI75 responder at Week 4 if the PASI score at Week 4 has improved by at least 75% from Baseline.

Change from Baseline in CDLQI total score at Week 16 is defined as Week 16 CDLQI total score minus Baseline CDLQI total score.

The binary secondary efficacy variables of PASI90 response at Week 16, IGA 0/1 response at Week 16, and PASI75 response at Week 4 will be summarized descriptively with counts and percentages. Any participant who has missing data for the respective efficacy variable will be classified as a nonresponder for analysis. An observed case (OC) method will also be implemented to assess the impact of the main method of handling missing data.

The continuous efficacy variable change from Baseline in CDLQI response at Week 16 will be summarized descriptively. In addition to the standard set of summary statistics for continuous variables defined in Section 9.2, the upper and lower quartiles will also be reported. Multiple imputation will be used to account for missing continuous data in the analysis. The multiple imputation method will be described in more detail in the SAP. An OC method will be implemented to assess the impact of the main method of handling missing data.

#### 9.3.2.1 Efficacy estimands

The following 4 attributes describe the estimand (International Council for Harmonisation [ICH] Addendum, 2019) that will be used to define the treatment effect of interest for the secondary efficacy endpoint PASI90 response at Week 16:

1. Population = Adolescents meeting the protocol-specified inclusion/exclusion criteria.
2. Participant-level outcome = PASI90 response at Week 16.
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving PASI90 response at Week 16 and not discontinuing IMP through Week 16.
4. Population-level summary measure = Percentage of participants achieving PASI90 response at Week 16 in each dose group.

The following 4 attributes describe the estimand that will be used to define the treatment effect of interest for the secondary efficacy endpoint IGA 0/1 response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Week 16:

1. Population = Adolescents meeting the protocol-specified inclusion/exclusion criteria.

2. Participant-level outcome = IGA 0/1 response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Week 16.
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of IMP prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving IGA 0/1 response at Week 16 and not discontinuing IMP through Week 16.
4. Population-level summary measure = Percentage of participants achieving IGA 0/1 response (Clear or Almost Clear with at least 2-category improvement from Baseline) at Week 16 in each dose group.

The following 4 attributes describe the estimand that will be used to define the treatment effect of interest for the secondary efficacy endpoint PASI75 response at Week 4:

1. Population = Adolescents meeting the protocol-specified inclusion/exclusion criteria.
2. Participant-level outcome = PASI75 response at Week 4.
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of IMP prior to Week 4. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving PASI75 response at Week 4 and not discontinuing IMP through Week 4.
4. Population-level summary measure = Percentage of participants achieving PASI75 response at Week 4 in each dose group.

The following 4 attributes describe the estimand that will be used to define the treatment effect of interest for the secondary efficacy endpoint Change from Baseline in CDLQI response at Week 16:

1. Population = Adolescents meeting the protocol-specified inclusion/exclusion criteria.
2. Participant-level outcome = Change from Baseline to Week 16 in CDLQI.
3. Intercurrent event handling = An intercurrent event is defined as discontinuation of IMP prior to Week 16. A hypothetical strategy will be implemented in which participants with an intercurrent event are treated as though they had completed the randomized IMP through Week 16.
4. Population-level summary measure = Mean change from Baseline to Week 16 in CDLQI in each dose group.

### 9.3.3 Other analyses

The other efficacy variables will be analyzed based on the RS for analyses based on the combined Initial Treatment Period and OLE Period. Other efficacy variables will also be analyzed based on the OLS for analyses based on the OLE Period. Other efficacy variables will be summarized descriptively by visit, with counts and percentages for binary (responder) variables and descriptive statistics for continuous variables as defined in Section 9.2. Objectives and endpoints related to other efficacy analyses are described in Section 3.

Binary (responder) variables will be analyzed as done for the binary secondary efficacy variables. Continuous variables will be analyzed as done for the continuous secondary efficacy variable. Further details will be provided in the SAP.

An E-R analysis will be performed to evaluate the relationship between the plasma concentration of bimekizumab and PASI and IGA responses. The analysis may be performed by combining the data from PS0020 and data from adult Phase 2 and 3 studies in PSO to characterize the similarities and differences, if any, between the adult and adolescent participants. The derived model will be used to perform simulations to define the dose and dose regimen for the PS0021 study.

## 9.4 Planned safety and other analyses

### 9.4.1 Safety analyses

Safety variables will be analyzed for all study participants in the SS for analyses based on the Initial Treatment Period and the combined Initial Treatment Period and OLE Period. Safety variables will be analyzed for all study participants in the OLS for analyses based on the OLE Period. Objectives and endpoints related to safety and other analyses are described in Section 3.

#### 9.4.1.1 Adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA Version 23.1). Treatment-emergent AEs are defined as those AEs that have a start date on or following the first dose of IMP through the final dose of IMP +20 weeks.

The frequency of all TEAEs will be presented for each dose group separately by system organ class, high level term, and preferred term. The data will be displayed as number of participants experiencing the TEAE, percentage of participants, and number of TEAEs. Additional tables will summarize serious TEAEs, TEAEs leading to discontinuation, TEAEs by severity, and TEAEs categorized as safety topics of interest. Definitions for categorizing TEAEs as safety topics of interest will be provided in the SAP.

Selected AE summaries will also be adjusted for exposure and reported by 100 patient-years with associated 95% CIs. Further definitions will be provided in the SAP.

Summaries will be performed separately for the Initial Treatment Period and OLE Period, with selected additional summaries combining the Initial Treatment Period and OLE Period.

#### 9.4.1.2 Vital signs

Vital signs will be summarized by visit. Absolute values and change from Baseline in systolic and diastolic blood pressure and heart rate will be presented descriptively for each dose group.

Summaries will be performed for the Initial Treatment Period and OLE Period combined.

#### 9.4.1.3 Hematology/chemistry

Treatment-emergent markedly abnormal (TEMA) laboratory values are defined as those that have an assessment date on or following first dose of IMP through the final dose of IMP +20 weeks.

Laboratory assessments will be analyzed by visit. Absolute values and change from Baseline in each laboratory parameter will be presented descriptively for each dose group. The incidence rate

of TEMA laboratory values at the parameter level will also be presented descriptively for each dose group. Definitions for markedly abnormal laboratory values will be provided in the SAP.

Summaries of absolute values and change from Baseline will be performed for the Initial Treatment Period and OLE Period combined. Summaries of TEMA will be performed separately for the Initial Treatment Period and OLE Period, with additional summaries combining the Initial Treatment Period and OLE Period.

#### 9.4.1.4 Physical examination

Clinically significant changes from Baseline in physical examination findings will be reported as AEs. Changes from Baseline in physical examination findings will therefore be summarized as part of the TEAE summarization described in Section 9.4.1.1.

#### 9.4.1.5 Growth assessment (height and weight)

Height and weight data will be analyzed by visit. Absolute values and change from Baseline in height and weight will be presented descriptively for each dose group.

Summaries will be performed for the Initial Treatment Period and OLE Period combined.

#### 9.4.1.6 C-SSRS

The incidence of study participants with suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior will be summarized by treatment group through the Initial Treatment Period and through the Initial and OLE Treatment Periods combined.

A by-study participant listing of the C-SSRS questionnaire data will be provided by dose group.

#### 9.4.1.7 PHQ-9

The number and percentage of participants with scores below 5, between 5 and 9, between 10 and 14, between 15 and 19, and greater than 20 in PHQ-9 will be summarized as a shift from Baseline by visit and dose group based on observed values.

A by-study participant listing of the PHQ-9 questionnaire data will be provided by dose group.

### 9.4.2 Other analyses

Anti-bimekizumab antibody levels will be summarized descriptively for the SS.

## 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 PK, key safety, or other PK/PD outcomes for an individual 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 to confirm exclusion from analysis sets.

## 9.6 Handling of dropouts or missing data

Pharmacokinetic analyses, including those of the primary PK outcome, will be based on observed data, no imputation will be used. However, if plasma concentration measurements are below the level of quantification, then for calculation of the derived statistics the result will be set to half of the lower level of quantification.

Missing data for the binary (responder) efficacy variables will be imputed; participants with missing data will be considered as nonresponders for the respective analysis. Missing data for continuous efficacy variables will be imputed using multiple imputation. If the imputation model cannot converge, the OC method will be used. Sensitivity analyses for binary and continuous variables will be based on the OC method. See Section 9.3.2.1 for handling of intercurrent events.

For analyses of secondary efficacy variables related to TEAEs, a complete date must be established to correctly identify the AE as occurring during treatment or not. For purposes of imputing missing components of partially-reported start and stop dates for AEs, algorithms will be defined in the SAP.

## 9.7 Planned interim analysis and data monitoring

### 9.7.1 Planned interim analysis

There will be no formal interim analysis in this open-label study.

All available study PK data and clinical data (including selected efficacy and safety data) starting from when 25% of participants have reached Week 16 will be assessed periodically until all participants have completed the Initial Treatment Period. The Phase 3 study (PS0021) dosing will be determined from this information.

### 9.7.2 Data Monitoring Committee

The DMC membership will include experienced clinicians and a statistician, all of whom have expertise in clinical studies. The DMC members will not be permitted to participate in the study as principal or co-Investigators, or as study participant care physicians. The duration of membership for the committee will be inclusive of planned analyses for PS0020. Detailed role, scope, responsibilities, and complete procedures, as well as the identity of members, will be described in a separate DMC charter.

## 9.8 Determination of sample size

The number of study participants, at least 40 total participants randomized 1:1 across the 2 dose arms, is considered to be sufficient to assess bimekizumab population PK and E-R in adolescents. The sample size is based on simulations from an adult PASI E-R model, adjusted for body weight differences in PK for adolescents (ie, allometric scaling in clearance [CL/F] and V/F) and assuming the same efficacy response in adolescents as in adults (ie, same parameter estimates for simulation were assumed). A total of 40 participants allocated evenly to 2 dose arms was found in the modeling and simulation to be sufficient for the estimation of PK/PD parameters with precision in a combined adult-adolescent analysis.

# 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, ICH-Good Clinical Practice (GCP), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

The Investigator/UCB will ensure that an appropriately constituted IRB/IEC that complies with the requirements of the current ICH-GCP version or applicable country-specific regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the Investigator/UCB will forward copies of the protocol, Informed Consent/Assent Form, IB, Investigator's curriculum vitae (if applicable), advertisement (if applicable), and all other 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 participants or others, and any protocol deviations, to eliminate immediate hazards to 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 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 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 each concerned country. Where applicable, Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

### 10.1.2 Finance and insurance

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 participants' and/or their parents'/legal representatives' informed consent/assent 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/assent, information should be given in a language and at a level of complexity understandable to the participant (and/or parent/legal representative) in both oral and written form by the Investigator (or designee). Each participant (and/or parent/legal representative) will have the opportunity to discuss the study and its alternatives with the Investigator.

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

Upon reaching 18 years of age, if continuing in the study, a study participant may need to sign a new ICF depending on the local IRB/IEC requirements.

UCB will provide a sample Informed Consent/Assent Form, and study participant information sheet. The final ICF and Assent Form must be approved by the IRB/IEC and should contain the applicable ICH-GCP elements in a language readily understood by the study participant (ie, lay terminology).

If any new information that could influence the study participant's decision to stay in the study becomes available, this information will be transmitted to the study participant's parent(s)/legally acceptable representative(s) (or the study participant, if he/she has become ≥18 years old) without delay. In addition, the ICF (and Assent Form where applicable) must be amended accordingly or a separate consent form (and Assent Form) be created and submitted to the IRB/IEC for approval prior to being implemented for reconsent (and assent) of all ongoing study participants in the study and for use in obtaining assent and consent from all parent(s)/legally acceptable representative(s) of study participants who enter the study from that point forward.

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

The participant (and/or parent/legal representative) may withdraw consent/assent to participate in the study at any time. A participant is considered as enrolled in the study when he/she (and/or a parent/legal representative) has signed the Informed Consent/Assent Form. An eCRF must not be started, nor may any study specific procedure be performed for a given participant, without having obtained written consent/assent to participate in the study.

### 10.1.4 Data protection

UCB staff (or designee) will affirm and uphold the participant's confidentiality. Each participant will be assigned a unique identifier by UCB. Any study participant records or data sets transferred to UCB (or designee) will contain only the study identifier. Participant names or any information which would make the study participant identifiable will not be transferred.

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 participant's primary medical records that directly concerns this study (including, but not limited to, laboratory test result reports, admission/discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports for deaths occurring during the study).

The participant/caregiver will be informed that the participant's personal study-related data may be used by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, the Sponsor, their affiliates, IRB/IEC members, and inspectors from regulatory authorities in accordance with local data protection law. The participant/caregiver must be also informed that in case of home visits the visiting health care professional will be provided with the participant's personal information (eg, name, phone number, address). The level of disclosure will also be explained to the participant within the ICF.

### 10.1.5 Committees structure

Central laboratories will be used to analyze laboratory and PK samples.

An independent DMC will periodically review and monitor safety data from this study and advise UCB. Details are provided in a separate DMC charter.

An IBD Adjudication Committee will also periodically review data from this study. Details will be provided in the IBD Adjudication Committee charter.

Contract research organizations may be used for study conduct and their roles will be outlined in transfer of obligation forms.

### 10.1.6 Data quality assurance

All participant data relating to the study will be recorded on printed or electronic CRF 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 CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. During home visits, health care professionals will collect study data.

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, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of 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.

#### 10.1.6.1 Case Report Form completion

The Investigator is responsible for prompt reporting of accurate, complete, and legible 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 CRF Completion Guidelines.

#### 10.1.6.2 Apps/Telehealth system

Each study participant will be provided with a mobile phone with a pre-installed application (app). The study-specific app will collect data from each participant throughout the study. The app will support the participant to complete study-specific activities, as follows:

- Receiving reminders and notifications
- Completing electronic patient-reported outcomes (ePRO)
- Scheduling and conducting telehealth virtual visits with the Investigator and/or authorized site representative(s)

The Investigator and authorized site representative(s) will have access to a secure website portal via unique access credentials to access the study data from the completed activities noted above.

Data will be reviewed by the Investigator via the website portal view of participant-entered data results.

### 10.1.7 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, laboratory results, printouts, pharmacy records, care records, completed scales, quality of life questionnaires, or video, for example. Source documents should be kept in a secure, limited access area.

Electronic PRO measures (eg, CDLQI) will be completed by each study participant and will be collected via an app. Refer to Section 10.1.6.2 for more details.

The data collection and database management system will be supplied by a vendor and will be compliant with the relevant regulations. The data collected on the ePROs will be uploaded to a central server database and will be sent electronically to UCB (or a designated CRO).

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 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).

### 10.1.8 Study and site closure

The Sponsor 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 participants by the Investigator
- Discontinuation of further bimekizumab development

### 10.1.9 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 the table below 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. Pregnancy tests may be performed at home during the OLE Period and test results will be monitored by a telehealth system or, if present, by the visiting health care professional.
- 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 and exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol, 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>%Reticulocytes | WBC Count with Differential:<br>Neutrophils<br>Lymphocytes<br>Monocytes<br>Eosinophils<br>Basophils | |
| Clinical Chemistry [a] | Blood Urea Nitrogen | Potassium | AST/serum glutamic-oxaloacetic transaminase | Total and direct bilirubin |
| | Creatinine | Sodium | ALT/serum glutamic-pyruvic transaminase | Total Protein |
| | Glucose (nonfasting) | Calcium | Alkaline phosphatase | |
| Routine Urinalysis | • Specific gravity<br>• pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase by dipstick<br>• Microscopic examination (if blood or protein is abnormal) | | | |
| Other Screening Tests | • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) by central laboratory at Screening and urine pregnancy test locally for all assessments after Screening (or at home during the OLE Period)<br>• IGRA testing<br>• Serology (HBsAg and hepatitis C virus antibody)<br>• Plasma sample for HIV antibody assessment<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; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; RBC=red blood cell count; ULN=upper limit of normal; WBC=white blood cell count

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

Investigators must document their review of each laboratory safety report.

## 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 Meeting the AE Definition** |
|---|
| • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, 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 it 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 fulfil the definition of an AE or SAE. |

| **Events NOT 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 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 an 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 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 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 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 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 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.

**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 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 at least 1 of the predefined outcomes as described in the definition of an 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 an 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 participant is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AEs of special interest.
- 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 eCRF.
- The Investigator will submit any updated SAE data to UCB within 24 hours of receipt of the information.

## Reporting of SAEs

| SAE Reporting to UCB via an Electronic Data Collection Tool |
|---|
| • The primary mechanism for reporting an SAE to UCB will be the electronic data collection tool.<br>• 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).<br>• The site will enter the SAE data into the electronic system as soon as it becomes available.<br>• 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.<br>• 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.<br>• Contacts for SAE reporting can be found in SERIOUS ADVERSE EVENT REPORTING. |

## 10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

### Definitions

**Woman of Childbearing Potential**

A woman is considered fertile following menarche and until becoming post-menopausal 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 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 1 of the non-estrogen 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 participants**

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

**Highly Effective Contraceptive Methods [a]**

| |
|---|
| **Highly Effective Contraceptive Methods That Are User Dependent [b]**<br>Failure rate of <1% per year when used consistently and correctly. |
| Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [c]<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 [c]** |
| Implantable progestogen only hormonal contraception associated with inhibition of ovulation<br>• Intrauterine device (IUD)<br>• Intrauterine hormone-releasing system (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 participant. |

[a] In case of newly started contraception pills/IUDs, PI should consider the correct timing of starting/applying such methods in relation to the menstrual cycle and the manufacturing instruction as when these newly started methods would become effective.
[b] 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 participants participating in clinical studies.
[c] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 20 weeks after the final dose of IMP.

### Pregnancy testing

- WOCBP 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 Schedule of Activities (Table 1-1 and Table 1-2) and as required locally. Pregnancy test results at home will be monitored via a telehealth system or, if present, by the visiting health care professional.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

**Male participants with partners who become pregnant**

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study.
- In cases where the partner of a male participant enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the participant to request consent/assent of the partner via the Partner Pregnancy Consent/Assent 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/Assent form. UCB's Patient Safety 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/Assent 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 1 working day of learning of the partner's pregnancy. 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 at least 12 months 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 Participants who become pregnant**

- Any female participant who becomes pregnant while participating in the study will discontinue IMP and be withdrawn from the study as soon as pregnancy is known.
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 1 working day of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, the follow up will be at least 12 months 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 post-study 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

Participants with potential drug-induced liver injury must be assessed to determine if IMP must be discontinued, as outlined in Section 7.1.1.

All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AE of special interest (see Section 8.3.6), and, if applicable, also reported as an SAE (see Section 8.3).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10-2 (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 7.1.1.1.1).

## Table 10-2: 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] | NA | 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 | NA | Yes | | | | |
| ≥8×ULN | NA | NA | | | | |
| ≥5×ULN (and ≥2× Baseline) and <8×ULN | <2×ULN | No | Discussion with Medical Monitor required.<br>Consider need for hepatology consult if there is no evidence of resolution (see Follow-up requirements).[c] | Further investigation – immediate IMP discontinuation not required (see Section 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 | 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]<br>• Immediate IMP discontinuation required if liver chemistry values continue to increase.<br>After 2 weeks of monitoring liver chemistry values:<br>• ALT or AST remains ≥5×ULN <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 |

## Table 10-2: 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** |
| | | | | monitoring without evidence of resolution | | least twice per week until values normalize, stabilize, or return to within baseline values.<br>If ALT or AST remains ≥5×ULN after second re-test, immediate IMP discontinuation required.<br>Continue to monitor until values normalize, stabilize, or return to within baseline values.[d] |

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

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

[b] If the study participant also has ≥2xULN 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 UCB responsible physician. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

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 7.1.1.1), 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 are met, rechallenge with IMP may be appropriate.

The approach to investigate PDILI is summarized in Table 10-2.

### 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 10-2 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 10-2), 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 7.1.1.1.1 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 ≥3×ULN.
- Study participant's total bilirubin is <1.5×ULN.
- Study participant has no signs or symptoms of hypersensitivity.
- 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 10-3 (laboratory measurements) and Table 10-4 (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 10-3: 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 ≥1.5xULN, 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=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

[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 (>5%), rash, and fever (without clear alternative cause).

[c] For women of childbearing potential.

Additional information to be collected is presented in Table 10-4.

**Table 10-4: PDILI information to be collected**

| New or updated information |
|---|
| • Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included. |
| • Pertinent medical history, including the following:<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 Adverse Events, Adverse Device Effects, Serious Adverse Events, and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Not applicable.

## 10.8 Appendix 8: Rapid Alert Procedures

Not applicable.

## 10.9 Appendix 9: Country-specific Requirements

Country-specific requirements will be provided separately, as applicable.

## 10.10 Appendix 10: Abbreviations and Trademarks

| | |
|---|---|
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| BKZ | bimekizumab |
| BSA | body surface area |
| CAT | computed axial tomography |
| CDLQI | Children's Dermatology Life Quality Index |
| CI | confidence interval |
| CRO | contract research organization |
| DLQI | Dermatology Life Quality Index |
| DMC | Data Monitoring Committee |
| eCRF | electronic Case Report Form |
| C-SSRS | electronic Columbia Suicide Severity Rating Scale |
| EDV | Early Discontinuation Visit |
| ePRO | Electronic patient-reported outcome |
| E-R | exposure-response |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| 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 |
| IgG1 | immunoglobulin G1 |
| IGRA | interferon-gamma release assay |
| IL | interleukin |
| IMP | investigational medicinal product |
| IRB | Institutional Review Board |

| | |
|---|---|
| IUD | intrauterine device |
| IVRS | interactive voice response system |
| IWRS | interactive web response system |
| LTBI | latent tuberculosis infection |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NTMB | nontuberculous mycobacterial |
| OC | observed case |
| OLE | Open-label Extension |
| OLS | Open-label Set |
| PASI | Psoriasis Area and Severity Index |
| PD | pharmacodynamic |
| PDILI | potential drug-induced liver injury |
| PHQ-9 | Patient Health Questionnaire 9 |
| PK | pharmacokinetics |
| PK-PPS | Pharmacokinetics Per-Protocol Set |
| PRN | as needed |
| PRO | patient-reported outcome |
| PsA | psoriatic arthritis |
| PSO | psoriasis |
| Q4W | every 4 weeks |
| RNA | ribonucleic acid |
| RS | Randomized Set |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| sc | subcutaneous(ly) |
| scalp IGA | scalp-specific Investigator’s Global Assessment |
| SFU | Safety Follow up |
| SIB | suicidal ideation/behavior |
| SS | Safety Set |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |

| | |
|---|---|
| TEMA | treatment-emergent markedly abnormal |
| ULN | upper limit of normal |
| 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.

# 11 REFERENCES

Augustin M, Glaeske G, Radtke MA, Christophers E, Reich K, Schäfer I. Epidemiology and comorbidity of psoriasis in children. Br J Dermatol. 2010;162:633-6.

Farber EM, Nall ML. The natural history of psoriasis in 5,600 patients. Dermatologica. 1974;148:1-18.

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

Feldman SR. Epidemiology, clinical manifestations, and diagnosis of psoriasis. UpToDate. 2015.

Icen M, Crowson CS, McEvoy MT, Dann FJ, Gabriel SE, Maradit Kremers H. Trends in incidence of adult-onset psoriasis over three decades: a population-based study. J Am Acad Dermatol. 2009;60:394-401.

ICH Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1) Nov 2019.

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–13.

Krueger G, Ellis CN. Psoriasis–recent advances in understanding its pathogenesis and treatment. J Am Acad Dermatol. 2005;53(1 Suppl 1):S94-100.

Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003-2004. J Am Acad Dermatol. 2009;60:218-24.

Kurd SK, Smith N, VanVoorhees A, Troxel AB, Badmaev V, Seykora JT, et al. Oral curcumin in the treatment of moderate to severe psoriasis vulgaris: a prospective clinical trial. J Am Acad Dermatol. 2008;58:625-31.

Lara-Corrales I, Xi N, Pope E. Childhood psoriasis treatment: Evidence published over the last 5 years. Rev Recent Clin Trials. 2011;6:36-43.

Mundt JC, Greist JH, Gelenberg AJ, et al. Feasibility and validation of a Computer-Automated Columbia-Suicide Severity Rating Scale using Interactive Voice Response Technology. J Psychiatr Res. 2010;44(16):1224-8.

Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: A systematic review of incidence and prevalence. J Invest Dermatol. 2013;133:377-85.

Posner K, Brown GK, Stanley B, et al. The Columbia Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. Am J Psychiatry. 2011;168(12):1266-77.

Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol. 2014;70:512-6.

Raychaudhuri SP, Gross J. A comparative study of pediatric onset psoriasis with adult onset psoriasis. Pediatr Dermatol. 2000;17(3):174-8.

Richardson LP, McCauley E, Grossman DC, et al. Evaluation of the Patient Health Questionnaire-9 Item for detecting major depression among adolescents. Pediatrics. 2010 Dec;126(6): 1117-23.

Shah KN. Diagnosis and treatment of pediatric psoriasis: current and future. Am J Clin Dermatol. 2013;14:195–213.

Tollefson MM, Crowson CS, McEvoy MT, Maradit Kremers H. Incidence of psoriasis in children: a population based study. J Am Acad Dermatol. 2010;62:979-87.

van Geel MJ, Maatkamp M, Oostveen AM, de Jong EMGJ, Finlay AY, van de Kerkhof PCM, et al. Comparison of the Dermatology Life Quality Index and the Children's Dermatology Life Quality Index in assessment of quality of life in patients with psoriasis aged 16-17 years. Br J Dermatol. 2016;174:152-7.

Varni JW, Globe DR, Gandra SR, Harrison DJ, Hooper M, Baumgartner S. Health-related quality of life of pediatric patients with moderate to severe plaque psoriasis: comparisons to four common chronic diseases. Eur J Pediatr. 2012;171:485-92.

Wu JJ, Black MH, Smith N, Porter AH, Jacobsen SJ, Koebnick C. Low prevalence of psoriasis among children and adolescents in a large multiethnic cohort in southern California. J Am Acad Dermatol. 2011;65:957-64.

# SPONSOR DECLARATION

I confirm that I have carefully read and understand this protocol and agree to conduct this clinical study as outlined in this protocol and according to current Good Clinical Practice.

# Approval Signatures

**Name:** ps0020-protocol-amend-1

**Version:** 1.0

**Document Number:** CLIN-000163091

**Title:** PS0020 Protocol - Phase 2, Open-label, Randomized

**Approved Date:** 11 Nov 2020

| Document Approvals | |
|---|---|
| Approval<br>Verdict: Approved | Name: Philippa Charlton<br>Capacity: Clinical<br>Date of Signature: 10-Nov-2020 14:23:51 GMT+0000 |
| Approval<br>Verdict: Approved | Name: Fabienne Staelens<br>Capacity: Medical<br>Date of Signature: 10-Nov-2020 16:07:27 GMT+0000 |
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# Approval Signatures

| | |
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| Document Approvals | | |
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