A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY EVALUATING THE EFFICACY AND SAFETY OF BIMEKIZUMAB IN STUDY PARTICIPANTS WITH MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA

PROTOCOL HS0004 AMENDMENT 4

PHASE 3

SHORT TITLE:

A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Bimekizumab in Study Participants with Moderate to Severe Hidradenitis Suppurativa

Sponsor:
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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Document History		
Document	**Date of Issue**	**Type of Amendment**
Amendment 4	06 May 2022	Substantial
Amendment 3	09 Feb 2021	Substantial
Amendment 2.1 (Japan)	19 Dec 2019	Not applicable
Amendment 2	16 Dec 2019	Nonsubstantial
Amendment 1.1 (Japan)	10 Dec 2019	Not applicable
Amendment 1	06 Dec 2019	Nonsubstantial
Original Protocol	29 Oct 2019	Not applicable

Amendment 4 (06 May 2022)

Overall rationale for the amendment

It is recommended that a threshold for within-patient clinically meaningful change to define treatment success be used in order to establish efficacy for skin pain in Phase 3 trials of patients with moderate to severe hidradenitis suppurativa. The Sponsor conducted analyses to estimate the threshold for within-patient clinically meaningful change that can be used for a responder definition based on the Hidradenitis Suppurativa Symptom Daily Diary worst skin pain item score using established guidelines and analytical methods. Pain response status at Week 16 using this definition has been added as a secondary endpoint to the study.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3 Objectives and endpoints	• An additional secondary efficacy endpoint was added to the protocol assessing pain response at Week 16 using a threshold for within-patient clinically meaningful change as recommended by the U.S. Food and Drug Administration. • Other pain endpoints clarified and updated accordingly.	To align with FDA recommendations.
9.3.2 Analysis of the secondary efficacy endpoints	• Section updated to include the new pain response endpoint in the statistical hierarchy, and description of planned analysis • Figure 9-1 updated to include the new pain response endpoint.	To accommodate the new pain response endpoint.
9.8 Determination of sample size	• Sample size assumptions updated based on additional secondary endpoint.	The addition to the protocol of the HSSDD worst skin pain response as a ranked secondary endpoint resulted in an addition to the power calculation section, including assumptions for sample size, response rates, and statistical power.
Throughout	• Minor editorial and formatting revisions	Minor edits and formatting revisions that do not impact content were made for readability and/or clarity

SERIOUS ADVERSE EVENT REPORTING

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

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol title:

A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Bimekizumab in Study Participants with Moderate to Severe Hidradenitis Suppurativa

Short Title:

A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Bimekizumab in Study Participants with Moderate to Severe Hidradenitis Suppurativa

Rationale:

UCB is investigating bimekizumab (a humanized, full-length immunoglobulin [Ig] G1 monoclonal antibody [mAb] with high affinity for human interleukin [IL] 17 [IL-17A and IL 17F]) for the treatment of hidradenitis suppurativa (HS). Antibodies targeting IL-17A are effective in treating patients with moderate to severe psoriasis (PSO) and other immuno-inflammatory conditions. Data from clinical studies with bimekizumab suggest that inhibition of both IL-17A and IL-17F could be beneficial to patients with such conditions, including HS. Based on results from a Phase 2a study in study participants with HS (HS0001); and a Phase 2b study in study participants with PSO (PS0010) and its 48 week extension study (PS0011), bimekizumab doses of 320mg every 2 weeks (Q2W) in HS and 320mg every 4 weeks (Q4W) in PSO appeared to have an acceptable safety profile, and achieved clinically meaningful efficacy in both primary and key secondary endpoints in their respective studies. Based on these data and considering the high unmet need for safe and effective therapies for HS, confirmatory studies are being conducted with bimekizumab for the treatment of moderate to severe HS.

Objectives and Endpoints

The primary and secondary objectives and associated endpoints are as follows:

Objectives	Endpoints
Primary	
Evaluate the efficacy of bimekizumab in study participants with moderate to severe HS	• $HiSCR_{50}$ at Week 16
Secondary	
Evaluate the efficacy of bimekizumab on other measures of disease activity in study participants with moderate to severe HS	• $HiSCR_{75}$ at Week 16 • Flare (defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline) by Week 16 • Absolute change from Baseline in DLQI Total Score at Week 16 • Absolute change from Baseline in the Worst HS Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HSSDD • Pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) at Week 16
Evaluate the safety of bimekizumab in study participants with moderate to severe HS	• Treatment-emergent AEs • Serious TEAEs • TEAEs leading to withdrawal from study

AE=adverse event; AN=abscess and inflammatory nodule; DLQI=Dermatology Life Quality Index; $HiSCR_{50}$=a 50% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{75}$=a 75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HS= hidradenitis suppurativa; HSSDD=Hidradenitis Suppurativa Symptom Daily Diary; TEAE=treatment-emergent adverse event

Overall Design

HS0004 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, pivotal study evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS.

Number of Participants

Approximately 490 study participants will be randomly assigned to study treatment: 140 for bimekizumab [redacted], 140 for bimekizumab [redacted], 140 for bimekizumab [redacted], and 70 for placebo/[redacted]. The Randomized Set (ie, all randomized study participants) is the primary analysis set for efficacy analyses.

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment (Section 5.4).

Treatment Groups and Duration

Study participants meeting the inclusion criteria who do not meet any exclusion criteria will complete a Screening Period of 14 days to up to 5 weeks; a double-blind, 48-week Treatment Period comprising a 16-week Initial Treatment Period and 32-week Maintenance Treatment Period; and a 20-week Safety Follow-up (SFU) Period following the final injection of investigational medicinal product (IMP) if study participants do not enter a subsequent extension study (HS0005) or withdraw prematurely from treatment. The total duration of study participation in HS0004 will be 68 to 71 weeks for those who complete HS0004 and do not participate in the extension study HS0005 and 50 to 53 weeks for those who participate in HS0005 and, thus, do not participate in the 20-week SFU Period.

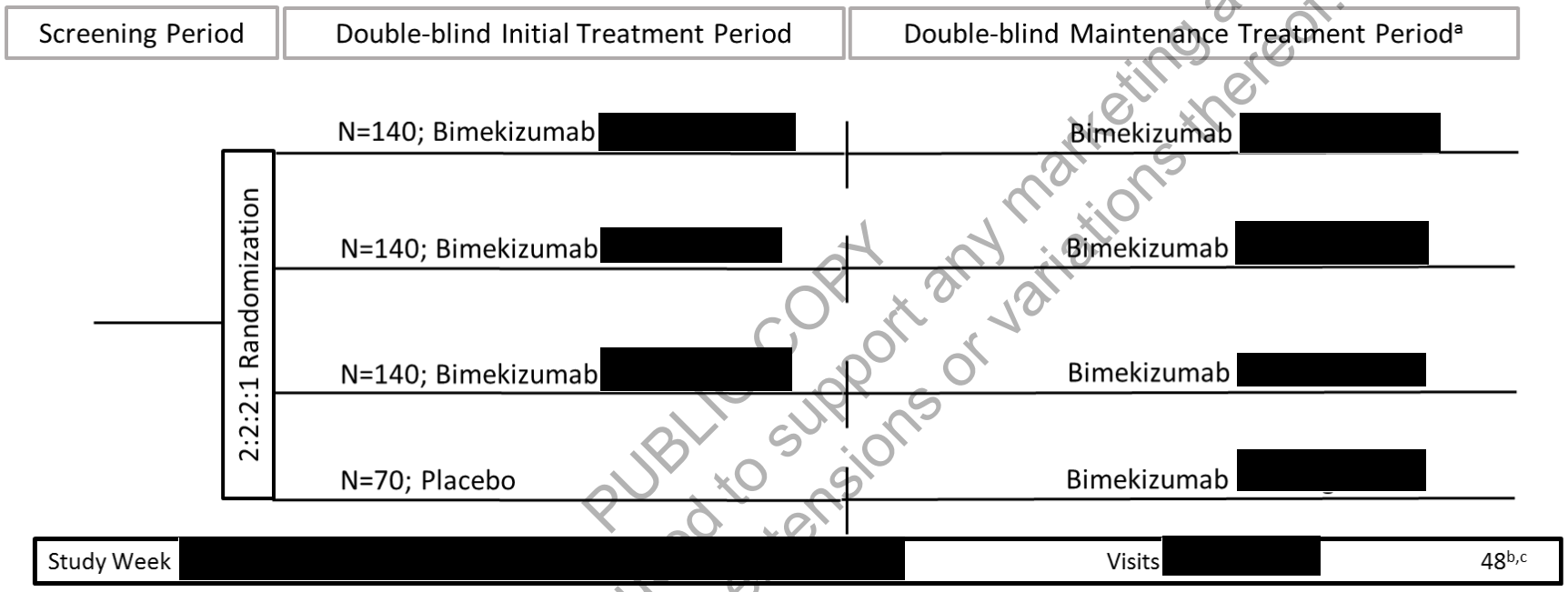
Study participants will be randomized in a 2:2:2:1 ratio (stratified by Hurley Stage and current antibiotic use) to 1 of 3 dose regimens of bimekizumab or placebo as shown in the schematic (Figure 1-1). All doses of IMP will be administered by subcutaneous (sc) injection. The primary efficacy variable at Week 16 is $HiSCR_{50}$ (a 50% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count). Study visits will occur at Screening; Baseline (Week 0); Weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16; [redacted] from Week 16 through Week 48 for assessments of efficacy, safety, and other measures of quality of life/health status/work productivity; and a SFU visit 20 weeks after the last dose of IMP for participants who do not enter the extension study.

An independent Data Monitoring Committee (DMC) will periodically review unblinded efficacy and safety data to assess the benefit/risk of bimekizumab in study participants with moderate to severe HS. In addition, aggregated unblinded efficacy data is planned to be provided to the DMC when approximately 66% of study participants have reached the primary efficacy endpoint at Week 16. Efficacy data will be provided to the DMC to put the safety review in the context of risk/benefit. Measures to ensure that unblinded interim results are not disseminated beyond the DMC will be implemented.

1.2 Schema

A schematic diagram for the study is presented in Figure 1-1.

Figure 1-1: Study Schematic



$HiSCR_{50}$=a 50% reduction in the total abscess and inflammatory nodule count with no increase from Baseline in abscess or draining tunnel count; IMP=investigational medicinal product; [redacted]

*Week 16 = primary endpoint ($HiSCR_{50}$ bimekizumab versus placebo)

[a] Study participants should discontinue from the study from Week 32 on if no partial response is achieved (partial response is defined as ≥25% improvement in abscess and inflammatory nodule count relative to Baseline [Week 0] lesion values,)

[b] Study participants achieving an improvement of at least 25 % in abscess and inflammatory nodule count continue in HS0005 (Extension Study).

[c] 20-week Safety Follow-up (from last IMP injection) for any study participant who discontinues from study prior to Week 48, or who does not continue in HS0005.

1.3 Schedule of activities

The Schedule of Activities is presented in Table 1–1.

Table 1–1: Schedule of activities

Visit Name or Weeks After 1st Dose[a] / Protocol activity	Screening[b]	Initial Treatment Period (weeks after first dose)										Maintenance Treatment Period (weeks after first dose)																	PEOT	SFU[c]
		Bsl 1st dose 0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48		
Study Visit	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	X	X
Informed consent	X																										X[d]			
Study participant number assigned	X																													
Inclusion/exclusion	X	X																												
Demographic and Baseline disease characteristics	X	X																												
Hidradenitis suppurativa history	X																													
Significant past medical history/ concomitant diseases[e]	X	X[f]																												
Physical examination[g]	X	X							X		X				X						X						X	X	X

Table 1–1: Schedule of activities

Visit Name or Weeks After 1st Dose[a] / Protocol activity	Screening[b]	Initial Treatment Period (weeks after first dose)										Maintenance Treatment Period (weeks after first dose)																PEOT	SFU[c]
		Bsl 1st dose 0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48		
Height		X																											
Body weight		X													X												X	X	
Vital signs[h]	X	X	X	X	X		X		X		X	X	X		X		X		X		X		X		X		X	X	X
12-lead ECG	X										X								X								X	X	X
Hematology/ biochemistry	X	X		X	X		X		X		X	X	X		X		X		X		X		X		X		X	X	X
hs-CRP		X							X		X								X								X	X	
Urinalysis	X	X									X				X				X				X				X	X	X
Urine drug screen	X																										X	X	
Pregnancy testing[i]	X	X			X		X		X		X		X		X		X		X		X		X		X		X	X	X
Hepatitis B and C testing[j]	X																												
HIV testing[k]	X																												
Chest x-ray[l]	X																												
IGRA TB test[m]	X																								X				
TB questionnaire	X	X							X						X						X						X	X	X
Lesion count (includes Hurley Stage)[n]	X	X		X	X		X		X		X		X		X		X		X		X		X		X		X	X	

Table 1–1: Schedule of activities

Visit Name or Weeks After 1st Dose[a] / Protocol activity	Screening[b]	Initial Treatment Period (weeks after first dose)										Maintenance Treatment Period (weeks after first dose)																PEOT	SFU[c]
		Bsl 1st dose 0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48		
Photography[o]		X			X						X								X							X	X	
Blood sample – bimekizumab plasma concentrations[p]		X	X	X	X		X		X		X	X	X		X						X					X	X	X
Blood sample for anti-drug antibodies[p]		X			X		X		X		X		X		X						X					X	X	X
Blood sample for genomic/ proteomic/ metabolomics, and candidate biomarker analyses[p, q]		X					X		X		X															X	X	
Blood sample for genetic/ epigenetic analyses[p, q]		X									X															X	X	
Urine samples for biomarker research		X									X															X	X	
DLQI		X			X		X		X		X		X						X		X					X	X	
PHQ-9	X	X			X		X		X		X		X		X		X		X		X		X		X	X	X	X

Table 1–1: Schedule of activities

Visit Name or Weeks After 1st Dose[a] / Protocol activity	Screening[b]	Initial Treatment Period (weeks after first dose)										Maintenance Treatment Period (weeks after first dose)																PEOT	SFU[c]
		Bsl 1st dose 0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48		
eC-SSRS	X	X			X		X		X		X		X		X		X		X		X		X		X		X	X	X
WPAI-SHP		X							X		X								X								X	X	
TSQM-9											X																X	X	
HiSQOL		X			X						X								X								X	X	
HSSDD[r]	●	—	—	—	—	—	—	—	—	—	●																		
HSSQ		X									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PGI-S-HS		X			X						X								X								X	X	
PGI-C-HS					X						X								X								X	X	
PGI-S-SP		X			X						X								X								X	X	
PGI-C-SP					X						X								X								X	X	
EQ-5D-3L		X			X				X		X								X		X						X	X	
Concomitant medications	●	—	—	—	—	—	—	—	—	—	●																		
Adverse events	●	—	—	—	—	—	—	—	—	—	●																		
Randomization[s]		X																											
IRT	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	X
[redacted]																													

AN=abscess and inflammatory nodule; Bsl=Baseline; CAT=computed axial tomography; CRF=case report form; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eC-SSRS=electronic Columbia-Suicide Severity Rating Scale; EQ-5D-3L=Euro-Quality of Life 5-Dimensions, 3 levels; $HiSCR_{25}$=a 25% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{50}$=a 50% reduction in the total

Table 1–1: Schedule of activities

Visit Name or Weeks After 1st Dose[a] / Protocol activity	Screening[b]	Initial Treatment Period (weeks after first dose)										Maintenance Treatment Period (weeks after first dose)																PEOT	SFU[c]
		Bsl 1st dose 0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48		

AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{75}$=a 75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{90}$=a 90% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{100}$=a 100% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HiSQOL=Hidradenitis Suppurativa Quality of Life; HIV=human immunodeficiency virus; HS=hidradenitis suppurativa; hs-CRP=high sensitivity C-reactive protein; HSSDD=Hidradenitis Suppurativa Symptom Daily Diary; HSSQ=Hidradenitis Suppurativa Symptom Questionnaire; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; IRT=interactive response technology; PEOT=Premature End of Treatment Visit; PGI-C-HS=Patient Global Impression of Change in HS Severity; PGI-C-SP=Patient Global Impression of Change in Severity of Skin Pain; PGI-S-HS=Patient Global Impression of HS Severity; PGI-S-SP=Patient Global Impression of Severity of Skin Pain; PHQ-9=Patient Health Questionnaire 9; SFU=Safety Follow-Up; TB=tuberculosis; TSQM=Treatment Satisfaction Questionnaire for Medication; WPAI-SHP=Work Productivity and Impairment Questionnaire-Specific Health Problem

Note: Some study-specific assessments may be conducted remotely according to the study protocol during a pandemic or other exceptional circumstance (eg, hurricanes) due to the need to implement safety measures and guidance from regulatory authorities. Refer to Section 8 for additional information.

[a] Visit windows are ±3 days (based on the date of the first dose). However, the minimum of 8 days between injection visits (eg, Visit 2 +3 days occurs on Day17; Visit 4 -3 days occurs on Day 25) may be used only 1 time in the Initial Treatment Period and 1 time in the Maintenance Treatment Period, if needed. The study participant should be dosed according to the administration schedule thereafter. The 20-week SFU Visit window is ±7 days (based on the date of the final dose).

[b] The Screening Period will last a minimum of 14 days up to a maximum of 5 weeks prior to randomization.

[c] All study participants not continuing in the extension study, including those withdrawn from IMP as well as those completing all study visits, will have an SFU Visit 20 weeks after his or her final dose of IMP.

[d] A separate informed consent form will be required to be completed for participation in extension study HS0005. Study participants continuing in HS0005 will receive first dose of bimekizumab in that study on Week 48.

[e] Past medical history includes tobacco and alcohol use.

[f] Ensure no significant changes from Baseline in medical history and concomitant disease.

[g] The physical examination will be performed as detailed in Section 8.2.1. Includes evaluation of signs and symptoms of active TB and risk for exposure to TB.

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

[i] Pregnancy testing will consist of serum testing at the Screening Visit. Urine pregnancy tests will be performed at all other visits where specified.

[j] See Exclusion Criterion 9.

Table 1–1: Schedule of activities

Visit Name or Weeks After 1st Dose[a] / Protocol activity	Screening[b]	Initial Treatment Period (weeks after first dose)										Maintenance Treatment Period (weeks after first dose)																PEOT	SFU[c]
		Bsl 1st dose 0	1	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48		

[k] The HIV test result will not be recorded in the eCRF.
[l] A chest x-ray must be performed at the Screening Visit, or must occur within 2 months prior to Screening and results must be available at Baseline. A CAT scan of chest at Screening or within 2 months prior to Screening is acceptable, if available. The official report of the imaging must specifically indicate the absence of findings suggestive of current active TB or prior inactive TB.
[m] Quantiferon Gold Plus will be used for this analysis. Details on IGRA assessment are provided in Section 8.2.6.3.4.
[n] Lesion count will be performed at the specified study visits, and must address all relevant anatomical regions in each study participant; Hurley Stage is included as an assessment performed during the lesion count. The data collected from the lesion count will be used for the derivation of the $HiSCR_{25}$, $HiSCR_{50}$, $HiSCR_{75}$, $HiSCR_{90}$, $HiSCR_{100}$, HS Physician's Global Assessment, and International Hidradenitis Suppurativa Severity score system (IHS4).
[o] At certain sites, where feasible, representative photographs of the changes in skin will be captured. Photographs will be anonymized.
[p] All blood samples taken prior to dosing.
[q] All genomic, proteomic, and metabolomic samples and the genetic/epigenetic samples will be stored at -80°C at the central biorepository for up to 20 years.
[r] The HSSDD (pain, smell or odor, drainage or oozing from HS lesions, and itch) will be completed daily from Screening through Week 16.
[s] Randomization occurs at the Baseline Visit for all study participants.
[t] IMP administration is based on randomization at the Baseline Visit for all study participants. Double-dummy IMP administration will occur [redacted] in all study participants to maintain the study blind. The dosing window is ±3 days relative to the scheduled dosing visit.

2 INTRODUCTION

2.1 Study rationale

UCB is investigating bimekizumab (a humanized, full-length immunoglobulin [Ig] G1 monoclonal antibody [mAb] with high affinity for human interleukin [IL] 17 [IL-17A and IL 17F]) for the treatment of hidradenitis suppurativa (HS). Antibodies targeting IL-17A are effective in treating patients with moderate to severe psoriasis (PSO) and other immuno-inflammatory conditions. Data from clinical studies with bimekizumab suggest that inhibition of both IL-17A and IL-17F could be beneficial to patients with such conditions, including HS. Based on results from a Phase 2a study in study participants with HS (HS0001; European Union Drug Regulating Authorities Clinical Trials [EudraCT] Number 2017-000892-10, NCT03248531) and a Phase 2b study in study participants with PSO (PS0010) and its 48 week extension study (PS0011), bimekizumab doses of 320mg every 2 weeks (Q2W) in HS and 320mg every 4weeks (Q4W) in PSO, appeared to have an acceptable safety profile, and achieved clinically meaningful efficacy in both primary and key secondary endpoints in their respective studies. Based on these data and considering the high unmet need for safe and effective therapies for HS, confirmatory studies are being conducted with bimekizumab for the treatment of moderate to severe HS.

2.2 Background

Hidradenitis suppurativa or acne inversa is a chronic, inflammatory, recurrent, debilitating skin disease that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillaries, inguinal, and anogenital regions (Dessau definition, First International Conference on HS, 30 Mar to 01 Apr 2006, Dessau, Germany). The nodules are often inflamed, can progress to abscess formation, and may rupture to form fistulas and subsequent scarring. Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved skin areas. Hidradenitis suppurativa is also associated with several complications (eg, the development of anal, urethral, and rectal strictures and fistulas), and the excessive scarring and fibrosis produced by HS lesions can lead to contractures and limitations in limb mobility (Alikhan, 2009; Danby, 2010).

Hidradenitis suppurativa is estimated to affect about 1% of the adult European population, with a female to male ratio of approximately 3:1 (Revuz, 2008; Naldi, 2006). The prevalence of diagnosed HS in the US may be lower (<0.1%), although further research is needed to determine the prevalence of undiagnosed HS in the US (McMillan, 2014). Patients diagnosed with HS often experience a significant reduction in quality of life (QOL), equivalent to severe PSO (Sartorius, 2009), due to the location of, and discharge from, the lesions that leads to an often persistent morbidity due to pain and sequelae from uncontrolled inflammation (von der Werth, 2001; Wolkenstein, 2007). The reduction in QOL and persistent morbidity result in functional impairment in patients with HS similar or greater to that of heart disease, diabetes, or asthma, when measured by the European Quality-of-Life 5 dimensions 3-level questionnaire (EQ-5D-3L) scale (Riis, 2016).

Bimekizumab is a humanized full-length mAb of IgG1 subclass being developed for the treatment of patients with inflammatory diseases such as PSO, psoriatic arthritis, axial spondyloarthritis, and HS. Bimekizumab has high affinity for human IL-17A and human IL-17F,

and selectively and potently inhibits the activity of both isoforms in vitro. The key pro-inflammatory cytokine IL-17A has been demonstrated to, and IL-17F is believed to, play important roles in autoimmune and inflammatory diseases. Published data and immunohistochemistry studies performed by UCB have shown that expression of both IL-17A and IL-17F is present in HS lesions, and there are published reports highlighting the potential for IL-17A and IL-17F to drive HS disease pathology (UCB Research Report 40001864; Cho, 2012; Schlapbach, 2011). This supports the hypothesis that the IL-17 cytokine family is a potential therapeutic target in HS. Bimekizumab is hypothesized to demonstrate a treatment response in HS because it selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro.

2.3 Benefit/risk assessment

Overall, the Phase 2a POC study in HS (HS0001) demonstrated that the safety profile (during 10 weeks of dosing for a 12-week treatment period) for bimekizumab 320mg sc Q2W appears consistent with that of bimekizumab in other indications (PSO, psoriatic arthritis, axial spondyloarthritis) for which bimekizumab is being developed.

Treatment-emergent adverse events (TEAEs) experienced by study participants with HS receiving repeated doses of bimekizumab occurred at incidences similar to those with placebo and adalimumab (range: 61.9% to 71.4%). In both the bimekizumab and adalimumab groups, the most frequently reported TEAEs were in the system organ classes of Infections and infestations (43.5% and 42.9%, respectively), Skin and subcutaneous tissue disorders (28.3% and 42.9%, respectively), and General disorders and administration site conditions (21.7% and 23.8%, respectively). The most frequently reported TEAEs in the placebo group were in the SOCs of Nervous system disorders (28.6%) and Infections and infestations and Skin and subcutaneous tissue disorders (19.0% each). The most frequently reported TEAEs (by preferred term) were hidradenitis (17.4%) and fatigue (8.7%) in the bimekizumab group, hidradenitis (33.3%) and influenza (14.3%) in the adalimumab group, and headache and hidradenitis (14.3% each) and arthralgia (4.8%) in the placebo group. Events of hidradenitis were not unexpected in a population of study participants with moderate-to-severe HS.

With regard to TEAEs of special interest and other safety topics of interest, there were no major adverse cardiovascular events, serious fungal/opportunistic infections (including tuberculosis [TB]), malignancies (including lymphoma), neuropsychiatric events, cases of inflammatory bowel disease (IBD), evidence of hepatotoxicity (per Hy's Law criteria), or hypersensitivity/anaphylactic reactions reported with bimekizumab treatment. No new safety signals were identified in HS0001 compared with those observed with bimekizumab across other development programs to date.

No clinically relevant patterns of changes were observed in any treatment group in hematology, clinical chemistry, vital signs, or electrocardiogram (ECG) findings. Few markedly abnormal post-Baseline liver function test values were reported during the study.

With respect to benefit, the totality of the data from HS0001 demonstrated that bimekizumab results in clinically meaningful and consistent improvements versus placebo across all HS outcome measures assessed. Improvements began early after initiation of treatment, and persisted through the last assessment (Week 12). The efficacy data for the primary endpoint, $HiSCR_{50}$ (ie, a 50% reduction in the total abscess and inflammatory nodule [AN] count with no

increase from Baseline in abscess or draining tunnel count) at Week 12, were comparable with that of adalimumab, and other efficacy measures suggested improved therapeutic outcomes (larger proportions of study participants achieving $HiSCR_{75}$ [a 75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count], $HiSCR_{90}$ [a 90% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count], and Dermatology Life Quality Index [DLQI] total scores of 0 and 1).

Overall, results of HS0001 show that bimekizumab appears to have an acceptable safety profile considering the anticipated benefit at a dose of 320mg Q2W for the treatment duration evaluated to date. No new safety concerns were raised in study participants with moderate to severe HS, and the benefit/risk remains positive and supports continued investigation of bimekizumab at 320mg Q2W.

More detailed information about the known and expected benefits and risks of bimekizumab may be found in the Investigator's Brochure.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
Evaluate the efficacy of bimekizumab in study participants with moderate to severe HS	• $HiSCR_{50}$ at Week 16
Secondary	
Evaluate the efficacy of bimekizumab on other measures of disease activity in study participants with moderate to severe HS	• $HiSCR_{75}$ at Week 16 • Flare (defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline) by Week 16 • Absolute change from Baseline in DLQI Total Score at Week 16 • Absolute change from Baseline in Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HSSDD • Pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) at Week 16
Evaluate the safety of bimekizumab in study participants with moderate to severe HS	• Treatment-emergent AEs • Serious TEAEs • TEAEs leading to withdrawal from study
Other	
Evaluate the efficacy of bimekizumab on HiSCR, other HS Scores, and other clinical measures of disease activity at various timepoints in study participants with moderate to severe HS	• Time to response of $HiSCR_{25}$, $HiSCR_{50}$, $HiSCR_{75}$, $HiSCR_{90}$, and $HiSCR_{100}$ • $HiSCR_{25}$, $HiSCR_{50}$, $HiSCR_{75}$, $HiSCR_{90}$, and $HiSCR_{100}$ • Absolute change from Baseline in International Hidradenitis Suppurativa Severity Score System • Change from Baseline in the HS-Physician's Global Assessment 6-point scale • Absolute and percentage change from Baseline in hs-CRP • Initiation of systemic antibiotic rescue therapy • $HiSCR_{25}$, $HiSCR_{50}$, $HiSCR_{75}$, $HiSCR_{90}$, and $HiSCR_{100}$ at both Weeks 16 and 48 • Time to loss of response of $HiSCR_{50}$, $HiSCR_{75}$, $HiSCR_{90}$, and $HiSCR_{100}$ in Week 16 responders

Objectives	Endpoints
	• Partial responders (defined as a ≥25% reduction in AN count from Baseline [Week 0]) at Week 16 who progress to $HiSCR_{50}$ during the Maintenance Treatment Period • Partial responders (defined as a ≥25% reduction in AN count from Baseline [Week 0]) at Week 16 who progress to $HiSCR_{75}$, $HiSCR_{90}$, and $HiSCR_{100}$ response during the Maintenance Treatment Period
Evaluate the efficacy of bimekizumab on abscesses, nodules, and draining tunnels at various timepoints in study participants with moderate to severe HS	• Change and percentage change from Baseline in lesion counts (abscess count, inflammatory nodule count, AN count, and draining tunnel count) • AN count of 0, 1, or 2 • AN_{25}, AN_{50}, AN_{75}, AN_{90}, AN_{100} • Flare (defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Week 16) by Week 48 • Time to flare from Weeks 0 to 16 • Time to flare from Week 16 to 48
Evaluate the efficacy of bimekizumab on patient-reported outcome measures at various timepoints in study participants with moderate to severe HS	• Absolute and percentage change (worst and average pain) from Baseline in HS Skin Pain score (11-point numeric rating scale) • Pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) • Pain response (defined as a decrease from Baseline in HSSQ weekly worst skin pain score at or beyond the threshold for clinically meaningful change) • Pain response (at least a 30% reduction and at least a 1-unit reduction from Baseline in HSSDD weekly worst skin pain score [11-point numeric rating scale]) among study participants with a score of ≥3 at Baseline • Pain response (at least a 30% reduction and at least a 1-unit reduction from Baseline in HSSDD weekly average skin pain score [11-point numeric rating scale]) among study participants with a score of ≥3 at Baseline • Pain response (at least a 30% reduction and at least a 1-unit reduction from Baseline in HS Skin Pain score [11-point numeric rating scale]) assessed by the HSSQ among study participants with a score of ≥3 at Baseline • Absolute change from Baseline in DLQI Total Score • DLQI Total Score of 0 or 1

Objectives	Endpoints
	• Minimum clinically important difference (improvement from Baseline of 4 or more) in the DLQI Total Score among study participants with a Baseline score of at least 4) • Absolute change from Baseline in HiSQOL domain scores (symptoms, psychosocial, activities, adaptations) • Absolute change from Baseline in Patient Global Impression of HS Severity • Absolute change from Baseline in Patient Global Impression of Severity of HS Skin Pain • Absolute change from Baseline in each of the other HS Symptoms - itch, drainage or oozing of HS lesions, and smell or odor. • Response on other HS Symptoms (11-point numeric rating scale) - itch, drainage or oozing of HS lesions, and smell or odor • Responses to the EQ-5D-3L, absolute and changes from Baseline in EQ-5D-3L visual analog scale scores • Absolute change from Baseline in Work Productivity and Activity Impairment Questionnaire-Specific Health Problem v2.0 adapted to HS scores • Domain Scores (effectiveness, convenience and global satisfaction) on the Treatment Satisfaction Questionnaire – Medication-9
Evaluate the effect of bimekizumab on other safety measures at various timepoints in study participants with moderate to severe HS	• Adverse events of special interest (Hy's Law) • Other safety topics of interest: infections (serious, opportunistic, fungal, and TB), neutropenia, hypersensitivity (including anaphylaxis), suicidal ideation and behavior, , major adverse cardiovascular events, hepatic events and potential drug-induced liver injury (PDILI), malignancies, and inflammatory bowel disease. • Absolute change from Baseline in the PHQ-9 score • Absolute change from Baseline in vital signs • Absolute change from Baseline in clinical laboratory values (chemistry and hematology) • ECG results
Evaluate the pharmacokinetics of bimekizumab in study participants with moderate to severe HS	• Plasma bimekizumab concentrations over the study duration

Objectives	Endpoints
Evaluate the immunogenicity of bimekizumab (antidrug antibodies) in study participants with moderate to severe HS	• Bimekizumab antidrug antibodies • Bimekizumab neutralizing antibodies
Exploratory	
Evaluate biomarkers in study participants with moderate to severe HS.	• Genomic, genetic, epigenetic, proteins, and metabolite biomarkers may be measured to evaluate the relationship with response to treatment with bimekizumab, HS disease biology, and inflammatory and immune response processes. The candidate exploratory biomarkers are the blood or blood derivative (eg, plasma) concentrations of cytokines and chemokines of relevance to the IL-17A/F signaling pathway and HS biology. Additional biomarkers may include, but will not be limited to, plasma complement concentrations.

AE=adverse event; AN=abscess and inflammatory nodule; AN_{25}=a 25% reduction in the total abscess and inflammatory nodule count relative to Baseline; AN_{50}=a 50% reduction in the total abscess and inflammatory nodule count relative to Baseline; AN_{75}=a 75% reduction in the total abscess and inflammatory nodule count relative to Baseline; AN_{90}=a 90% reduction in the total abscess and inflammatory nodule count relative to Baseline; AN_{100}=a 100% reduction in the total abscess and inflammatory nodule count relative to Baseline; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; eC-SSRS=electronic Columbia Suicide Severity Rating Scale; EQ-5D-3L=Euro-Quality of Life 5-Dimensions, 3 levels; HiSCR=Hidradenitis Suppurativa Clinical Response; $HiSCR_{50}$=a 50% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{75}$=a 75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{90}$=a 90% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{100}$=a 100% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HiSQOL=Hidradenitis Suppurativa Quality of Life; HS=hidradenitis suppurativa; hs-CRP=high-sensitivity C-reactive protein; HSSDD=Hidradenitis Suppurativa Symptom Daily Diary; HSSQ=Hidradenitis Suppurativa Symptom Questionnaire; PDILI=potential drug-induced liver injury; PHQ-9=Patient Health Questionnaire Depression Module; QOL=quality of life; TB=tuberculosis; TEAE=treatment-emergent adverse event

4 STUDY DESIGN

4.1 Overall design

HS0004 is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, pivotal study evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS. Study participants meeting the inclusion criteria who do not meet any exclusion criteria will complete a Screening Period of 14 days to up to 5 weeks; a double-blind, 48-week Treatment Period comprising a 16-week Initial Treatment Period and 32-week Maintenance Treatment Period; and a 20-week Safety Follow-up (SFU) Period following the final injection of investigational medicinal product (IMP) if study participants do not enter a subsequent extension study (HS0005) or withdraw prematurely from treatment.

Study participants will be randomized in a 2:2:2:1 ratio (stratified by Hurley Stage and current antibiotic use) to 1 of 3 dose regimens of bimekizumab or placebo as shown in the schematic (Figure 1-1). All doses of IMP will be administered by sc injection. The primary efficacy variable at Week 16 is $HiSCR_{50}$. Study visits will occur at Screening; Baseline (Week 0); Weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16; and [redacted] from Week 16 through Week 48 for assessments of efficacy, safety, and other measures of QOL/health status/work productivity. An SFU visit will be conducted 20 weeks after the last dose of IMP for participants who do not enter the extension study, or who are prematurely withdrawn from the study.

4.1.1 Screening Period (Weeks -5 to 0)

The Screening Period will last a minimum of 14 days up to a maximum of 5 weeks prior to randomization.

4.1.2 Initial Treatment Period (Weeks 0-16) and Maintenance Treatment Period (Weeks 16-48)

Eligible study participants will be randomized in a 2:2:2:1 ratio as noted in the Study Schema to:

- Bimekizumab [redacted] from Weeks 0 to 48
- Bimekizumab [redacted] from Weeks 0 to 48
- Bimekizumab [redacted] to Week 16, continuing on [redacted] from Weeks 16 to 48
- Placebo to Week 16, continuing on bimekizumab [redacted] from Weeks 16 to 48

4.1.3 Safety Follow-up Visit

All study participants not continuing in the extension study, including those withdrawn from IMP as well as those completing all study visits, will have an SFU Visit 20 weeks after their final dose of IMP.

4.1.4 Visit Windows

Visit windows are ±3 days (based on the date of the first dose). The minimum number of days between 2 consecutive injection visits is 8 days (eg, Visit 2 +3 days occurs on Day 17; Visit 4 -3 days occurs on Day 25). However, the minimum of 8 days between injections may be used only 1 time in the Initial Treatment Period and 1 time in the Maintenance Treatment Period, if needed. The study participant should be dosed according to the administration schedule thereafter. The 20-week SFU Visit window is ±7 days (based on the date of the final dose).

4.2 Scientific rationale for study design

A randomized, double-blind, placebo-controlled study design has been selected to demonstrate efficacy and safety of bimekizumab for regulatory approval. The study population will include adults with moderate to severe HS. The inclusion and exclusion criteria were designed to ensure the safety of study participants, and to enroll a broad HS study participant population representative of clinical practice in terms of disease severity and morbidity (physical disability and discomfort) that warrants therapy with a systemic agent. Considering that study participants with moderate to severe HS are treated with different antibiotics, systemic tetracyclines have been selected as the most appropriate class of antibiotics for the study based on the current therapeutic guidelines for HS.

The primary efficacy outcome measure ($HiSCR_{50}$) is a validated clinical outcome measure for evaluating efficacy in study participants with moderate to severe HS.

In addition, a core domain set for HS study outcome established for HS calls for the concurrent measurement of 5 core outcome domains agreed by both patients and health care providers: pain, physical signs, HS specific quality of life, global assessment and progression of course. A sixth domain, symptoms, has also been recommended by the Steering Group because it received strong support from the patient stakeholder group (Thorlacius, 2018).

The Screening Period is included to ensure eligibility criteria are met, including collection of laboratory data, verification that the doses of concomitant and allowable medications are stable, and to enable washout of any medications not permitted for use during the study.

The randomization allocation and sample sizes have been selected to (1) maximize exposures to bimekizumab test doses/regimens, (2) ensure adequate power to demonstrate superiority of bimekizumab to placebo for the primary endpoint ($HiSCR_{50}$) at Week 16, and (3) have sufficient sample size to detect statistically significant differences between treatments as specified in the secondary endpoints at Week 16.

An initial treatment period of 16 weeks will be used to demonstrate the efficacy of bimekizumab over placebo. The 32-week Maintenance Treatment Period will collect information on safety and efficacy beyond initial treatment.

The Maintenance Treatment Period is designed to assess the durability of response of the study endpoints and to provide sufficient longer-term (up to 48 weeks, including the Initial Treatment Period) safety and exposure to bimekizumab for regulatory filings. Continuous (up to 48 weeks) exposure to both the [redacted] bimekizumab [redacted] and [redacted] bimekizumab [redacted] dose regimens allow for the following assessments:

- Durability of response and longer-term safety
- Optimal dosing interval for maintenance treatment

This period will also allow study participants who received placebo in the Initial Treatment Period to begin receiving bimekizumab at Week 16 in the randomized, controlled Maintenance Treatment Period of the study.

4.3 Justification for dose

The pathophysiology of HS is an active area of research, with investigations targeting identification of the cytokines and immune pathways in HS. Recent reviews on the subject indicate the potential diversity of these inflammatory pathways and mediators, and the impact on treatment response to various pharmacologic interventions. As concluded by Frew, Hawkes, and Krueger, no current schema accurately predicts treatment efficacy to date (Prens, 2015; Frew, 2018). Furthermore, the inflammatory burden in HS seems greater than other autoinflammatory conditions affecting the skin (Van der Zee, 2011; Riis, 2015, Martorell, 2015). These data, and the current pharmacologic treatment of HS suggest that a more intensive dosing regimen (ie, dose level and/or frequency of administration) may be needed for the treatment of HS.

Consistent with the above literature, a [redacted] dose regimen of bimekizumab is being evaluated in the Phase 3 program for HS. This dose regimen is higher than those used in other

indications currently in Phase 3 development for bimekizumab; however, HS0001 results revealed that bimekizumab 320mg Q2W demonstrated consistent, clinically meaningful efficacy in the treatment of HS when compared to placebo, with safety results consistent with those of studies of bimekizumab in other indications in development. In addition, pharmacokinetic (PK) data from HS0001 demonstrated that study participants with HS have a lower exposure to bimekizumab than study participants with PSO given the same dose and regimen, thus necessitating higher bimekizumab doses for HS (maximum monthly bimekizumab dose of 640mg).

In addition to the 320mg Q2W dose used in HS0001, the highest dose being used in other bimekizumab indications (PSO dose regimen of [redacted]) is being used in this study. The assessment of both the [redacted] and [redacted] dosing frequencies in this study will help determine the optimal monthly bimekizumab dose required to sustain efficacy with long-term (maintenance) treatment.

4.4 End of study definition

A study participant will be considered to have completed the study if he or she completed the Week 48 visit.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities (Table 1–1) for the last study participant in the study globally, including the SFU, as applicable.

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

Age

1. Participant must be at least 18 years of age, at the time of signing the informed consent. If a study participant is under the local age of consent and is at least 18 years of age, written informed consent will be obtained from both the study participant and the legal representative.

Type of participant and disease characteristics

2a. Study participants must have a diagnosis of HS based on clinical history and physical examination for at least 6 months prior to the Baseline visit; diagnosis must be verifiable through medical notes and documentation.

3. Study participant must have HS lesions present in at least 2 distinct anatomic areas (eg, left and right axilla), 1 of which must be at least Hurley Stage II or Hurley Stage III at both the Screening and Baseline visits.

4. Study participant must have moderate to severe HS defined as a total of ≥5 inflammatory lesions (ie, number of abscesses plus number of inflammatory nodules) at both the Screening and Baseline visits.

5a. Study participant must have had a history of inadequate response to a course of a systemic antibiotics for treatment of HS at the Screening Visit as assessed by the Investigator through study participant interview and review of medical history; inadequate response must be verifiable through medical notes and documentation. Study participants who meet any of the following are NOT automatically excluded from the study:

- Demonstrated intolerance to (or during therapy became intolerant to) systemic antibiotics
- Had a contraindication to systemic antibiotics
- Responded to course(s) of systemic antibiotic(s) and subsequently exhibited recurrence after discontinuation of the antibiotic

Sex

6. Males and females may be study participants.

- A female study participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one 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 treatment period and for at least 20 weeks after the last dose of IMP.

Informed consent

7. Study participant was capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 Exclusion criteria

Study participants are excluded from the study if any of the following criteria apply:

Medical conditions

1. Study participant has any medical or psychiatric condition that, in the opinion of the Investigator, could jeopardize or would compromise the study participant's ability to participate in this study as determined by the Investigator based on protocol-required assessments.

<u>HS, Skin-Specific, and Other Inflammatory Disease</u>

2. Study participant has a draining tunnel count of >20 at the Baseline Visit.
3. Study participant has any other active skin disease or condition (eg, bacterial cellulitis, candida intertrigo, extensive condyloma) that may, in the opinion of the Investigator, interfere with the assessment of HS.
4. Study participant has a diagnosis of sarcoidosis, systemic lupus erythematosus, or active IBD. Note: Study participants with a diagnosis of Crohn's disease or ulcerative colitis are allowed if they have no active symptomatic disease at Screening or Baseline.

5. Study participant has a primary immunosuppressive condition, including taking immunosuppressive therapy following an organ transplant, or has had a splenectomy.

Other Medical Conditions

6. Female study participant who is breastfeeding, pregnant, or plans to become pregnant during the study or within 20 weeks following the final dose of IMP.
7. Study participant has an active infection or history of infection(s) as follows:
   - Any infection requiring systemic treatment within 14 days prior to Baseline
   - A serious infection, defined as requiring hospitalization or intravenous anti-infective(s) within 2 months prior to the Baseline Visit
   - A history of opportunistic, recurrent, or chronic infections that, in the opinion of the Investigator, might cause this study to be detrimental to the study 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)
8. Study 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 and Prevention 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 a course of prophylaxis prior to IMP dosing. Participants can be rescreened after completion of a full course of prophylaxis plus a wash-out of least 5 half-lives of the prophylactic medication(s) prior to Baseline to avoid any interference with the study efficacy measurements (eg, concomitant antibiotics). 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
   - Current pulmonary nontuberculous mycobacterial (NTM) infection or history of pulmonary NTM infection 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 NTM infection refer to Section 8.2.6.
9. Study participant has an acute or chronic hepatitis B virus, hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection. Study participants who have evidence of, or tested positive for, hepatitis B or hepatitis C will be excluded. A positive test for hepatitis B virus is defined as: 1) positive for hepatitis B surface antigen, or 2) positive for anti-hepatitis B core antibody. A positive test for HCV is defined as: 1) positive for hepatitis C antibody, and 2) positive via a confirmatory test for HCV (for example, HCV polymerase chain reaction).

10. Study participants with concurrent malignancy are excluded. Study participants with a history of malignancy within the past 5 years prior to the Screening Visit are excluded, EXCEPT if the malignancy was a cutaneous squamous or basal cell carcinoma, or in situ cervical cancer that has been treated and is considered cured.
11. Study participant has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
12. Study participant has had major surgery within the 3 months prior to the Baseline Visit, or has planned major surgery after entering the study.
13. Study participant has any systemic disease (ie, cardiovascular, neurological, renal, liver, metabolic, gastrointestinal, hematological, immunological, etc.) considered by the Investigator to be uncontrolled, unstable, or likely to progress to a clinically significant degree during the course of the study.
14. Study participant has had a myocardial infarction or stroke within the 6 months prior to the Screening Visit.
15. Study participant has a history of chronic alcohol or drug abuse within 6 months prior to Screening as evaluated by the Investigator based on medical history, interview, and/or results of the Screening urine drug screen.

16a. Study participant has the presence of active suicidal ideation, or positive suicide behavior using the "Screening" version of the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) with either of the following criteria:

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

17. Study participant has presence of moderately severe major depression or severe major depression indicated by a score of ≥15 using the screening Patient Health Questionnaire Depression Module (PHQ-9). Medication used to treat depression should be stable for 8 weeks prior to Baseline.
18. Study participant has a known hypersensitivity to any components of bimekizumab or comparative drugs as stated in this protocol.

Prior/Concomitant therapy

19a. Study participant has had prior treatment with an IL-17 biologic response modifier or has participated in IL-17 biologic response modifier study unless an appropriate washout has been performed since the last dose of IMP (within 6 months prior to the Baseline Visit or 5 half-lives [whichever is greater]).
20. Study participant received prescription topical therapies for the treatment of HS within 14 days prior to the Baseline Visit.

21. Study participant is currently receiving systemic nonbiologic or biologic therapies for HS with potential therapeutic impact for HS. Note: If study participant received systemic nonbiologic or biologic therapies for HS and stopped these treatments, washout periods should be applied as shown in Table 6–3. Note: this does not apply to study participants who may be eligible for randomization into the antibiotic strata.
22. If study participant is using concomitant, non-opioid analgesics for HS-related or non-HS-related pain as permitted by protocol, they should be on a stable (scheduled) dose for at least 14 days prior to the Baseline Visit and anticipate continuing that dose through Week 16 unless a decrease in dose is warranted based on symptoms. Opioid analgesics are excluded. Note: As needed (PRN) use is not considered a stable dose, but (for example) taking a nonsteroidal anti-inflammatory drug (NSAID) 3 times per week, every week is considered a stable dose.
23. Study participant has received any live (including attenuated) vaccination within the 8 weeks prior to the Baseline Visit (eg, inactivated influenza and pneumococcal vaccines are allowed, but nasal influenza vaccination is not permitted). Live vaccines are not allowed during the study, including the SFU Period (20 weeks after the last dose of IMP).
24. Study participant has received Bacillus Calmette-Guerin vaccination within 1 year prior to IMP administration.

Prior/Concurrent clinical study experience

25. Study participant has previously participated in this study or study participant has previously been assigned to treatment in a study of the medication under investigation in this study, and received at least 1 dose of IMP (including placebo).
26. Study participant is currently participating in another study of a systemic medication under investigation, including SFU. Study participant must be washed out of the medication as indicated in Table 6–3.
27. Study participant is currently participating in another study of a topical medication under investigation, including SFU. Study participant must be washed out of the medication for 4 weeks prior to the Baseline Visit.
28. Study participant is currently, or was within the 4 weeks prior to the Baseline Visit, participating in another study of a medical device under investigation.

Diagnostic assessments

29. Study participant has laboratory abnormalities at Screening, including any of the following:
    - ≥3× the upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)
    - Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
    - White blood cell count $<3.00\times10^3/\mu L$
    - Absolute neutrophil count $<1.5\times10^3/\mu L$

- Lymphocyte count <500 cells/µL
- Hemoglobin <8.5g/dL

Note: 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, study participants whose results remain outside this threshold should not be randomized.

30. Study participant has any other laboratory abnormality, which, in the opinion of the Investigator, will prevent the study participant from completing the study or will interfere with the interpretation of the study results.

Other exclusions

31. Study participant is a UCB employee or is an employee of third-party organizations involved in the study.
32. Study participant and/or his or her immediate family member is an employee, volunteer, or other worker at the investigative site either affiliated or not affiliated with this study. Immediate family is defined as a spouse, parent, child, or sibling whether biological or legally adopted.

5.3 Lifestyle restrictions

Not applicable to this study.

5.4 Screen failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized to study treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAE). Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened, following discussion with the Medical Monitor or Sponsor's study physician.

Participants who are rescreened should be assigned a new participant number for rescreening.

A study participant may be rescreened 1 time for reasons including, but not limited to, the following:

- Individual laboratory screening tests for which the results are exclusionary can be retested (eg, tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation. Test can also be repeated during rescreening.) Of note, repetition of laboratory screening tests within the Screening Period is permitted for technical reasons (eg, frozen sample, expired laboratory kit) without contacting the Medical Monitor.
- Eligibility assessments that could not be completed as planned (eg, for technical reasons) within the defined Screening Period of 5 weeks without approval by Medical Monitor.
- Abnormal ECG results.

- Did not meet the required washout period for concomitant medications.
- Study participant needs to complete a full course of antibiotic therapy for LTBI plus a wash-out of least 5 half-lives of the prophylactic medication(s) prior to Baseline as described in Exclusion Criterion 8 (Section 5.2).
- If the study participant requires an incision and drainage procedure for a HS lesion(s) during the Screening Period, the study participant should be screen failed. The participant can be rescreened when the lesion is considered healed. The study participant must have completed antibiotics/analgesic treatment if required for the procedure before rescreening as described in Table 6–3.

Study participants who fail to meet the eligibility criteria for PHQ-9, eC-SSRS, or the TB questionnaire are not allowed to be rescreened.

The Medical Monitor must be contacted for confirmation of rescreening/retesting in all other cases.

6 STUDY TREATMENTS

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

6.1 Treatments administered

Eligible study participants will be randomized in a 2:2:2:1 ratio as noted in the Study Schema (Figure 1-1).

A summary of the treatments administered is provided in Table 6–1.

Table 6–1: Study medications administered

ARM Name	Bimekizumab	Placebo
Intervention name	Bimekizumab	Placebo
Type	Biologic	Drug
Dose formulation	Solution for injection (pre-filled 1-mL syringe)	Solution for injection (pre-filled 1-mL syringe)
Unit dose strengths	160mg/mL	0.9% sodium chloride aqueous solution (physiological saline, preservative free) of US Pharmacopoeia/European Pharmacopoeia quality appropriate for injection; same volume to maintain blinding to the study participant
Dosage levels	[redacted]	Not applicable
Route of administration	Subcutaneous injection	Subcutaneous injection
Use	Experimental	Placebo comparator
Investigational Medicinal Product and Non-Investigational Medicinal Product	Investigational Medicinal Product	Investigational Medicinal Product
Sourcing	Provided centrally by the Sponsor.	Provided centrally by the Sponsor.
Packaging and labeling	Study Intervention will be provided in a kit. Each kit will be labeled as required per country requirement	Study Intervention will be provided in a kit. Each kit will be labeled as required per country requirement
Current/Former names or aliases	Bimekizumab	Not applicable

Because of differences in the dosing schedules and in order to maintain blinding, all study participants will receive 2 injections sc [redacted] from Week 0 to Week 46 as depicted in Table 6–2.

[redacted]

6.2 Preparation, handling, storage, and accountability requirements

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

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

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment 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 study treatment are provided in the IMP Handling Manual.

6.2.1 Drug accountability

A 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 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

6.3.1 Randomization and numbering of participants

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

To enroll a study participant at Screening, the Investigator or designee will contact the IRT and provide brief details about the study participant to be enrolled. Each study participant will receive a unique number assigned at Screening that serves as the study participant identifier throughout the study. The study participant number will be required in all communication between the Investigator or designee and the IRT regarding a particular study participant. Study participant numbers and kit numbers will be tracked via the IRT.

To randomize a study participant, the Investigator or designee will contact the IRT and provide brief details about the study participant to be randomized. The IRT will automatically inform the Investigator or designee of the study participant's randomization number. The IRT will allocate kit numbers to the study participant based on the study participant number during the course of the study. The randomization number must be incorporated into the case report form (CRF).

6.3.2 Procedures for maintaining and breaking the treatment blind

6.3.2.1 Maintenance of study treatment blind

All study participant treatment details will be allocated and maintained by the IRT system.

The IRT provider will receive the randomization code at the start of the study.

Due to differences in presentation between bimekizumab and placebo treatments, special precautions will be taken to ensure study blinding; study sites will have blinded and unblinded personnel. Bimekizumab and placebo injections will be administered at the investigational sites by unblinded, dedicated study personnel according to the site-specific blinding plan. Unblinded study personnel will be responsible for recording the administration information on source documents, and administration of the IMP as sc injections. Study site pharmacists or other suitably qualified site personnel who are responsible for preparation and administration of IMP treatments will have access to treatment allocations for individual study participants via the IRT. The unblinded pharmacy monitors from the Contract Research Organization (CRO), and the UCB Clinical Trial Supply representative will also have access to the treatment allocations and to the drug accountability records, if applicable.

The following individuals may, as necessary, have access to the randomization code as indicated:

- Members of the Data Monitoring Committee (DMC) who participate in unblinded sessions will be given information about the IMP allocation for those study participants for whom data are provided.
- The unblinded, independent CRO staff supporting preparation of the data outputs for the DMC reviews.

The unblinded study site personnel will not be involved in the study in any way other than assuring the IMP is taken from the correct kit and prepared according to the IMP-handling manual, and administering the IMP to the study participants.

In addition, high-sensitivity C-reactive protein (hs-CRP) results will not be reported to any blinded study personnel as long as the study remains blinded.

6.3.2.2 Breaking the treatment blind in an emergency situation

In the event of an emergency, it will be possible to determine to which treatment arm and dose the study participant has been allocated by contacting the IRT. The Investigator is responsible for

breaking the treatment blind in case of emergency. All sites will be provided with details of how to contact the system for code breaking at the start of the study. The Medical Monitor and/or UCB study physician or equivalent should be consulted prior to unblinding, whenever possible.

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

Inadvertent unblinding will be listed as a major protocol deviation.

6.4 Treatment compliance

During the double-blind Initial Treatment and Maintenance Treatment Periods, IMP will be administered in the clinic and compliance will be recorded at the visit by study personnel in the eCRF. Drug accountability must be recorded on the Drug Accountability form.

6.5 Concomitant medications/treatments

6.5.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications are permitted during the study:

- Wound care: Concomitant use of wound care dressings on HS wounds is allowed; however, options are limited to alginates, hydrocolloids, and hydrogels and use of these will be recorded in the eCRF.
- Lesion care: Concomitant use of saline, water, and/or Vaseline (petroleum jelly) is allowed for care of skin lesions and use of these will be recorded in the eCRF.
- Analgesic therapy:
  - Study participants will be required to wash out of all analgesics for HS-related pain 14 days prior to Baseline. However, if a study participant is on a stable (scheduled) dose of a non-opioid analgesic for HS-related pain, or for a non-HS medical condition (eg, osteoarthritis, neuropathic pain), the study participant may continue the analgesic. Opioid analgesics (including tramadol) are excluded for any indication.

    Notes: (1) Dose should be stable for 14 days prior to Baseline, and is anticipated to remain stable throughout study participation. (2) Dosing PRN is not considered stable, but (for example) taking an NSAID 2 or 3 times per week every week is considered a stable dose.
  - If a study participant's pain (HS-related or non–HS-related) worsens after Baseline, the study participant may initiate analgesic therapy at any time and/or per local labeling as follows: For HS-related pain, permitted analgesics are limited to ibuprofen at a dose of up to 800mg orally every 6 hours, not to exceed 3.2g/24 hours; and/or acetaminophen/paracetamol as per local labeling. For non-HS-related pain, initiation of any new analgesic/treatment must not include exclusionary medications (eg, opioids and tramadol), and must be recorded on the eCRF.
  - All analgesic use (start dates, end dates, dose, reason) will be recorded on the eCRF.

- Antibiotic therapy:
  - For study participants entering the study in the antibiotic strata, they should be on a stable dose and regimen of doxycycline, minocycline, or an equivalent systemic tetracycline for 28 days prior to Baseline (Visit 2). The dose and regimen should remain stable throughout study participation, but at least through Week 16. Antibiotics taken on a PRN basis are not considered as a stable dose. After Week 16, participants may receive an antibiotic if required in the judgement of the Investigator. Also see Section 6.5.3.1 for details on systemic antibiotic rescue medication.
  - All antibiotic use (start dates, end dates, dose, reason) will be recorded on the eCRF.

6.5.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications and therapies are prohibited during the study (also see Table 6–3):

- All biologic therapy with a potential therapeutic impact on the disease being studied, including those listed in Table 6–3.
- Phototherapy (psoralen and ultraviolet A and/or ultraviolet B) or photochemotherapy.
- Immunomodulatory therapy, including topical or systemic steroids except as noted in Section 6.5.3.1 (Rescue Medications/Lesion Intervention), and Table 6–3.
- Topical and systemic therapies for HS (see Table 6–3).
- Surgical or laser intervention for an HS lesion except as outlined in Section 6.5.3.1 (Rescue Medications/Lesion Intervention).

Table 6–3: Exclusions for prior medications

Drug class	Exclusion criteria
Systemic antibiotics	Used within 2 weeks prior to the Baseline Visit. Note: See exception for permitted, stable doses of antibiotics in Section 6.5.1.
Systemic retinoids	Used within 4 weeks prior to the Baseline Visit
Systemic treatment (non-biologic) • Apremilast • Systemic immunosuppressant agents (eg: methotrexate, cyclosporine, azathioprine, thioguanine) • Systemic fumarate • Systemic oral or injectable corticosteroids • Phototherapy and radiotherapy (eg, psoralen and ultraviolet A and/or ultraviolet B) or photoradio/chemotherapy	Used within 4 weeks prior to the Baseline Visit. Note: See exception for permitted, stable doses of antibiotics in Section 6.5.1.
Anti-tumor necrosis factors (including biosimilars) adalimumab, etanercept, certolizumab, golimumab, infliximab	Used within 12 weeks prior to the Baseline Visit. Note: For etanercept, used within 1 month prior to the Baseline Visit.
Other biologics Abatacept Anakinra Natalizumab Belimumab Tocilizumab Efalizumab Or other biologics approved by regulatory agencies after the protocol is approved	Used within 12 weeks prior to the Baseline Visit Note: for other biologics approved by regulatory agencies after the protocol is approved: Washout of 6 months prior to the Baseline Visit or 5 half-lives prior to the Baseline Visit, whichever is greater.
Secukinumab, brodalumab, ixekizumab and other IL-17 inhibitors approved by regulatory agencies after the protocol is approved	Washout of 6 months prior to the Baseline Visit or 5 half-lives prior to the Baseline Visit, whichever is greater.
IL-12, IL-23 inhibitors: Ustekinumab Risankizumab Tildrakizumab Guselkumab Or other biologics approved by regulatory agencies after the protocol is approved	Used within 6 months prior to the Baseline Visit Note: for other biologics approved by regulatory agencies after the protocol is approved: Washout of 6 months prior to the Baseline Visit or 5 half-lives prior to the Baseline Visit, whichever is greater.

Table 6–3: Exclusions for prior medications

Drug class	Exclusion criteria
Janus kinase inhibitors Tofacitinib Baricitinib Filgotinib Upadacitnib Or other janus kinase inhibitors approved by regulatory agencies after the protocol is approved	Used within 12 weeks of the Baseline Visit or 5 half-lives prior to the Baseline Visit, whichever is greater
Any other systemic HS drug under investigation (or approved after the protocol is approved)	Used within 12 weeks or 5 half-lives prior to the Baseline Visit, whichever is greater
Rituximab	Used within 2 years of the Baseline Visit
Topical drugs for HS (including intralesional corticosteroids, over-the-counter and prescription drugs, as well as disinfectants for skin lesions, eg, chlorhexidine, povidone iodine)	Used within 14 days of the Baseline Visit
Topical corticosteroids (in HS-affected areas) for dermatological use	Used within 14 days of the Baseline Visit. Note: Topical steroids in non-HS affected areas are permitted.
Herbal medications for HS	Used within 14 days of the Baseline Visit
Vaccines	Administration of live (including attenuated) vaccines is not allowed within 8 weeks prior to Baseline, during the conduct of the study, and for 20 weeks after the final dose of IMP (see Exclusion Criteria #23 and #24). 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.
Analgesics	See Section 6.5.1.
Spironolactone	Permitted if indicated for non-HS-related condition (eg, polycystic ovary syndrome); and if study participant meets all other entry criteria. Study participant must be on a stable dose for at least 28 days prior to the Baseline visit.
Metformin	Permitted if indicated for non-HS-related condition (eg, diabetes mellitus); and if study participant meets all other entry criteria. Study participant must be on a stable dose for at least 28 days prior to the Baseline visit.

Table 6–3: Exclusions for prior medications

Drug class	Exclusion criteria
Finasteride and other 5α-reductase inhibitors	Permitted if indicated for non-HS-related condition (eg, benign prostatic hypertrophy); and if study participant meets all other entry criteria. Study participant must be on a stable dose for at least 28 days prior to the Baseline visit.

HS=hidradenitis suppurativa; IL=interleukin; IMP=investigational medicinal product

6.5.3 Rescue medication

The Sponsor will not supply rescue medication. The following rescue medications may be used:

6.5.3.1 Antibiotic Rescue Medication/Antibiotics

Any systemic antibiotic that is initiated (new antibiotic or change in the dose/type of current antibiotic) on or after Baseline (first day of study drug administration) will be considered rescue medication for both the Initial Treatment Period and Maintenance Treatment Period. If a newly initiated systemic antibiotic (or increase in dose/type of antibiotic) is required during the Initial Treatment Period based on disease flare or other extenuating circumstances, the Investigator should discuss the decision with the Medical Monitor.

6.5.3.2 Rescue Medications/Lesion Intervention

There are no absolute restrictions on the use of rescue medications for study participants whose HS deteriorates during the study. While the objectives of the study should be protected as much as possible through observance of the restrictions detailed above in Section 6.5, the well-being of the study participant will always take priority; study participants should be managed as deemed appropriate by the Investigator.

In the event an acutely painful lesion occurs that requires an immediate intervention, Investigators will have the option to perform interventions. Interventions can include analgesics for a limited period of time (see below), intralesional injections of triamcinolone, and/or incision and drainage of the abscess. Intralesional injections of triamcinolone (up to 20mg across all lesions at a given visit, and using a concentration of no more than 20mg/mL [suspension for injection]) must be consistent with the maximum number of interventions described below and clinical practice. Concomitant use of wound care dressings is permitted; however, options are limited to alginates, hydrocolloids, and hydrogels. Concomitant medications associated with the lesion intervention(s) must be captured in source documents and on the appropriate eCRF.

Any analgesic that is initiated (new analgesic, new class of analgesic, increased dose of an analgesic stable since Baseline, regardless of duration of treatment) after Baseline (first day of study drug administration) will be considered rescue pain medication for the Initial Treatment Period and Maintenance Treatment Period (Weeks 0 to 48).

A total of 2 protocol-allowed interventions are permissible during the Initial Treatment Period (from Baseline Visit to Week 16). Do not include analgesic rescue treatment in the number of protocol-allowed interventions. An intervention can occur on maximally 2 different lesions at the same visit, or on the same lesion at 2 different study visits. The same lesion cannot be treated

2 times at the same visit. If a study participant requires more than 2 interventions within the first 16 weeks of the study, then the study participant should be discontinued from the study.

During the Maintenance Treatment Period (Weeks 16 to 48), a maximum of 2 interventions every 4 weeks are permitted. Do not include analgesic rescue treatment in the number of protocol-allowed interventions. An intervention can occur on 2 different lesions at the same visit or on the same lesion at 2 different study visits. Within each 4-week period, the same type of intervention cannot be used 2 times on the same lesion. If a study participant requires more than 2 interventions within a 4-week period, or has 2 of the same interventions on the same lesion within that period, then the study participant should be discontinued from the study.

6.6 Dose modification

Dose modification is not applicable in this study.

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. See Section 9.7 for details on interim analyses to be evaluated by the DMC (ie, study may be stopped for futility but not for superior efficacy).

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.

Detailed procedures for reporting SAEs and other safety events which may meet study hold criteria are provided in Appendix 8.

6.8 Treatment after the end of the study

Study participants who complete HS0004 will have the option of enrolling in a Phase 3, multicenter, extension study (HS0005).

Study participants who elect not to enroll in HS0005 at Week 48 will be scheduled to have the SFU Visit 20 weeks after the final injection of IMP. During the SFU, if study participants' HS deteriorates, the Investigator may consider standard of care for HS 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 HS treatments during the SFU period. All concomitant medications and HS 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

Study medication will be stopped if the study participant develops a medical condition, adverse event (AE), or laboratory abnormality that, in the opinion of the Investigator, compromises the safety of the study participant or his or her ability to continue participation in the study. Study participants who are discontinued from IMP should be encouraged by the Investigator to return for all scheduled visits through Week 48, and the SFU Visit (if the Week 48 Visit is ≥20 weeks after the final dose of IMP, the SFU Visit is not required). 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 as agreed by the Investigator and the UCB study physician. Investigators should contact the Medical Monitor and/or UCB study physician, in advance whenever possible, to discuss the withdrawal of a study participant.

Study medication will be stopped if the study participant has a confirmed positive coronavirus disease 2019 (COVID-19) test result or a suspected COVID-19 infection. Study medication can be resumed after the participant's recovery from COVID-19, based on the Investigator's clinical judgement. All such cases must be discussed with the Medical Monitor or UCB study physician.

7.1.1 Study participant does not achieve partial response

If a study participant does not achieve a partial response (defined as a ≥25% reduction in AN count from Baseline [Week 0]) at any visit from Week 32 to 46, the Investigator should contact the Medical Monitor to discuss whether the study participant should continue on study.

7.1.2 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.

7.1.2.1 PDILI Discontinuation Criteria

The PDILI criteria below require immediate discontinuation of IMP for study participants with either of the following (see Section 10.6.2.1):

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

Similarly, the PDILI criterion below requires immediate discontinuation of IMP for:

- Study participants with ALT or AST ≥3×ULN 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 10.6.2.1 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 ≥5×ULN and <8×ULN, total bilirubin <2×ULN, and no eosinophilia (ie, ≤5%), with no fever, rash, or symptoms of hepatitis (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness).

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

7.1.2.1.1 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 10–1. 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.

7.1.3 Treatment interruptions

If a study participant is found to be persistently noncompliant (for example, missing 2 or more of the doses in the Initial Treatment Period or 3 or more doses during Maintenance Treatment Period) the Sponsor, in conjunction with the Investigator, will make a decision as to whether the study participant should be withdrawn from the study.

Note: Doses of IMP that were missed due to a reasonable interfering AE that does not allow administration of IMP due to safety reasons will not be considered for the evaluation of study participant discontinuation. Evaluation of the reasonability of the AE should be discussed immediately with the Medical Monitor.

Any participant who develops a clinically important infection or recurrent infections not responsive to standard therapy during the study must discontinue IMP until resolution of the

infection. The Investigator should use clinical judgement in deciding whether the participant should restart IMP and contact the Medical Monitor and UCB study physician to confirm the participant's suitability for continued participation in the study.

7.2 Participant discontinuation/withdrawal from the study

Note: For female study participants, please see Section 8.3.5 for pregnancy that occurs during the study as evidenced by a positive pregnancy test.

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

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

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

If a study participant withdraws from the study, he or 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) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If a study participant does not achieve a partial response (defined as a ≥25% reduction in AN count from Baseline [Week 0]) at any visit from Week 32 to 46, the Investigator should contact the Medical Monitor to discuss whether the study participant should continue on study.

Study participants will be withdrawn from the study, after being encouraged to complete the Premature End of Treatment (PEOT) and the SFU Visit if either of the following events occur:

1. Study participant withdraws his or her consent.
2. The Sponsor or a regulatory agency requests withdrawal of the study participant.

Study participants should be withdrawn from IMP and encouraged by the Investigator to return for all scheduled visits through Week 48, and the SFU Visit (if the Week 48 Visit is ≥20 weeks after the final dose of IMP, the SFU Visit is not required) if any of the following events occur:

1. Study participant develops an illness that would interfere with his or her continued participation.
2. Study participant is noncompliant with the study procedures or medications in the opinion of the Investigator.
3. Study participant takes prohibited concomitant medications as defined in this protocol (Section 6.5.2) that may present a risk to the safety of the participant or the integrity of the study data, in the opinion of the Investigator and/or the Medical Monitor and/or UCB study physician.
4. Study participant requires more than the number of protocol-allowed lesion interventions (see Section 6.5.3.2).

5. Study participant has a clinical laboratory value meeting any of the following criteria:
   a. Hepatotoxicity as described in Section 7.1.2.
   b. A laboratory value meeting any of the following criteria:
      – Absolute neutrophil count <1.0 x10^3/µL
      – Absolute lymphocyte count <200 cells/µL

   Study participants may remain on IMP 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 discontinued from the IMP. If the repeat absolute neutrophil count or absolute lymphocyte count is above the allowable values, the participant may continue to receive IMP.
6. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test (see Section 8.3.5 for more information regarding pregnancies).
7. A study participant considered as having either a suspected new LTBI or who develops active TB or an NTM infection during the study (including but not limited to, conversion demonstrated by interferon gamma release assay [IGRA] or other diagnostic means) must be immediately discontinued from IMP.
   – The study participant must immediately be permanently withdrawn from the study if further examinations result in a diagnosis of the following:
      – active TB or
      – an NTM infection, or
      – latent TB infection and study participant does not initiate TB prophylactic therapy, prematurely discontinues TB prophylactic therapy, or, in the opinion of the Investigator or Sponsor, is noncompliant with TB prophylactic therapy.

      The PEOT Visit must be scheduled as soon as possible, but not later than the next regular visit.
   – If the study participant is diagnosed with LTBI during the study and desires to continue in the study, he or she must immediately discontinue IMP and start TB prophylactic therapy. After at least 4 weeks of TB prophylaxis, the IMP can be restarted after discussion with the UCB study physician regarding results of laboratory assessments, physical examination, and TB questionnaire. The full course of TB prophylaxis treatment will be completed during the study.

   Confirmed active TB is an SAE and must be captured on an SAE Report Form and provided to the Sponsor in accordance with SAE reporting requirements. As with all SAEs, periodic follow-up reports should be completed as per protocol requirements until such time as the TB infection resolves.

   Additional information on TB policies is provided in Section 8.2.6.
8. Study participants with newly diagnosed IBD or with IBD flares during the study must:

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

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

9 Study participants must be referred immediately to a mental healthcare professional and may be withdrawn from the study based upon the Investigator's judgment of benefit/risk for:

- Active suicidal ideation as indicated by a positive response ("Yes") to Question 4 of the "Since Last Visit" version of the eC-SSRS
- Moderately severe major depression as indicated by a PHQ-9 score of 15 to 19 if this represents an increase of at least 3 points compared to the last visit

The mental health consultation must be recorded in the study participant's source documentation.

10. Study participants must be referred immediately to a mental healthcare professional and must be withdrawn from the study in case of:

- Active suicidal ideation as indicated by a positive response ("Yes") to Question 5 of the "Since Last Visit" version of the eC-SSRS.
- Any suicidal behavior since last visit.
- Severe major depression as indicated by a PHQ-9 score ≥20.

The mental health consultation must be recorded in the study participant's source documentation.

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

Study participants withdrawing from the study who are not continuing for all scheduled visits through Week 48, will undergo the PEOT Visit and the SFU Visit 20 weeks after their final dose of IMP, as applicable.

The eCRF must document the primary reason for withdrawal or discontinuation.

Investigators should contact the Medical Monitor and/or UCB study physician, whenever possible, to discuss the withdrawal of a study participant in advance.

Withdrawn participants will not be replaced.

7.3 Lost to follow up

A study 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 study participant fails to return to the clinic for a required study visit:

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

Should the study participant continue to be unreachable, he or 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).

Some study-specific assessments may be conducted remotely according to the study protocol during a pandemic or other exceptional circumstance (eg, hurricanes) due to the need to implement safety measures and guidance from regulatory authorities. In such a situation, which may be accompanied by local or global containment or other measures, sites may need to prohibit access to study participants and study-related personnel. Study participants' visits to the study site may be replaced by contingency measures. These measures are primarily established to ensure the safety of study participants during the course of the study and to maintain the study participants' treatment schedules, if the Investigator considers it appropriate. These measures include, but are not limited to, virtual visits or home-nursing visits replacing site visits, eg, telemedicine contacts or home-nursing visits when treatment and/or blood sampling is scheduled. Any study specific assessments not conducted due to such circumstances must be recorded appropriately in the source documents and eCRF. If it is related to the COVID-19 pandemic, then it must be captured in the COVID-19 impact eCRF page. The contingency measures are described in a contingency plan that will be maintained by UCB for the respective study. The contingency measures are shared with the Investigator and the respective study-related personnel as soon as there are indications that it is necessary to implement any of the measures.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor and/or UCB study physician immediately upon occurrence or awareness to determine if the study participant should continue or discontinue study treatment.

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 study participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all study participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the study participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may not be utilized for screening or Baseline purposes.

The maximum amount of blood collected from each study participant over the duration of the study, including any extra assessments that may be required, will not exceed the usual volume of blood taken for a blood donation. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

The timing for all assessments described below is specified in Table 1–1.

8.1.1 Lesion count

The lesion count is defined as an assessment of all the various skin "appearances" that are termed "lesions" in HS study participants. The lesion count will include the following:

- Abscesses (circumscribed collection of purulent exudate frequently associated with swelling and other signs of inflammation, such as fluctuance, tenderness, and pain)
- Draining tunnels (fistulas/sinus tracts) (pathologic passageway connecting to the skin surface from dermis or sc tissue/pathologic passageway that develops into a channel to the skin surface that drains serous or purulent fluid, either spontaneously or by gentle palpation)
- Non-draining tunnels (fistulas/sinus tracts) (pathologic passageway connecting to the skin surface from dermis or sc tissue/pathologic passageway that develops into a channel to the skin surface that does not drain serous or purulent fluid)
- Noninflammatory nodules (nontender or minimally tender, nonerythematous nodules)
- Inflammatory nodules (a tender, erythematous, well-defined nodule. The lesion has no evidence of fluctuance. A pyogenic granuloma lesion is considered an inflammatory nodule; a papule or pustule is not considered an inflammatory nodule)
- Scars of HS lesions (enlargement or overgrowth of a scar so that it extends above the surrounding skin surface)

The data collected from the lesion count will be used for the derivation of study variables including, but not limited to $HiSCR_{25}$ (a 25% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count), $HiSCR_{50}$, $HiSCR_{75}$, $HiSCR_{90}$, $HiSCR_{100}$ (a 100% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count), HS Physician's Global Assessment, AN count, and International HS Severity score system (IHS4).

8.1.1.1 Hidradenitis Suppurativa Clinical Response (HiSCR)

The HiSCR; defined as at least a 50% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count; was developed to address issues with

available HS scoring systems. It is a validated endpoint that is responsive to improvement in disease activity, simplifies the scoring process, and increases the sensitivity to detect HS-specific lesions (Kimball, 2014; Kimball, 2016b). HiSCR has been labeled $HiSCR_{50}$ in this protocol.

The $HiSCR_{75}$, $HiSCR_{90}$, and $HiSCR_{100}$ also will be evaluated in this study. These measures of clinical response differ from $HiSCR_{50}$ only in the percent decrease in AN count from Baseline.

The $HiSCR_{xx}$ is derived by the statistical programming group based on Investigator documentation of lesion count, and does not require calculation on the part of the Investigator from the lesion count.

8.1.1.2 Hidradenitis Suppurativa Physician's Global Assessment

The HS Physician's Global Assessment is a validated 6-point scale that is used to measure improvement in inflammatory nodules, abscesses, and draining tunnels (Kimball, 2012; Zouboulis, 2015). The HS Physician's Global Assessment scale is defined by the following:

- Clear: No inflammatory or noninflammatory nodules
- Minimal: Only the presence of noninflammatory nodules
- Mild: ≥1 and ≤4 inflammatory nodules or 1 abscess or draining tunnel and no inflammatory nodules
- Moderate: ≥5 inflammatory nodules or 1 abscess or draining tunnel and 1 or more inflammatory nodules or 2 to 5 abscesses or draining tunnels and ≤10 inflammatory nodules
- Severe: 2 to 5 abscesses or draining tunnels and >10 inflammatory nodules
- Very severe: >5 abscesses or draining tunnels

This assessment (clear, minimal, mild, moderate, severe, or very severe) is derived based on totals across all affected body regions by the statistical programming group and does not require calculation on the part of the Investigator.

8.1.1.3 International Hidradenitis Suppurativa Severity Score System (IHS4)

The IHS4 is a validated tool to dynamically assess HS severity to be used both in real-life and the clinical trials setting (Zouboulis, 2017). The IHS4 achieved consensus among European HS Foundation members. This IHS4 score is calculated as follows: (number of nodules multiplied by 1) + (number of abscesses multiplied by 2) + [number of draining tunnels (fistulae/sinuses) multiplied by 4]. A score of 3 or less signifies mild HS, a score of 4–10 signifies moderate HS and a score of 11 or higher signifies severe HS.

The determination of IHS4 requires counting the nodules, abscesses and draining tunnels/sinus tracts.

The IHS4 score is derived by the statistical programming group, and does not require calculation on the part of the Investigator.

8.1.2 Partial response

A partial response is defined as a ≥25% reduction in AN count from Baseline [Week 0]) at a particular timepoint.

The partial response is derived by the statistical programming group, and does not require calculation on the part of the Investigator.

8.1.3 High-sensitivity C-reactive protein (hs-CRP)

Blood will be collected for measurement of hs-CRP. The hs-CRP data will not be sent to any blinded study personnel to protect the blinded nature of the treatment assignments and response.

8.1.4 Patient-reported outcomes

The patient-reported outcome (PRO) instruments should be completed by the study participants themselves in a quiet place. The PRO instruments to be completed at the study site, should be completed prior to all other protocol-specified assessments at each visit (including dosing on dosing days).

8.1.4.1 HS symptom measures of skin pain, smell or odor, drainage or oozing from HS lesions, and itch

8.1.4.1.1 HS symptom daily diary (HSSDD)

The 5 items on the HS Symptom Daily Diary (HSSDD) assesses patients' perception of the core symptoms of HS experienced in the past 24 hours: pain, smell or odor, drainage or oozing from HS lesions, and itch on an 11-point numeric rating scale (NRS). Two items assess skin pain (ie, worst skin pain and average skin pain). The remaining 3 items assess smell or odor, itch at its worst, and amount of drainage or oozing from HS lesions.

The HSSDD will be completed daily by the study participant, at the end of the day on an electronic hand-held device from the start of Screening through the Week 16 visit.

8.1.4.1.2 HS symptom questionnaire (HSSQ)

The 4 items on the HS Symptom Questionnaire (HSSQ) assesses patients' perception of the core symptoms of HS experienced in the past 7 days - pain, smell or odor, drainage or oozing from HS lesions, and itch on an 11-point NRS. The HSSQ will be completed on an electronic device during study visits (ie, Baseline and Weeks 16-48/PEOT).

8.1.4.2 Patient Global Impression of HS Severity (PGI-S-HS) and Change in HS Severity (PGI-C-HS)

The Patient Global Impression of HS Severity (PGI-S-HS) is a single item to assess study participants perceptions of the overall severity of HS over the past 7 days (none, mild, moderate, severe, very severe). The Patient Global Impression of Change in HS Severity (PGI-C-HS) is a single item to asses study participants perception of the change in HS since they started taking the study medication (much better, a little better, no change, a little worse, much worse). Data collected using the PGI-S-HS and PGI-C-HS will be used as anchors for interpreting change scores on the Hidradenitis Suppurativa Quality of Life (HiSQOL).

8.1.4.3 Patient Global Impression of Severity of Skin Pain (PGI-S-SP) and Change in Severity of Skin Pain (PGI-C-SP)

The Patient Global Impression of Severity of Skin Pain (PGI-S-SP) is a single item to assess study participants' perceptions of the severity of their skin pain from their HS lesions, over the past 7 days (none, mild, moderate, severe, very severe). The Patient Global Impression of Change in Severity of Skin Pain (PGI-C-SP) is a single item to assess study participants'

perceptions of change in their skin pain from their HS lesions, since they started taking the study medication (much better, a little better, no change, a little worse, much worse). PGI-S-SP and PGI-C-SP will be used to evaluate outcomes related to Skin Pain.

8.1.4.4 Hidradenitis Suppurativa Quality of Life Questionnaire (HiSQOL)

The 17 item HiSQOL questionnaire has a recall period of 7 days. The HiSQOL includes 3 subscales: symptom status, psychosocial impact, and impact on physical activities.

8.1.4.5 Dermatology Life Quality Index (DLQI)

The DLQI is a questionnaire designed for use in adult participants with inflammatory skin diseases and has been used in patients with HS (Finlay, 1998; Esmann, 2010; Basra, 2012). The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect participants' health-related QOL. This instrument asks participants about symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. The DLQI total score ranges from 0 to 30 with higher scores indicating lower health related QOL. In other dermatological/skin conditions, a 4-point change in the DLQI total score (DLQI response) has been reported to be meaningful for the participant (within participant minimal important difference); while a DLQI total absolute score of 0 or 1 indicates no or small impact of the disease on health related QOL.

8.1.4.6 Euro-Quality of Life 5-Dimensions, 3 levels

The EQ-5D-3L comprises 5 questions on mobility, self-care, pain, usual activities, and psychological status with 3 possible answers for each item (1=no problem, 2=moderate problem, 3=severe problem). In addition, the questionnaire includes a visual analogue scale to indicate the general health status, with 100 indicating the best health status.

8.1.4.7 Workers Productivity and Activity Impairment Questionnaire: Specific Health Problem

The Workers Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI-SHP) V2.0 is a patient-reported questionnaire that assesses study participant's employment status, work absenteeism, work impairment while working (presenteeism), overall work, and daily activity impairment attributable to a specific health problem (Reilly, 1993). It has been used in several clinical studies of biologic therapy in participants with plaque PSO (Kimball, 2012; Vender , 2012).

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

8.1.4.8 Treatment Satisfaction Questionnaire for Medication

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) is an abbreviated 9-item version of the TSQM, excluding the side effects of medication domain. The domains included in the TSQM-9 include effectiveness (3 items), convenience (3 items) and global satisfaction (3 items). The TSQM-9 domain scores range from 0 to 100 with higher scores representing higher satisfaction (Bharmal, 2009).

8.1.5 Hurley Stage

The Hurley Stage is a severity classification for HS that was developed in 1989 and is widely used for the determination of the severity of HS (Hurley, 1989).

The Hurley Stage is defined by the following criteria:

- Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
- Stage II: Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions.
- Stage III: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

Hurley Stage is assigned to a given anatomic region. The overall worst Hurley Stage (ie, the highest Hurley Stage across all anatomic regions) for a given study participant at a given visit is then the study participant-level Hurley Stage. This study participant-level Hurley Stage is important for baseline stratification and disease severity assessment.

Hurley stage is included as a stratification factor for randomization.

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the Schedule of Activities (Table 1–1).

8.2.1 Physical examination

A complete physical examination will include, at a minimum, general appearance; ear, nose, and throat; eyes, hair, and skin; and assessments of the cardiovascular, respiratory, gastrointestinal musculoskeletal, and hepatic, neurological (including limb reflexes) systems, and mental status. Each physical examination also includes evaluation of signs and symptoms of active TB and risk for exposure to TB (Section 8.2.6).

Height and weight will also be measured and recorded. The same scale for measuring body weight should be utilized throughout the study where possible.

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

Clinically relevant findings or worsening of previous findings since the physical examination at the Screening Visit will be recorded as AEs.

8.2.2 Vital signs

Vital signs will be measured in a sitting position after 5 minutes rest and will include body temperature (oral, axillary, otic or noncontact forehead), systolic and diastolic blood pressure, and pulse. Vital signs are to be measured prior to blood sampling, and prior to dosing, where applicable.

Vital signs will consist of single pulse and blood pressure measurements.

8.2.3 Electrocardiograms

A single 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT corrected for heart rate intervals.

All ECG recordings should be taken with the study participant resting in the supine position for at least 10 minutes before the recording and prior to taking blood samples or dosing.

ECG machines will be provided to study centers, and ECGs will be read by a central ECG laboratory. Full details of ECG recordings will be provided in the ECG Manual.

8.2.4 Clinical safety laboratory assessments

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed.

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 CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the study participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 20 weeks after the last 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, 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 CRF.

8.2.5 Depression and suicidal risk monitoring

8.2.5.1 PHQ-9

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring, and measuring the severity of depression. 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 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.

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

8.2.5.2 eC-SSRS

The eC-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Mundt, 2010; Posner, 2011). Study participants respond to standardized clinical questions that are presented in a uniform fashion.

The eC-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The eC-SSRS takes approximately 3 to 10 minutes to complete.

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

8.2.6 Assessment and management of tuberculosis and tuberculosis risk factors

All participants will be assessed for TB through physical examination for signs and symptoms of TB, laboratory testing (Section 8.2.4), chest x-ray (CXR) (Section 8.2.6.3.2), and TB questionnaire (Section 8.2.6.3.3).

8.2.6.1 Assessments at Screening

At Screening, all participants will have an IGRA test (QuantiFERON Gold Plus TB test is recommended), a CXR (unless already performed within 2 months of Screening; a computed axial tomography (CAT) scan of the chest at Screening or within 2 months prior to Screening is acceptable, if available), and examination for signs and symptoms of TB. In addition, the Investigator or designee will complete a TB questionnaire directed at the participants 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 have completed a full course of prophylaxis prior to IMP dosing and can be rescreened after completion of a full course of prophylaxis plus a wash-out of least 5 half-lives of the prophylactic medication(s) prior to Baseline. (See also Section 8.2.6.3.5.)

8.2.6.2 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 NTM 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 healthcare delivery setting or institution where individuals infected with TB are housed or where the risk of transmission of infection is high.

c. Latent TB infection is defined as an infection by *Mycobacterium tuberculosis* with:

- A positive IGRA (or 2 indeterminate IGRAs) AND
- Chest imaging (or other imaging) negative for TB infection, AND
- Absence of signs, symptoms (eg, evidence of organ-specific involvement), or physical findings suggestive of TB infection.

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

8.2.6.3 Assessment and reporting of TB and TB risk factors during the study

8.2.6.3.1 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 inflammatory bowel disease), etc. Unusual presentations should always be considered.

8.2.6.3.2 Chest x-ray for tuberculosis

Chest radiographic imaging is performed at screening and results must be available at baseline before first drug administration unless a CXR or CAT scan is available from 2 months prior to screening.

Additional CXR or other imaging test 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.

8.2.6.3.3 Tuberculosis 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; it is administered by the Investigator or their designee. 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.

8.2.6.3.4 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 tuberculosis 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 a 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, CXRs, 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.

8.2.6.3.5 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 a full course of prophylaxis. Eligible study participants can be included after a wash-out of least 5 half-lives of the prophylactic medication(s) prior to Baseline.

Study participants who initiate treatment for LTBI during the study must repeat study assessments after TB prophylactic therapy has been received for at least 4 weeks. The Investigator and Medical Monitor and/or UCB study physician will decide which investigations (safety laboratory parameters, physical exams and questionnaires) need to be performed after required LTBI prophylaxis period and before the IMP will be restarted.

The IMP can be restarted no sooner than 4 weeks after the start of TB prophylactic therapy if it is deemed likely that the TB prophylactic therapy will be continued to full completion. If no TB prophylactic therapy is initiated for the newly diagnosed LTBI, the study participant must permanently stop IMP and be withdrawn from the study. Every related action should be discussed in advance with the Medical Monitor.

Study participants who prematurely discontinue treatment for LTBI or who, in the opinion of the Investigator or Sponsor, are noncompliant with anti-TB therapy must discontinue further intake of IMP and be immediately withdrawn. Once withdrawn from study treatment, study participants should return for the PEOT visit, complete all assessments, and complete the SFU visit. LTBI must be reported as an AE. Follow-up reports should be completed as per protocol requirement until such time as the LTBI resolves.

8.2.6.3.6 Active TB or non-tuberculosis mycobacterium infection

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

Confirmed active TB is always considered an SAE. UCB's process requires that these must be captured on an SAE report form and provided to the Sponsor in accordance with SAE reporting requirements. Follow-up reports should be completed as per protocol requirement until such time as the TB infection resolves.

8.2.6.3.7 Tuberculosis management of LTBI, active TB, or other NTB infection identified during study

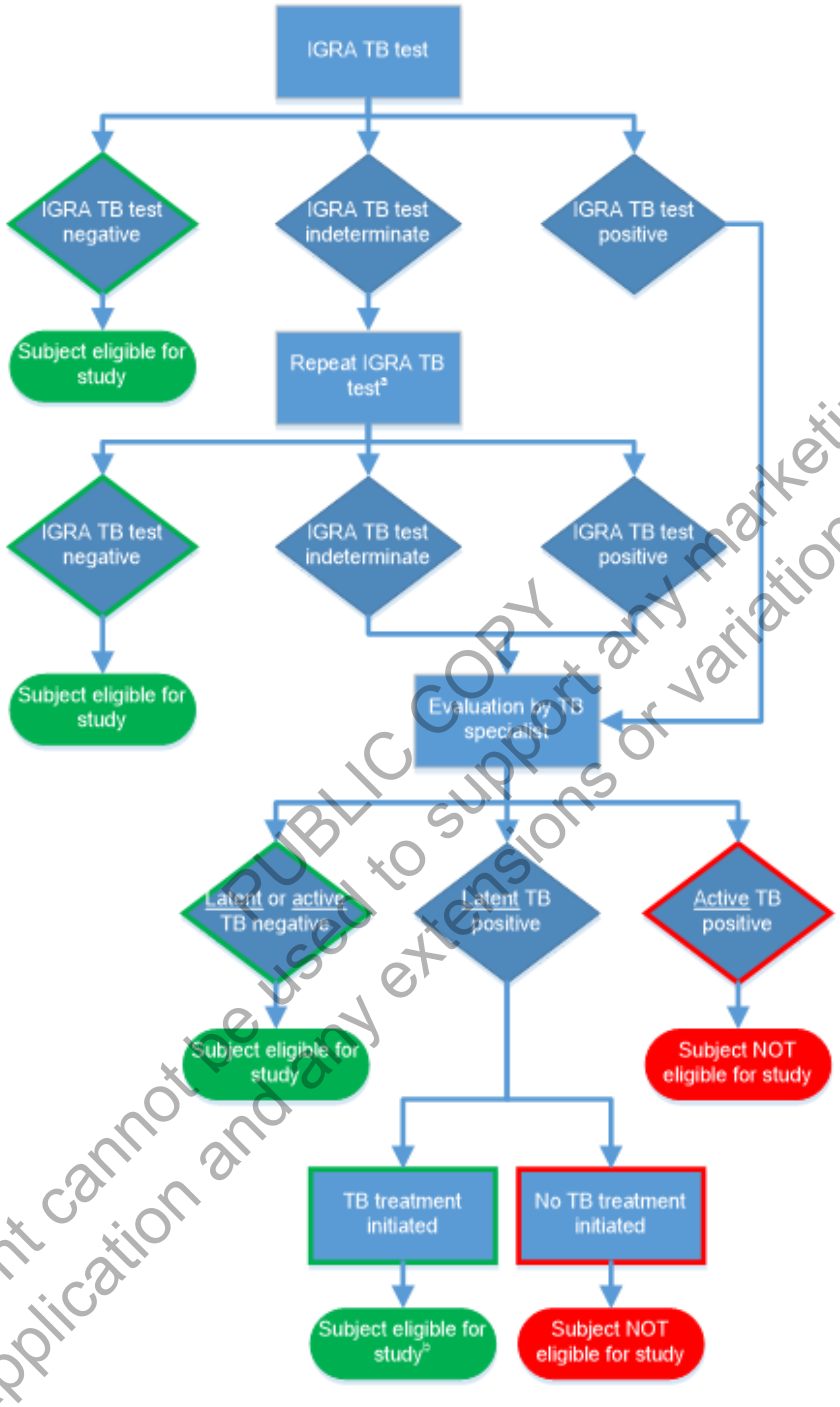
During the study, study participants who develop evidence of LTBI, active TB or NTB infection must immediately stop further administration of IMP and will be referred to a TB specialist (pulmonologist or infectious disease specialist) for further evaluation. Study participants diagnosed with active TB or LTBI should receive appropriate TB or prophylaxis therapy. If a TB specialist excludes active TB, the study participant can restart the IMP no earlier than 4 weeks after the start of an appropriate TB prophylactic therapy. The study participant should be transferred to the care of his or her physician and managed according to the standard of care.

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

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

Study participant eligibility, retesting requirements, and treatment requirements are shown in Figure 8-1 (screening) and Figure 8-2 (during the study). Additional details on TB detection and management are provided in the UCB TB Detection Procedure Guideline.

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

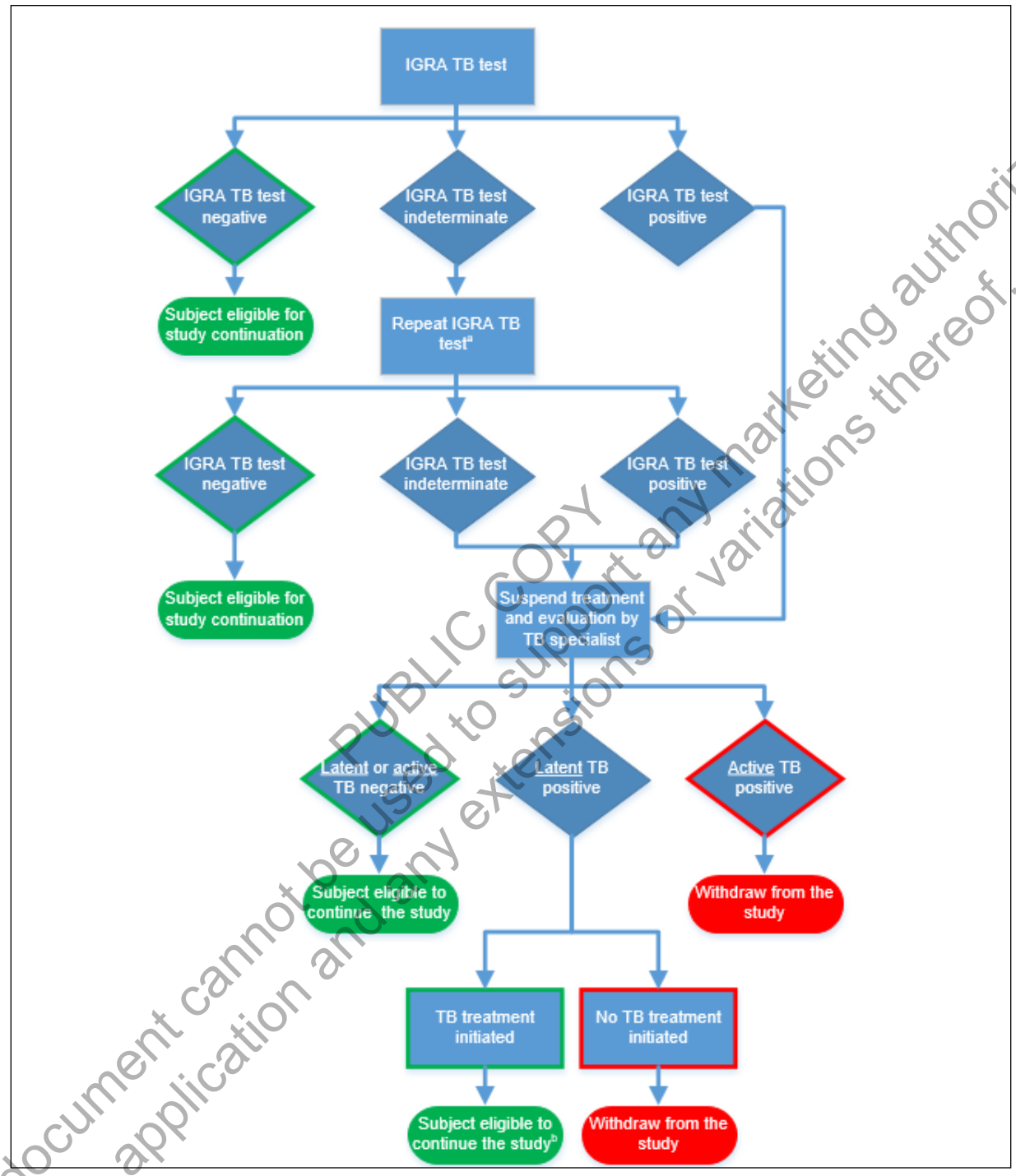


IGRA=interferon gamma release assay; IMP=investigational medicinal product; LTBI=latent tuberculosis infection; TB=tuberculosis

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

[b] Study participants with LTBI diagnosed during Screening must have completed a course of prophylaxis prior to IMP dosing. Participants can be rescreened after completion of a course of prophylaxis plus a wash-out of least 5 half-lives of the prophylactic medication(s) prior to Baseline.

Figure 8-2: Decision tree for IGRA TB results during a study



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

[a] IGRA retest must be done ASAP and prior to the next IMP dose

[b] Study participants with LTBI diagnosed during the study may continue the study only after they have completed at least 4 weeks of appropriate prophylactic therapy and thereafter, will continue and complete the entire regimen.

8.3 Adverse events and serious adverse events

AE will be reported by the study participant (or, when appropriate, by a caregiver, surrogate, or the study 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 that are serious, considered related to the study treatment or study procedures, or that caused the study participant to discontinue the study treatment or the study (see Section 7).

Confirmed and suspected cases of COVID-19 infection will be recorded as AEs (or SAEs, as required).

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 (except for those study participants who enroll in extension study HS0005) or until the first dose administration in extension study HS0005 (for study participants enrolling in HS0005).

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 CRF even if no IMP was taken but specific study procedures were conducted. This includes all AEs not present prior to the initial visit and all AEs that recurred or worsened after the initial visit.

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

The Investigator is specifically requested to collect and report to UCB (or its representative) any SAEs (even if the Investigator is certain that they are in no way associated with the IMP), up to 20 weeks from the last dose of IMP for each study participant, and to also inform study participants of the need to inform the Investigator of any SAE within this period. Serious AEs that the Investigator thinks may be associated with the IMP must be reported to UCB regardless of the time between the event and the end of the study.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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 study participant at subsequent visits/contacts. All AEs and SAEs, will be followed until resolution, stabilization, the Investigator determines that it is no longer clinically significant, the event is otherwise explained, or the study participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment 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 a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants who become pregnant will be collected after the start of study treatment and through the SFU visit (ie, 20 weeks after last 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.

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 study participant should return for an early discontinuation visit.
- The study participant should immediately stop the intake of the IMP.
- An SFU Visit should be scheduled 20 weeks after the study participant has received her last dose of 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.Potential Hy's Law cases, defined as ≥3×ULN ALT or AST with coexisting ≥2×ULN total bilirubin in the absence of ≥2×ULN ALP, with no alternative explanation for the biochemical abnormality, must ALWAYS be reported to UCB as an AE of special interest (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the participant.

8.3.7 Other safety topics of interest

Prespecified safety topics of interest for the study are infections (serious, opportunistic, fungal, and TB), neutropenia, hypersensitivity (including anaphylaxis), suicidal ideation and behavior, major adverse cardiovascular events, hepatic events and PDILI, malignancies, and inflammatory bowel disease.

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 serious adverse events

The following list of Anticipated SAEs (Table 8–1) is predicted to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol. Note that listed events will not be regarded as anticipated SAEs if they are life threatening or if they result in the death of the study participant.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 8.3.1 and Section 10.3.

Table 8–1: Anticipated SAEs for the Population of Participants with HS

MedDRA System Organ Class	MedDRA Preferred Term
Gastrointestinal disorders	Crohn's disease Colitis ulcerative
Psychiatric disorders	Depression Anxiety
Musculoskeletal and connective tissue disorders	Arthropathy
Skin and subcutaneous tissue disorders	Pyoderma gangrenosum Pilonidal cyst Acne conglobate Hidradenitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Lymphoma Squamous cell carcinoma of skin
Infections and infestations	Cellulitis
Metabolism and nutritional disorders	Diabetes mellitus Dyslipidaemia Metabolic syndrome
Endocrine disorders	Thyroid disorder Polycystic ovaries

HS=hidradenitis suppurativa; MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event

8.3.9 Suspected transmission of an infectious agent

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

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 UCB study physician or medically qualified designee/equivalent will conduct an ongoing review of SAEs and perform ongoing SAE reconciliations in collaboration with the Patient Safety (PS) representative.

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

An independent DMC will be used in this study; see Section 9.7 and Section 10.1.5 for details.

8.5 Treatment of overdose

For this study, any dose of IMP 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. Bimekizumab will not be self-administered by the study participant.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the study participant for any AE/SAE and laboratory abnormalities until they have resolved, have a stable sequelae, the Investigator determines that it is no longer clinically significant, or the study participant is lost to follow up.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

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

8.6 Pharmacokinetics

Blood samples will be collected prior to dosing for measurement of plasma concentrations of bimekizumab at all timepoints described in Table 1–1. A total of 9mL will be collected at timepoints for which PK, anti-drug antibodies (ADAb), and neutralizing antibodies are all measured and 3mL will be collected at timepoints for which only PK is measured. Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

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

Genetic analyses will not be performed on these samples. Study participant confidentiality will be maintained. At visits during which blood samples for the determination of plasma concentrations of bimekizumab will be taken, 1 sample of sufficient volume can be used.

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

8.7 Genetics

For individuals consenting to the pharmacogenetic substudy, blood samples will be drawn for exploratory genetic/epigenetic analyses at the timepoints specified in Table 1–1. Collection of these samples will enable evaluation of genetics/epigenetics biomarkers relative to disease biology and progression, drug treatment and inflammatory and immune response processes. The nature and format of these tentative analyses will be determined when the results of the main study are made available. A separate ICF will be required for those study participants who agree to participate in the pharmacogenetics substudy. The substudy will be conducted only where

ethically accepted and authorized by the regulatory agencies. Refusal to participate in the substudy will not affect a study participant's ability to participate in the main study.

The samples will be stored at -80°C at the central biorepository for up to 20 years.

In the event of deoxyribonucleic acid (DNA) extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 (Section 10.5) for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in laboratory manual for this study. Detailed information on sample analysis will be provided in a bioanalytical report.

8.8 Pharmacodynamics

See Section 8.9.

8.9 Biomarkers

Where local regulations permit, blood samples will be drawn for exploratory ribonucleic acid, proteins and metabolites biomarker analysis at the timepoints specified in Table 1–1. Where local regulations permit, urine samples will be drawn for exploratory proteins and metabolites biomarker analysis at the timepoints specified in Table 1–1. Collection of these samples will enable evaluation of biomarkers relative to disease biology and progression, drug treatment and inflammatory and immune response processes. Candidate biomarker evaluations may include, but are not limited to, IL-17A/IL17-F pathway signaling and HS biology (eg, IL-17A, IL-17F). These samples may be used for additional analyses of other exploratory biomarkers.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. The nature and format of these tentative analyses will be determined at a later stage. The samples will be stored at the secure long-term storage facility selected by UCB for up to 20 years.

These samples will only be used to further our understanding of HS and/or how biomarkers, including genetic variation, may affect response or be affected by treatment with bimekizumab in HS.

8.9.1 Immunogenicity assessments

Blood samples for the measurement of ADAb and neutralizing antibodies will be collected. A total of 9mL will be collected at timepoints for which PK, ADAb, and neutralizing antibodies are all measured. Immunogenicity data will not be sent to the Investigator to protect the blinded nature of the treatment assignments and response.

Antibodies to bimekizumab will be evaluated in plasma samples collected from all participants according to the Schedule of Activities. 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.

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. All samples collected for detection of antibodies to bimekizumab will also be evaluated for bimekizumab plasma concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of bimekizumab. Samples may be stored for a maximum of 20 years (or according to local regulations) following the last study participant's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to bimekizumab.

8.10 Medical resource utilization and health economics

Health-related outcomes and medical resource utilization will be collected as part of standard eCRF pages during the study (eg, concurrent medical procedures, concomitant medications, hospitalizations, WPAI-SHP).

8.11 Photography

At certain sites, where feasible, representative photographs of the changes in skin will be captured. Photographs will be anonymized. This is optional for study participants and requires a separate informed consent. A decision not to consent does not exclude the study participant from the 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

9.1.1 Enrolled Set

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

9.1.2 Randomized Set

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

9.1.3 Safety Set

The Safety Set will consist of all study participants who received at least 1 full or partial dose of IMP and will be used for the demographic, safety, and immunogenicity analyses.

9.1.4 Full Analysis Set

The Full Analysis Set (FAS) will consist of all study participants who received at least 1 dose (full or partial) of IMP and had a valid Baseline measurement and a post-Baseline measurement for abscess, inflammatory nodules, and draining tunnel counts.

9.1.5 Per-Protocol Set

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

9.1.6 Pharmacokinetics Per-Protocol Set

The Pharmacokinetics Per-Protocol Set will consist of study participants who received at least 1 full dose of bimekizumab and provided at least 1 quantifiable plasma concentration post-dose without important protocol deviations that would affect the PK. The Pharmacokinetics Per-Protocol Set is defined separately for each of the treatment periods (ie, separately for the Initial Treatment Period and the Maintenance Treatment Period).

9.1.7 COVID-19 Free Set

The COVID-19 Free Set will consist of all study participants randomized into the study and who have no COVID-19 impact through Week 16. This analysis set will be used for sensitivity analysis of the primary efficacy endpoint.

9.2 General statistical considerations

All analyses will be performed using SAS® version 9.4 or later (SAS Institute, Cary, NC, US).

Descriptive statistics will be used to provide an overview of the Baseline, efficacy, and safety results. For categorical parameters, the number and percentage of study participants in each category will be presented by treatment group. The denominator for the percentages will be based on the number of study participants appropriate for the purpose of analysis. Unless otherwise noted, all percentages will be expressed to 1 decimal place. For continuous parameters, descriptive statistics will include n, mean, standard deviation, median, minimum, and maximum. Two-sided 95% confidence intervals, geometric means, and coefficient of variation will be presented for selected variables as appropriate.

Baseline for each assessment is defined as either the value obtained at Baseline or the last available value obtained prior to treatment administration (details to be specified in the SAP).

Formal statistical testing will be conducted for this study for the primary and secondary efficacy variables. Other efficacy variables will be summarized descriptively by treatment arm. P-values and confidence intervals may be produced for other or exploratory variables but will be interpreted as non-inferential (ie, nominal). Additionally, other analyses will be conducted as deemed appropriate and described in the SAP.

The primary treatment comparison for all formal statistical analyses of efficacy will be between bimekizumab and placebo.

9.3 Planned efficacy/outcome analyses

9.3.1 Analysis of the primary efficacy endpoint

The primary objective of this randomized, double-blind, placebo-controlled, multicenter, pivotal study in study participants with moderate to severe HS is to compare the efficacy of bimekizumab [redacted] and bimekizumab [redacted] with placebo at Week 16. For the purposes of Week 16 analyses, the bimekizumab treatment arms of [redacted] and bimekizumab [redacted] treatment groups will be pooled.

The primary and secondary efficacy analyses will be performed based on the RS.

The primary endpoint is the $HiSCR_{50}$ response at Week 16. The primary efficacy analysis will evaluate the composite estimand in the RS. The composite estimand combines the clinically meaningful improvement from Baseline based on the $HiSCR_{50}$ response and early receipt of

systemic antibiotic rescue medication, or discontinuation of IMP due to an AE or lack of efficacy.

The following 4 attributes describe the estimand that will be used to define the treatment effect of interest for the primary efficacy analysis:

1. Population=Study participants meeting the protocol-specified inclusion/exclusion criteria.
2. Study participant-level outcome=$HiSCR_{50}$ at Week 16.
3. Intercurrent event handling=An intercurrent event is defined as receipt of systemic antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A composite strategy will be implemented in which a positive clinical outcome is defined as achieving $HiSCR_{50}$ at Week 16 and not receiving systemic antibiotic rescue medication, and not discontinuing study treatment due to an AE or lack of efficacy through Week 16. Any missing data at Week 16 that are not preceded by an intercurrent event will be imputed using multiple imputation.
4. Population-level summary measure=conditional odds ratio comparing bimekizumab to placebo adjusted for stratification factors used in the randomization.

As a sensitivity analysis, any missing data at Week 16 that are not preceded by an intercurrent event (ie, receipt of systemic antibiotic rescue medication, or discontinuation of IMP due to an AE or lack of efficacy) will be imputed as non-response.

The statistical hypothesis for the $HiSCR_{50}$ response at Week 16 is that the conditional odds ratio for the $HiSCR_{50}$ response in the bimekizumab treatment group relative to the placebo group is equal to 1.

A logistic regression model will be used to assess the effect of bimekizumab vs placebo on $HiSCR_{50}$ response. The model will include a fixed effect for treatment. The stratification variables of Hurley stage and prior antibiotic use will be added to the model unless inappropriate. The odds ratio versus placebo, p-value (from Wald test), and confidence interval will be calculated.

To assess the impact of the COVID-19 pandemic on the primary efficacy endpoint analysis, additional sensitivity analyses will be performed as specified in Section 9.3.4.

9.3.2 Analysis of the secondary efficacy endpoints

The secondary efficacy variables supporting the primary efficacy variable are listed below, and will be included in the multiplicity adjustment:

1. Proportion of study participants who achieve $HiSCR_{75}$ at Week 16. A similar analysis to the primary responder analysis will be performed.
   a. bimekizumab [redacted] vs placebo
   b. bimekizumab [redacted] vs placebo
2. Proportion of study participants who experience at least 1 flare by Week 16, with flare defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline. A similar analysis to the primary responder analysis will be performed.
   a. bimekizumab [redacted] vs placebo

b. bimekizumab [redacted] vs placebo

3. Absolute change from Baseline in DLQI Total Score at Week 16. Analysis will be based on an analysis of covariance (ANCOVA) with treatment and stratification variables as fixed effects and the Baseline values as covariate.
   a. bimekizumab [redacted] vs placebo
   b. bimekizumab [redacted] vs placebo
4. Absolute change from Baseline in Skin Pain Score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HSSDD. Analysis will be based on an ANCOVA with treatment and stratification variables as fixed effects and the Baseline values as covariate.
   a. bimekizumab [redacted] vs placebo
   b. bimekizumab [redacted] vs placebo
5. Pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) at Week 16. A similar analysis to the primary responder analysis will be performed.
   a. bimekizumab [redacted] vs placebo
   b. bimekizumab [redacted] vs placebo

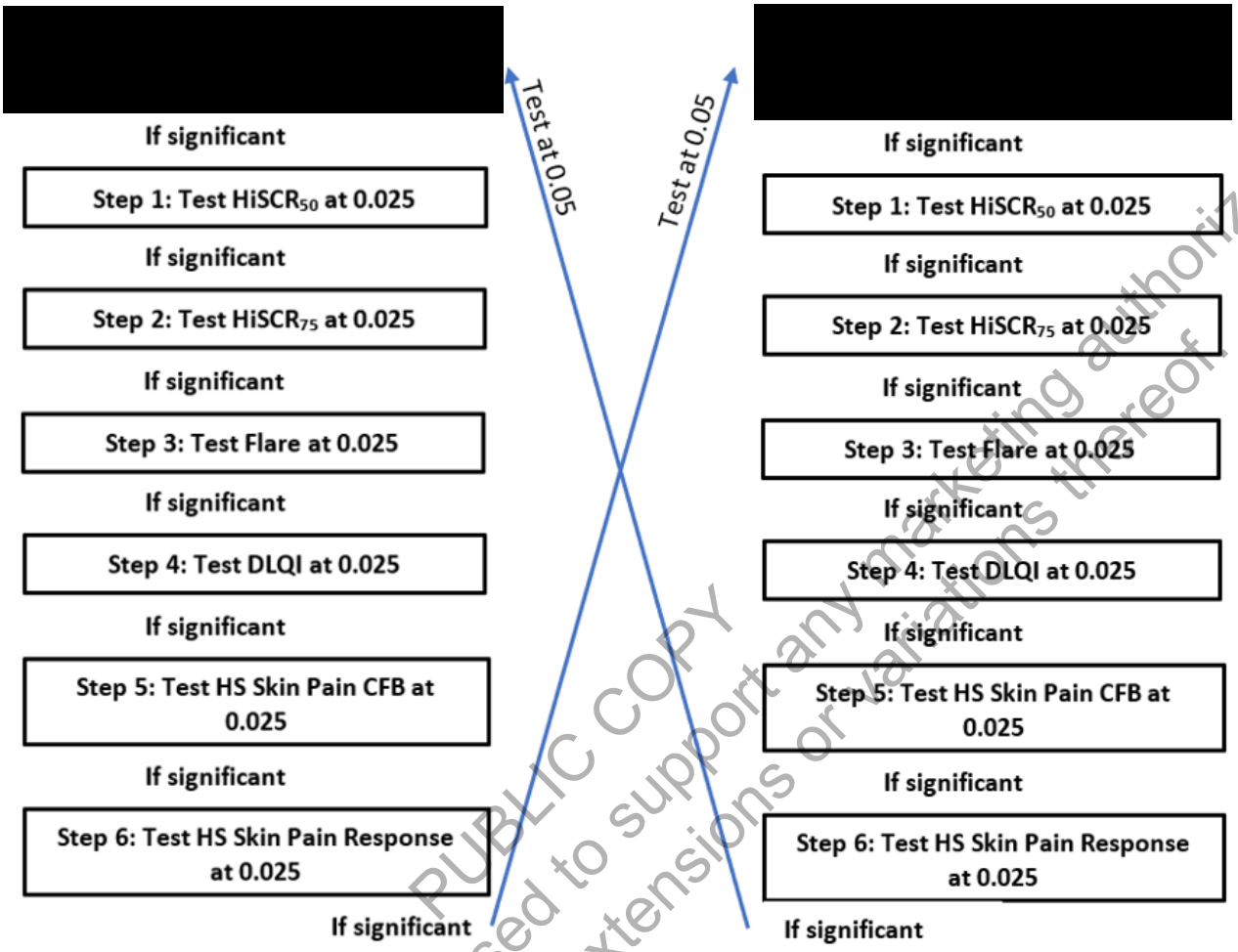
To control the overall type I error rate at 0.05 for the multiple comparisons in the primary and secondary efficacy variables, a closed testing procedure under a parallel gatekeeping framework will be applied (Sun, 2018).

Under this framework, each bimekizumab dose of [redacted] and [redacted] will be compared to placebo in the first instance at a familywise error rate of 0.025 (α/2). Simultaneously within each dose, closed testing for the primary and secondary efficacy endpoints will be performed as follows:

1. Step 1: Test $HiSCR_{50}$ at significance level 0.025.
2. Steps 2 to 6 – If Step 1 is significant at 0.025 then test each secondary endpoint sequentially in the order shown below, moving to the next step only if significance achieved at 0.025.
3. In the event that Step 6 is significant at 0.025 for a given dose, then Steps 1 to 6 will be repeated for the other dose using a significance level of 0.05.

A schematic of the procedure is shown in Figure 9-1.

Figure 9-1: Closed Testing Procedure



AN=abscess and inflammatory nodule; CFB=change from Baseline; DLQI=Dermatology Life Quality Index; $HiSCR_{50}$=a 50% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; $HiSCR_{75}$=a 75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HS=hidradenitis Suppurativa; [redacted]

9.3.3 Other efficacy/other outcome analyses

Analyses of the other efficacy measures will be detailed in the SAP.

9.3.4 COVID-19 impact analysis

To assess the impact of the COVID-19 pandemic on the primary efficacy endpoint analysis, the following additional sensitivity analyses will be performed:

- Imputation as nonresponse for any missing data due to COVID-19 at Week 16 and analyzed using the same analysis model as for the primary analysis
- Separate inferential analysis of the primary and secondary efficacy endpoints based on the COVID-19 Free Set

- Separate summary statistics for the primary efficacy endpoint at Week 16, based on the COVID-19 Free Set
- Summary of the number of study participants with missing primary or secondary endpoint data, as applicable

In addition, to assess the broader impact of the COVID-19 pandemic on the study, the following summaries will be presented:

- Summary of study participant disposition based on enrollment before, during, and after COVID-19 pandemic onset
- A summary of study visits impacted by the COVID-19 pandemic
- A summary of protocol deviations related to COVID-19

Any additional COVID-19 related analyses will be specified in the study SAP. Note: the date of COVID-19 pandemic onset is defined as 11 March 2020, the date that the World Health Organization declared the COVID-19 pandemic. The end date of the COVID-19 pandemic end will be defined in the study SAP, if applicable.

9.4 Planned safety and other analyses

9.4.1 Safety analyses

All TEAEs, SAEs, TEAEs leading to discontinuation, AEs of special interest (eg, cases meeting Hy's Law criteria), and other safety topics of interest (Section 8.3.7) will be collected during the study and for up to 20 weeks after the last dose of IMP (for study participants who do not participate in the extension study, HS0005). Safety analyses will be carried out using the Safety Set (study participants who received at least 1 full or partial dose of IMP). Summaries of Confirmed and Suspected COVID-19 TEAEs, respectively, will be presented. The definition of Confirmed and Suspected COVID-19 TEAEs will be provided in the SAP.

9.4.2 PK and ADAb analyses

Plasma concentrations of bimekizumab will be summarized by treatment group at each timepoint using descriptive statistics. In addition, PK model-based analyses may be performed.

Antidrug antibody data will be evaluated for each study participant and each regimen, and rates and classification of ADAb-positive study participants will be calculated.

9.5 Handling of protocol deviations

Important protocol deviations are identified as part of the data cleaning process as specified in the study-specific data cleaning schedule/plan. Ongoing, blinded data cleaning meetings will be held throughout the duration of the study. Objectives of these meetings include to review protocol deviations and to document potential impact that these deviations might have on the study objectives. Furthermore, overall trends in protocol deviations will be discussed at the Data Evaluation Meeting(s). Through this ongoing data cleaning and evaluation process, all decisions regarding important protocol deviations are made on an ongoing basis. Protocol deviations (eg, missing assessments or visits) related to COVID-19 will be listed and summarized separately.

9.6 Handling of dropouts or missing data

The analyses for the primary and secondary efficacy variables will include the use of multiple imputation. In multiple imputation, the missing value is replaced by a set of plausible values, where each value is a Bayesian draw from the conditional distribution of the missing data given the observed data.

Intermittent missing data will be imputed using the Markov-Chain Monte Carlo method, followed by regression for monotone missing data. The multiple imputation procedures planned for the primary and secondary efficacy analyses are based on an assumption of data missing at random.

The sensitivity of results to the approach for handling missing data will be evaluated via supportive analyses using different missing data mechanisms. The following supportive analyses for the primary efficacy variable will be conducted:

1. Deviations from the missing at random pattern will be evaluated using a reference-based multiple imputation approach. Intermittent missing data will be imputed using the Markov-Chain Monte Carlo method. The remaining monotone missing data will be assumed to follow a missing not at random pattern. These data will be imputed using a reference-based approach in which the multiple imputation model is based on data from the placebo group, thereby assuming that monotone missing data follow a trajectory similar to the placebo group.
2. Tipping point analyses will be performed to evaluate missingness assumptions. Various delta adjustments will be made to the assumed responses on the monotone missing data in each treatment group independently with various degrees of plausibility. It will include scenarios where study participants who have missing data and are randomized to bimekizumab have a lower probability of response compared to study participants who have missing data and were randomized to placebo. For binary variables, this includes the worst case scenario where study participants who have missing data and are randomized to bimekizumab are considered nonresponders, while study participants who have missing data and were randomized to placebo are considered responders. The goal of the tipping point analysis is to systematically vary assumptions until there is no evidence of a treatment effect (if possible). The plausibility of such required delta adjustment will then be assessed.
3. The treatment policy strategy for addressing intercurrent events will be considered. This will be based on an analysis of all available data at Week 16 regardless of the occurrence of intercurrent events. This analysis will use the same models specified for the primary analysis, where study participants are analyzed according to their randomized treatment, even if they discontinued study treatment for any reason prior to Week 16. Even though efforts will be made to collect the primary outcome data for all study participants at Week 16, there may still be some study participants for whom Week 16 efficacy data cannot be obtained. In this case, missing data will be imputed using multiple imputation under the assumption of MAR. Results will be combined into a single inference using Rubin's rule. It should be noted that this measures something different from the primary analysis and could be confounded by placebo study participants who withdraw and are subsequently on another active medication at the time of the Week 16 assessment. Therefore, the results of this analysis should be interpreted in the appropriate context.

4. An additional supportive analysis will be based on observed data only for study participants who are still on the randomized treatment at Week 16. Study participants with missing data or who have prematurely discontinued study treatment will be treated as missing. The same procedure described as in the primary efficacy analyses will be used.

All imputation of other missing data will be detailed in the SAP.

9.7 Planned interim analysis and data monitoring

9.7.1 Data Monitoring Committee

An independent DMC will periodically review unblinded efficacy and safety data to assess the benefit/risk of bimekizumab in study participants with moderate to severe HS. Individual study participant-level efficacy data listings may be provided to the DMC to put the safety review in the context of risk/benefit. Any data to be provided will be specified per the DMC charter. In addition, unblinded efficacy data analysis is planned to be provided to the DMC when approximately 66% of study participants have reached the primary efficacy endpoint at Week 16. At this analysis, formal primary endpoint comparisons between active treatment groups and placebo will be provided so that the DMC can make an assessment regarding the futility of each dose group. However, no early stopping of a treatment group or study will be made on the basis of superior efficacy. Therefore, no alpha adjustment is planned since the efficacy analyses will only be for futility.

Measures to ensure that unblinded interim results are not disseminated beyond the DMC will be implemented. Details of futility stopping boundaries and decision rules will be detailed in the DMC Charter.

9.7.2 Interim Analysis

After the last study participant has completed the Week 48 visit, or after the last study participant has prematurely discontinued prior to reaching Week 48, an unblinded interim analysis will be performed and a corresponding interim clinical study report (CSR) may be written. The purpose of this interim analysis is to perform a comprehensive evaluation of all available double-blind data to prepare regulatory submissions for approval of the HS indication. A final analysis and updated final CSR will be prepared once all data (through to the SFU visit) have been collected.

9.8 Determination of sample size

A total of 490 study participants will be randomly assigned in a 2:2:2:1 ratio to the following treatment arms:

- Bimekizumab [redacted] during Initial Treatment Period (Weeks 0-16) and Maintenance Treatment (Weeks 16-48) Periods, N=140
- Bimekizumab [redacted] during Initial Treatment Period (Weeks 0-16), and Bimekizumab [redacted] during Maintenance Treatment Period (Weeks 16-48), N=140
- Bimekizumab [redacted] during Initial Treatment (Weeks 0-16) and Maintenance Treatment Periods (Weeks 16-48), N=140
- Placebo during Initial Treatment Period (Weeks 0-16), and Bimekizumab [redacted] during Maintenance Treatment Period (Weeks 16-48), N=70

The analysis of the primary efficacy endpoint and secondary efficacy endpoints are based on a comparison of bimekizumab versus placebo at Week 16, with alpha adjustment strategy as indicated in Section 9.3.1 and Section 9.3.2.

The power to detect a statistically significant difference for each of the endpoints are shown in Table 9–1. Notably, with a 2-sided significance level of 0.025, the sample size of 140:70 provides 73% power for detecting at least a difference of 1.5 (bimekizumab [redacted] vs placebo) for the Worst Pain change from Baseline (CFB) endpoint.

Given the high level of power for each of the primary and key secondary endpoints at the 0.025 significance level for the [redacted] comparison (power≥0.89), and per the alpha spending strategy, there is a high likelihood that the [redacted] comparison of Worst Pain CFB vs placebo will be allowed to be tested against the 0.05 level of significance. The power for this latter test is 81%. The sample size is thus ultimately driven by the Worst Pain CFB endpoint. Furthermore, the randomization ratio of 2:2:2:1 has been chosen to provide study participants with a high probability (6/7 ~ 86%) of being randomized to active study drug.

After randomization for this study was complete, an additional endpoint to assess Worst Pain response was included in the sequential testing procedure. This additional endpoint is defined as HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change at Week 16. Note that the power calculations reported in Table 9–1 for this endpoint are based on the sample size that was initially driven by the Worst Pain CFB endpoint as described above. With a 2-sided significance level of 0.025, the sample size of 104:52 in the subset of participants reporting Baseline HSSDD worst skin pain score at or beyond the threshold for clinically meaningful change (ie, Baseline HSSDD ≥threshold value) provides 53% power for detecting a statistically significant difference between bimekizumab [redacted] and placebo in the proportion of Worst Pain responders.

Note that the power at the 0.025 level of significance associated with this endpoint for the comparison between bimekizumab [redacted] and placebo is 95%. The [redacted] comparison of Worst Pain response vs placebo against the 0.05 level of significance is therefore likely, and the power at this significance level is 65%. Given the strength of the power for the bimekizumab [redacted] arm vs placebo across endpoints, it is considered acceptable to have a relatively low power for this final endpoint in the testing sequence for the bimekizumab [redacted] treatment arm vs placebo

Table 9–1: Power calculation assumptions and methods

Endpoint	Power α = 0.025, 2-sided [redacted]	Power α = 0.025, 2-sided [redacted]	Assumptions: Week 16 Bimekizumab [redacted] N=280[a]	Assumptions: Week 16 Bimekizumab [redacted] N=140	Assumptions: Week 16 Placebo N=70
$HiSCR_{50}$	0.99	0.90	Proportion responders=0.60	Proportion responders=0.50	Proportion responders=0.25
$HiSCR_{75}$	0.99	0.98	Proportion responders=0.45	Proportion responders=0.35	Proportion responders=0.10
Flare	0.99	0.99	Proportion of participants with flare by Week 16=0.09	Proportion of participants with flare by Week 16=0.19	Proportion of participants with flare by Week 16=0.52
DLQI	0.99	0.96	Mean CFB=-5.4; SD=6.8	Mean CFB=-4.8; SD=6.8	Mean CFB=-0.8; SD=6.6
Worst Pain CFB[b]	0.89	0.73	Mean CFB=-2.2; SD=3.2	Mean CFB=-2.0; SD=3.2	Mean CFB=-0.5; SD=3.7
Worst Pain Response[c]	0.95	0.53	Proportion responders=0.53	Proportion responders=0.43	Proportion responders=0.23

CFB=change from Baseline; [redacted] SD=standard deviation
Note: Estimates for HS0004 are based on Week 12 data from the HS0001 study.
[a] Pooled [redacted] at Week 16 from [redacted] and [redacted] arms.
[b] Within-subject average of Worst Pain according to 24-hour recall.
[c] Assumes N=208, 104, 52 in [redacted] and placebo, respectively, to account for Worst Pain score at or above the threshold for clinically meaningful change from Baseline

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and ethical considerations

The study will be conducted under the auspices of an IRB/IEC, as defined in local regulations, International Council for Harmonisation (ICH)- 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, ICF, Investigator's Brochure, 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 Financial disclosure

Insurance coverage will be handled according to local requirements.

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

10.1.3 Informed consent process

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

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

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

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

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

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

10.1.4 Data protection

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

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

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

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

10.1.5 Committees structure

A DMC will be reviewing safety and efficacy data on an ongoing basis. The DMC membership includes experienced clinicians and a statistician, all of whom have expertise in clinical studies. Further details will be specified in the DMC Charter.

Cardiovascular, Gastrointestinal, and Neuropsychiatric Adjudication Committees will also periodically review data from this study. Details will be provided in the Cardiovascular, Gastrointestinal, and Neuropsychiatric Adjudication Committee charters.

Both DMC and Adjudication Committee members may not participate in the study as principal or co-Investigators, or as study participant care physicians and must not be members of the study team at UCB or the conducting CRO. The duration of membership for the committees will be inclusive of planned analyses for this study.

10.1.6 Data quality assurance

All study 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 CRF.

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 CRF by authorized site personnel are accurate, legible, contemporaneous, original, and attributable from source documents; that the safety and rights of study participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH-GCP, and all applicable regulatory requirements. Some study-specific assessments may be conducted remotely according to the study protocol during a pandemic or other exceptional circumstance (eg, hurricanes) due to the need to implement safety measures and guidance from regulatory authorities (refer to Section 8). Remote monitoring visits may be conducted during the COVID-19 pandemic or under other exceptional circumstances as deemed appropriate to ensure study participants' safety where local regulations permit.

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 or she relocate or move the study-related files to a location other than that specified in the Sponsor's trial master file.

Quality tolerance limits will be established for the study using parameters related to patient safety reporting and reliability of study results. The parameters will be monitored throughout the

study to identify systematic issues. Parameters used, parameter values, important deviations from the quality tolerance limits, and actions taken will be summarized in the clinical study report.

10.1.6.1 Case report form completion

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

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

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

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

Detailed instructions will be provided in the CRF Completion Guidelines.

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 CRFs are not considered acceptable source documents.

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

Electronic Patient-Reported Outcome (ePRO) measures (eg, DLQI, EQ-5D-3L, WPAI-SHP, TSQM-9, HiSQOL, Daily HS Symptom Diary, HS Symptom Questionnaire, PGI-S-HS, PGI-C-HS, PGI-S-SP, and PGI-C-SP) will be completed by each participant and will be collected electronically.

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

Electronic data records must be saved and stored as instructed by UCB (or designee).

10.1.8 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.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 and Section 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Mean corpuscular volume</td><td>White Blood Cell Count with Differential:
Neutrophils
Lymphocytes
Atypical lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="5">Clinical Chemistry</td><td>Blood urea nitrogen</td><td>Potassium</td><td>Alanine aminotransferase[a]</td><td>Total and direct bilirubin[a,b]</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>Aspartate aminotransferase[a]</td><td>Glucose (record fasting or nonfasting in CRF)</td></tr>
<tr><td>Bicarbonate</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Gamma glutamyltransferase</td></tr>
<tr><td>Uric acid</td><td>Chloride</td><td>Magnesium</td><td>hs-CRP[c]</td></tr>
<tr><td>Lactate dehydrogenase</td><td>Total cholesterol</td><td></td><td></td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">Specific gravity
pH, glucose, protein, ketones, nitrite, blood by dipstick
Microscopic examination (if blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">Pregnancy testing[d]
Follicle stimulating hormone[e]
Urine drug screen (amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines)
Serology (human immunodeficiency virus, Hepatitis B, Hepatitis C)</td></tr>
</table>

Protocol-Required Safety Laboratory Assessments

ALT=alanine aminotransferase; AST=aspartate aminotransferase; CRF=case report form; hs-CRP=high-sensitivity C-reactive protein; RBC=red blood cell; ULN=upper limit of normal

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1.2 and Appendix 6 (Section 10.6). All events of ≥3×ULN ALT or AST with coexisting ≥2×ULN total bilirubin in the absence of ≥2×ULN alkaline phosphatase, with no alternative explanation for the biochemical abnormality may indicate severe liver injury (possible Hy's Law) and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] If total bilirubin is >ULN, a direct bilirubin estimation (%) will be performed.

[c] hs-CRP will be tested at specified visits (Table 1–1).

[d] A serum pregnancy test will be performed at Screening for all women of childbearing potential. A urine pregnancy test (urine dipstick analyzed locally) is also required at the Baseline Visit and all other visits in the Schedule of Activities (Table 1–1). Pregnancy test results must be negative prior to administering IMP.

[e] A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.

Investigators must document his or her review of each laboratory safety report.

Laboratory and/or analyte results (eg, hs-CRP, immunogenicity, PK) that could unblind the study will not be reported to any blinded study personnel as long as the study remains blinded.

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. • 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, ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after IMP administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • 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. • "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. • 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. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • 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 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 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. 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 • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • 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: • 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. • 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 CRF.
- 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 CRF 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 (NCI-CTCAE) 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 Investigator's Brochure and/or Product Information, for marketed products, in his or her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he or 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 or 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 CRF.
- 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.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the UCB study physician by telephone.
- Contacts for SAE reporting can be found on the page after the title page of this protocol.

SAE Reporting to UCB via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor or UCB study physician.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found on the page after the title page of this protocol.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming 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 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 follicle stimulating hormone measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one 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 of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in the table below.

Highly Effective Contraceptive Methods[a]

Highly Effective Contraceptive Methods That Are User Dependent[b] Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable
Highly Effective Methods That Are User Independent
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device • Intrauterine hormone-releasing system • Bilateral tubal occlusion
Vasectomized partner 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 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.
NOTES: a) In case of newly started contraception pills/intrauterine devices, Investigator 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.

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) during the treatment period and at 20 weeks after the last dose of IMP and as required locally.
- 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. This applies only to male participants who receive IMP. If the study participant is later found to be on placebo, then pregnancy data collection can stop.
- In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/CRO contract monitor for the study. The Investigator will complete the information in the eCRF only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's 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 from the pregnant female partner directly, 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 or be withdrawn from the study.
- 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

Use and Analysis of DNA

Samples for potential future exploratory biomarker research will be collected and stored from consenting participants in the study. This sampling is optional for study participants and requires a separate informed consent. A decision not to consent does not exclude the study participant from the study:

- Blood sample for DNA.

These samples will only be used to further understanding of HS and/or how biomarkers, including genetic variation, may affect response or be affected by treatment with bimekizumab, background products, and/or concomitant medications in study participants with HS.

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 7.1.2.

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

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 10–1 (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 7.1.2.1.1).

Table 10–1: 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 subject 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				

Table 10–1: 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**
≥5×ULN (and ≥2× Baseline) and <8×ULN	<2×ULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow-up requirements).[c]	Further investigation – immediate IMP discontinuation not required (see Section 10.6.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase • Liver chemistry values remain ≥5×ULN (and ≥2× baseline) after 4 weeks of monitoring without evidence of resolution	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 10.6.3).	Monitoring of liver chemistry values at least twice per week for 2 weeks.[e] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • ALT or AST remains ≥5×ULN <8×ULN, IMP should be temporarily withheld and subject should undergo repeat test in 2 weeks. Continue IMP if ALT or AST values <5×ULN; continue to monitor at least twice per week until values normalize, stabilize, or return to within baseline values. If ALT or AST remains ≥5×ULN after second retest, immediate IMP discontinuation required. Continue to monitor until values normalize, stabilize, or return to within baseline values.[d]

Table 10–1: 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**

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

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

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

[c] Details provided in Section 10.6.1 . The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

[d] Details are provided in Section 10.6.2.

[e] Unless an alternative monitoring schedule is agreed by the Investigator and 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 7.1.2.1), 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 10–1.

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 7.1.2 and Table 10–1 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 7.1.2 and Table 10–1), 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 7.1.2.1.1 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 or 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 10–2 (laboratory measurements) and Table 10–3 (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 10–2: 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=pharmacokinetic; 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 10–3.

Table 10–3: PDILI information to be collected

New or updated information
• Concomitant prescription and over-the-counter medications (eg, acetaminophen, herbal remedies, vitamins); dosages and dates should be included.
• Pertinent medical history, including the following: – History of liver disease (eg, autoimmune hepatitis, nonalcoholic steatohepatitis or other "fatty liver disease") – Adverse reactions to drugs – Allergies – Relevant family history or inheritable disorders (eg, Gilbert's syndrome, alpha-1 antitrypsin deficiency) – Recent travel – Progression of malignancy involving the liver (Note: Metastatic disease to the liver, by itself, should not be used as an explanation for significant AST and/or ALT elevations.)
• The appearance or worsening of clinical symptoms of hepatitis or hypersensitivity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, decreased appetite, abdominal pain, jaundice, fever, or rash)
• Recent clinically significant hypotension or hypoxemia with compromised cardiopulmonary function
• Alcohol and illicit drug use
• Results of liver imaging or liver biopsy, if done
• Results of any specialist or hepatology consult, if done
• Any postmortem/pathology reports

ALT=alanine aminotransferase; AST=aspartate aminotransferase; PDILI=potential drug-induced liver injury

10.7 Appendix 7: Medical device AEs, Adverse device effects, SAEs, and device deficiencies: definition and procedures for recording, evaluating, follow-up, and reporting

Not applicable to this study.

10.8 Appendix 8: Rapid alert procedures

Not applicable to this study.

10.9 Appendix 9: Country-specific requirements

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

10.10 Appendix 10: Abbreviations and trademarks

ADAb	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
CAT	computed axial tomography
COVID-19	coronavirus disease 2019
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest x-ray
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic Case Report form
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EQ-5D-3L	European Quality-of-Life 5 dimensions-3 level questionnaire
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
GCP	Good Clinical Practice
HCV	hepatitis C virus
HiSCR	Hidradenitis Suppurativa Clinical Response
$HiSCR_{25}$	a 25% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count
$HiSCR_{50}$	a 50% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count
$HiSCR_{75}$	a 75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count

$HiSCR_{90}$	a 90% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count
$HiSCR_{100}$	a 100% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count
HiSQOL	Hidradenitis Suppurativa Quality of Life
HRT	hormonal replacement therapy
HS	hidradenitis suppurativa
hs-CRP	high-sensitivity C-reactive protein
HSSDD	Hidradenitis Suppurativa Symptom Daily Diary
HSSQ	Hidradenitis Suppurativa Symptom Questionnaire
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IGRA	interferon gamma release assay
IHS4	International Hidradenitis Suppurativa Severity score system
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
LTBI	latent tuberculosis infection
M.	*Mycobacterium*
mAb	monoclonal antibody
NTM	nontuberculous mycobacterial
NRS	numeric rating scale
NSAID	nonsteroidal anti-inflammatory drug
PDILI	potential drug-induced liver injury
PEOT	Premature End of Treatment Visit
PGI-C-HS	Patient Global Impression of Change in Hidradenitis Suppurativa Severity
PGI-C-SP	Patient Global Impression of Change in Severity of Skin Pain

PGI-S-HS	Patient Global Impression of Hidradenitis Suppurativa Severity
PGI-S-SP	Patient Global Impression of Severity of Skin Pain
PHQ-9	Patient Health Questionnaire Depression Module-9
PK	pharmacokinetic(s)
PRN	as needed
PRO	patient-reported outcome
PSO	psoriasis
[redacted]	[redacted]
[redacted]	[redacted]
QOL	quality of life
RS	Randomized Set
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SFU	Safety Follow-up
TEAE	treatment-emergent adverse event
TB	tuberculosis
TSQM-9	Treatment Satisfaction Questionnaire – Medication 9
ULN	upper limit of normal
WOCBP	woman of childbearing potential
WPAI-SHP	Workers Productivity and Activity Impairment Questionnaire: Specific Health Problem

10.11 Appendix 11: Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment (Amendment 4) is located directly before the Table of Contents.

Amendment 3 (09 Feb 2021)

Overall Rationale for the Amendment

The main reason for this protocol amendment is due to Regulatory Agency feedback and to provide procedural clarifications.

Section # and Name	Description of Change	Brief Rationale
Title page	• National Clinical Trial (NCT) number has been added	NCT number was received on 24 Jan 2020
Serious adverse event reporting	• Fax and email for Japan have been removed	To align with safety reporting guidelines
1.1 Synopsis 2.1 Study rationale 2.2 Background	• Updated description of bimekizumab and other minor edits • Order of secondary efficacy endpoints aligned with closed testing procedure (Figure 9-1)	Rationale is the same as the description
1.1 Synopsis (Treatment Groups and Duration)	• Updated Baseline antibiotic therapy strata to remove the 30% cap on enrollment • Sentences updated as unblinded efficacy data analysis is planned to be provided when approximately 66% of study participants have reached the primary efficacy endpoint at Week 16 rather than 50% and 100%.	Removed the Baseline antibiotic strata cap per US FDA advice (Baseline antibiotic use should coincide with the prevalence of antibiotic use for the disease) To align with the final Data Monitoring Committee Charter (DMC) Charter and DMC Statistical Analysis Plan (SAP)
1.3 Schedule of activities	• Extended the line for concomitant medications and adverse events to show they are collected through the Safety Follow-Up Visit • Added an additional footnote that past medical history includes tobacco and alcohol use • Added Note in footnotes that study assessments could be completed remotely in exceptional circumstances • Footnote “n” (formally footnote “m”) has been updated regarding collection of Hurley Stage	To align collection of adverse events and concomitant medications with the protocol body text To include/clarify that tobacco and alcohol use is part of the medical history Provided operational flexibility to allow assessments to be collected remotely due to COVID-19 or other exceptional circumstance (eg, hurricanes) Clarification to make footnote “n” consistent with the table

Section # and Name	Description of Change	Brief Rationale
		regarding collection of Hurley Stage
3 Objectives and endpoints Other	• Order of secondary efficacy endpoints aligned with closed testing procedure (Figure 9-1) • Other safety topics of interest endpoints were updated	With progressive development of bimekizumab and based on the ongoing review of emerging safety data, depression has been removed as a safety topic of interest. Nevertheless, depression will continue to be monitored as a safety parameter by the Patient Health Questionnaire 9 (PHQ-9) and will be captured via routine adverse event (AE) reporting during the study. This update is considered a procedural change. Rational for reordering the secondary efficacy endpoints is the same as the description.
4.1 Overall design 4.2 Scientific rationale for study design	• Updated Baseline antibiotic strata to remove the 30% cap on enrollment	Removed the Baseline antibiotic strata cap per US FDA advice (Baseline antibiotic use should coincide with the prevalence of antibiotic use for the disease)
5.1 Inclusion criteria	• Criteria #2 added text that diagnosis must be verifiable through medical notes and documentation Criteria #5 was edited for clarity, and added text that diagnosis/inadequate response must be verifiable through medical notes and documentation	Clarification of criteria
5.2 Exclusion criteria	• Criterion #16 text was updated to clarify use of the Screening Version of the electronic Columbia-Suicidality Severity Rating Scale (eC-SSRS) • Criterion #19 was updated to exclude participants with prior use of an IL-17 biologic response modifier or participation in an IL-17 biologic response modifier study unless an appropriate washout period (within 6 months	Clarification of criterion #16 as it is actually collected and assessed Criterion #19 was modified to allow enrollment of a moderate to severe HS population with real-world prior use of other medications with appropriate washout periods

Section # and Name	Description of Change	Brief Rationale
	prior to the Baseline Visit or 5 half-lives, whichever is greater) has been performed	
5.4 Screen failures	• Added bullet explaining that study participants who require incision and drainage procedures for HS lesions are to be screen failed	Updated the screen failure criteria
6.5.1 Permitted concomitant treatments	• Wound care updated to add that use of wound care dressings will be recorded • Added Lesion care • Updated Baseline antibiotic strata to remove the 30% cap on enrollment	Clarifications of and additions to allowed concomitant treatments Removed the Baseline antibiotic strata cap per US FDA advice (Baseline antibiotic use should coincide with the prevalence of antibiotic use for the disease)
6.5.2 Prohibited concomitant treatments	• Added washout periods for systemic antibiotics if applicable; other biologics; IL-17, IL-12, and IL-23 inhibitors; and janus kinase inhibitors • Filgotinib and Upadacitnib added under janus kinase inhibitors • Text added to clarify topical drugs • Added herbal medications for HS and a washout period • Updated vaccine criteria • Text added to clarify that medications listed are currently available medications, but the protocol will account for medicine approvals in a given class during the course of the study	Clarification of prohibited medications/therapies and the criteria for their exclusion and to allow enrollment of a moderate to severe HS population with real-world prior use of other medications (current and future) with appropriate washout periods
7.1 Discontinuation of study medication	• Added a paragraph to clarify procedures if a study participant tested positive for COVID-19 or a suspected COVID-19 infection	Updated for the COVID-19 pandemic
7.1.2.1 PDILI discontinuation criteria	• Removed ‘and permanent’ from the first sentence and a crossreference to Section 10.6.2.1 has been included	To be consistent with the PDILI criteria throughout the protocol and Appendix 10.6
7.1.3 Treatment interruptions	• Text was updated to clarify that doses of IMP that were missed due to a reasonable interfering AE that does not allow administration of IMP due to safety reasons, will not be considered for the evaluation of study participant discontinuation.	Clarification of study procedures. In line with the exclusion criterion regarding infections, a specific infection-related IMP

Section # and Name	Description of Change	Brief Rationale
	It is still used to calculate compliance. • A specific infection-related IMP interruption criterion has been added	interruption criterion was added to clarify that participants with serious or recurrent infections not responding to standard therapies are not exposed to immunomodulatory therapies until their infection has resolved. This is in line with most biologic therapies, including other anti-IL17s.
7.2 Participant discontinuation/withdrawal from the study	• Added cross-reference to pregnancy section	Clarification of study procedures
8 Study Assessments and Procedures	• Added text about allowing study assessments to be performed remotely during a pandemic or other exceptional circumstance	Updated to allow study to proceed during COVID-19, and other exceptional circumstances (eg, hurricanes)
8.1.1 Lesion count	• Removed "hypertrophic" from description of scars and added "HS lesions"	Clarification of lesion definition
8.1.4.6 Euro-Quality of Life 5-Dimensions, 3 levels	• Removed sentences #2 and #3 regarding summary index scores • Added a clarification to the last sentence	Sentence removed in line with SAP update as index scores are not required for the clinical study report
8.2.2 Vital signs	• Noncontact forehead added to body temperature measurement	Updated for the COVID-19 pandemic and to align with the electronic Case Report Form (eCRF)
8.2.6.1 Assessments at Screening	• Specified that the TB questionnaire is administered by the Investigator or their designee	Clarification of study procedure
8.2.6.3.3 Tuberculosis questionnaire	• Specified that the questionnaire is administered by the Investigator or their designee	Clarification of study procedure
8.3 Adverse events and serious adverse events	• Added statement that cases of COVID-19 infection will be recorded as AEs (or SAEs , as required)	Updated for the COVID-19 pandemic
8.3.5 Pregnancy	• Bulletpoint #2 "or be down-titrated as instructed at the early discontinuation visit" was deleted	Down titration of bimekizumab is not required if IMP needs to be discontinued
8.3.7 Other safety topics of interest	• Deleted depression from list of AEs considered safety topics of interest • Updated "liver function test changes/enzyme elevations" to	With progressive development of bimekizumab and based on the ongoing review of emerging safety data, depression has been

Section # and Name	Description of Change	Brief Rationale
	"hepatic events and potential drug-inducted liver injury (PDILI)" • Clarified major "adverse" cardiovascular events	removed as a safety topic of interest. Nevertheless, depression will continue to be monitored as a safety parameter by the PHQ-9 and will be captured via routine AE reporting during the study. This update is considered a procedural change To align with UCB internal documents regarding assessment of hepatic events and PDILI Typographical error corrected for major adverse cardiovascular events
9.1.7 COVID-19 Free Set	• Addition of subsection for a COVID-19 Free analysis set	Updated for the COVID-19 pandemic
9.3.1 Analysis of the primary efficacy endpoint	• Cross reference added to Section 9.3.4 for additional sensitivity analyses related to the assessment of COVID-19 pandemic on the primary efficacy endpoint analysis	Updated for the COVID-19 pandemic
9.3.2 Analysis of secondary efficacy endpoints	• Points #3 and #4 have been reordered to be consistent with Figure 9-1 (Closed Testing Procedure). • Missing figure caption was added	Rational is the same as the description
9.3.4 COVID-19 impact analysis	• Addition of subsection for COVID-19 impact analysis	Updated for the COVID-19 pandemic
9.4.1 Safety analysis	• Addition of sentence that Summaries of Confirmed and Suspected COVID-19 TEAEs, respectively, will be presented and their definitions will be provided in the SAP	Updated for the COVID-19 pandemic
9.5 Handling of protocol deviations	• Added statement that COVID-related protocol deviations would be listed and summarized separately	Updated for the COVID-19 pandemic
9.7.1 Data Monitoring Committee	• Sentences updated as unblinded efficacy data analysis is planned to be provided when 66% of study participants have reached the	To align with the final DMC Charter and DMC SAP

Section # and Name	Description of Change	Brief Rationale
	primary efficacy endpoint at Week 16 rather than at 50% and 100%.	
10.1.6 Data quality assurance	• Added statement about performing some study-specific assessments remotely under certain exceptional circumstances	Updated for the COVID-19 pandemic and other exceptional circumstances (eg, hurricanes)
10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information	• Deleted footnote "c" regarding hormonal contraception. "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 last dose of IMP"	To be consistent with other studies in the bimekizumab program
10.6 Appendix 6: Liver safety – suggested actions and follow-up assessments	• Paragraph #2 has been updated to add that PDILI events meeting SAE criteria should be reported to the Sponsor within 24 hours of learning of the occurrence. The requirement to report to the study site has been removed.	Correction of typographical error and clarification of reporting procedures
10.11 Appendix 11: Protocol amendment history	• Updated with changes from previous global amendment	Self-evident
Throughout	• Minor editorial and formatting revisions	Minor edits and formatting revisions that do not impact content were made for readability and/or clarity

Amendment 2 (16 Dec 2019)

Overall Rationale for the Amendment

The main reason for global protocol amendment 2 was to update the study discontinuation/withdrawal criteria for study participants with IBD.

Section # and Name	Description of Change	Brief Rationale
7.2 Participant discontinuation/withdrawal from the study	• Added text to IBD discontinuation/withdrawal criteria	Previously approved text relating to discontinuation/withdrawal criteria for IBD was inadvertently removed from the original version of the protocol dated

Section # and Name	Description of Change	Brief Rationale
		29 Oct 2019. It is now being replaced
7.2 Participant discontinuation/withdrawal from the study	• Fixed numbering in list of criteria	Corrected typographical error in list numbering
10.11 Appendix 11: Protocol amendment history	• Updated with changes from previous global protocol amendment 1	Updated

Amendment 1 (06 Dec 2019)

Overall Rationale for the Amendment

The main reason for global protocol amendment 1 was to update the company name in line with the new Code of Companies and Associations recently adopted by Belgium.

Section # and Name	Description of Change	Brief Rationale
Title page	• Updated company name from UCB Biopharma SPRL to UCB Biopharma SRL	Change in company name on 02 Dec 2019
3 Objectives and Endpoints	• Clarified wording of exploratory biomarker objective	Clarification of objective with current genetics and biomarkers sections (Section 8.7 and Section 8.9, respectively)
8.2.6.3.7 Tuberculosis management of LTBI, active TB, or other NTB infection identified during study	• Figure 8-1 was updated to reflect Screening terminology as follows: – Green ovals that said "subject eligible for study continuation" or "subject eligible to continue the study" in original protocol were changed to say "subject eligible for study" – Red ovals that said "withdraw from the study" were changed to say "subject NOT eligible for study"	Figure 8-1 was corrected to reflect Screening terminology
10.11 Appendix 11: Protocol amendment history	• Stated location of summary of changes table for the current amendment	Updated

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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

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