PROTOCOL HS0001 AMENDMENT 1

A PHASE 2 MULTICENTER, INVESTIGATOR-BLIND, SUBJECT-BLIND, PLACEBO-CONTROLLED STUDY OF THE EFFICACY, SAFETY, AND PHARMACOKINETICS OF BIMEKIZUMAB IN SUBJECTS WITH MODERATE TO SEVERE HIDRADENITIS SUPPURATIVA

PHASE 2

EudraCT Number: 2017-000892-10

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SERIOUS ADVERSE EVENT REPORTING

Serious adverse event reporting (24h)	
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ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AESM	adverse events for special monitoring
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APAC	Asia-Pacific
AST	aspartate aminotransferase
BA	absolute bioavailability
BMI	body mass index
BP	blood pressure
CAT	Computed Axial Tomography
CD	Crohn's disease
CDMS	clinical data management system
CRO	Contract Research Organization
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest x-ray
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic Case Report form
EDC	electronic data capture
EPM	Exploratory Project Manager
EQ-5D	European Quality-of-Life 5 dimensions questionnaire
ES	Enrolled Set
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HADS	Hospital Anxiety and Depression Scale
HADS-A	HADS-Anxiety
HADS-D	HADS-Depression
HBV	hepatitis B virus
HCV	hepatitis C virus
HiSCR	Hidradenitis Suppurativa Clinical Response
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
ICH	International Council for Harmonisation
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IGRA	interferon-gamma release assay
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
iv	intravenous
LTB	latent tuberculosis
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NRS	numeric rating scale
NTMB	nontuberculous mycobacteria
PD	pharmacodynamics
PDILI	potential drug-induced liver injury
PGA	Patient's Global Assessment

PK	pharmacokinetics
PK-PPS	Pharmacokinetics Per-Protocol Set
PPS	Per-Protocol Set
PRN	as needed
PsA	psoriatic arthritis
PSO	psoriasis
PS	Patient Safety
QOL	quality-of-life
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using Fridericia's correction
RA	rheumatoid arthritis
RNA	ribonucleic acid
RS	Randomized Set
S100A8/9	S100 calcium-binding protein A8/9
SAE	serious adverse event
SAP	statistical analysis plan
sc	subcutaneous
SFU	Safety Follow-Up
SOP	Standard Operating Procedure
SS	Safety Set
TB	tuberculosis
TEAE	treatment-emergent adverse events
Th17	IL-17-producing T helper cells
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
US	United States

1 SUMMARY

This is a Phase 2, multicenter, randomized, Investigator-blind, subject-blind, placebo-controlled, active-reference arm study to assess the efficacy, safety, and pharmacokinetics (PK) of bimekizumab (also known as UCB4940) an anti-interleukin (IL)-17A and IL-17F monoclonal antibody (mAb) in eligible adult subjects with moderate to severe hidradenitis suppurativa (HS). The active reference arm for this study will be adalimumab (Humira®; a tumor necrosis factor-alpha [TNF-α] inhibitor).

The study population will consist of adult subjects (18 to 70 years of age, inclusive) with a diagnosis of moderate to severe HS for at least 1 year prior to Baseline (lesions present in at least 2 distinct anatomic areas [1 of which must be at least Hurley Stage II or III] and a total abscess and inflammatory nodule count ≥3) that has been stable for at least 2 months prior to Screening with an inadequate response to at least a 3-month study of an oral antibiotic treatment for HS (or exhibited recurrence after discontinuation of, demonstrated intolerance to, or have a contraindication to, oral antibiotics for treatment of their HS).

A sufficient number of subjects will be screened in order to have 80 subjects randomized in the study. There will be approximately 40 subjects in the bimekizumab treatment group, 20 subjects in the placebo group, and 20 subjects in the adalimumab group. For each subject, the study will last a maximum of 34 weeks and will consist of 3 periods; a Screening Period (up to 4 weeks), a Treatment Period (up to 12 weeks), and a Safety Follow-Up (SFU) Period (up to 20 weeks after the last dose of investigational medicinal product [IMP]). The primary efficacy variable, as measured by Hidradenitis Suppurativa Clinical Response (HiSCR), will be assessed at Week 12.

During the Treatment Period, eligible subjects will be randomized 2:1:1 (bimekizumab to placebo to adalimumab, stratified by Baseline Hurley Stage) to receive blinded IMP (all administered by subcutaneous [sc] injection by unblinded study personnel).

- Subjects randomized to receive bimekizumab will receive the following:
  - 640mg at Baseline (loading dose)
  - 320mg at Weeks 2, 4, 6, 8, and 10
- Subjects randomized to receive adalimumab will receive the following:
  - 160mg at Baseline (loading dose)
  - 80mg at Week 2
  - 40mg at Weeks 4, 5, 6, 7, 8, 9, and 10
- Subjects randomized to receive placebo will receive placebo at Baseline (loading dose) and at Weeks 2, 4, 5, 6, 7, 8, 9, and 10

Because of differences in the dosing schedule between bimekizumab and adalimumab, placebo injections will be administered along with active drug such that all subjects will receive the same number of injections at each corresponding visit. The number of placebo and active injections will vary by visit and treatment group, as described in Section 7.2 and Table 7–1.

Subjects withdrawing early from the study will undergo the Early Withdrawal Visit assessments and will enter the SFU Period. Subjects who withdraw early from IMP will be asked to return for study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and for the SFU Visit.

The primary objective of this study is to evaluate the efficacy of bimekizumab in subjects with moderate to severe HS.

The secondary objective of this study is to assess the safety, tolerability, immunogenicity, and PK of bimekizumab in subjects with moderate to severe HS.

The exploratory objective of the study is to further assess efficacy of bimekizumab and to explore the effect of bimekizumab on gene and protein expression, and to explore the relationship between pharmacodynamics (PD), nonhereditary pharmacogenomics pharmacogenetic, and imaging biomarkers and HS disease biology, drug treatment, and inflammatory and immune responses.

The primary efficacy variable is the clinical response as measured by HiSCR (defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining fistula count) at Week 12. The exploratory efficacy variables are listed in Section 4.1.2.

Pharmacokinetic and immunological variables are listed in Section 4.2 and will be evaluated to assess their relationship to treatment response. Pharmacodynamic, nonhereditary pharmacogenomic, pharmacogenetic, and imaging variables are listing in Section 4.5 and will also be evaluated to assess their relationship to treatment response.

Safety variables to be assessed are the frequency and severity of adverse events (AEs) and serious adverse events (SAEs), withdrawal due to AEs, changes from Baseline in vital signs, electrocardiogram (ECG) parameters, clinical laboratory parameters, and physical examination.

2 INTRODUCTION

2.1 Hidradenitis suppurativa

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 March to 01 April 2006, Dessau, Germany). The nodules are often inflamed 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 et al, 2009; Danby and Margesson, 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 et al, 2008; Naldi, 2006). Recent studies have suggested that the prevalence of diagnosed HS in the United States (US) is lower (<0.1%), with a need for further research 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 psoriasis (PSO; Sartorius et al, 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 and Jemec, 2001; Wolkenstein et al, 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 questionnaire (EQ-5D) scale (Riis et al, 2016).

There is a strong association between HS and smoking, with a majority of patients being current or ex-smokers, and HS is associated with a variety of concomitant and secondary diseases, such as obesity, metabolic syndrome, inflammatory bowel disease (eg, Crohn's disease [CD]), spondyloarthropathy, follicular occlusion syndrome, and other hyperergic diseases (Sartorius et al, 2009; van der Zee, 2010; Fimmel and Zouboulis, 2010; Tzellos et al, 2015; Zouboulis et al, 2015b).

2.1.1 Hidradenitis suppurativa disease pathology

Neutrophilic abscess formation and influx of mainly macrophages, monocytes, and dendritic cells predominate in early HS lesions. In chronic disease, the infiltrate expands with increased frequencies of B cells and plasma cells (van der Zee et al, 2012). A large number of IL-17-producing T helper cells (Th17) are shown to infiltrate the dermis in chronic HS lesions. Interleukin-17A and IL-17F are known to stimulate the expression of key mediators that drive the recruitment of neutrophil expression in upregulation of IL-17A. Increased levels of Th17 cells may be, at least in part, responsible for the excessive neutrophilic inflammation and purulent drainage seen in primary and secondary HS lesional skin biopsies (Schlapbach et al, 2011). Immunohistochemistry studies performed by UCB have shown that the increased expression levels of IL-17A are accompanied with increased IL-17F expression.

Keratinocytes from HS patients have been shown to be dysfunctional, leading to an excessive tissue protective response and a chronic inflammatory response and perpetual inflammation at sites of infection in skin lesions (Hotz et al, 2016). Interleukin-17 is capable of upregulating S100 calcium-binding protein A8 (S100A8) and S100A9 in keratinocytes (Cho et al, 2012). Antimicrobial proteins S100A8 and S100A9, constitutively expressed at low levels in healthy individuals, are danger responses when upregulated and induce proinflammatory cytokine and chemokine expression. This induction of proinflammatory cytokine and chemokine expression drives infiltration of leukocytes and contributes to the amplification of inflammation. As a net result this leads to proliferation of keratinocytes, which is a key factor in the pathology of HS and its most impactful effects on patients such as fistula and scar formation (Baroja-Mazo et al, 2014; Ehrchen et al, 2009).

2.1.2 Current treatments and unmet need

Hidradenitis suppurativa is difficult and challenging to treat. Treatment depends on the stage of disease (eg, presence of inflammatory components and/or scarring). Most patients respond only partially to treatment, or the disease rapidly reoccurs after drug cessation. Historically, available treatment options for HS varied widely and with the exception of the recent European and German treatment guidelines, there were few formal treatment guidelines for this condition (Zouboulis et al, 2015b). Bacterial infection is believed to be a secondary event in the disease process (Nikolakis et al, 2015; Nikolakis et al, 2016). While antibiotics generally do not cure the

disease, they may relieve symptoms through either an antibacterial or an anti-inflammatory effect. Topical antimicrobials are generally given for mild disease (either topical antiseptics, such as chlorhexidine, or topical antibiotics, such as clindamycin), with modest results (Clemmensen, 1983). Further treatment of HS can depend on the extent and activity of the disease and include medical treatments (eg, systemic combination therapy with clindamycin and rifampicin, tetracyclines including doxycycline and minocycline, intralesional triamcinolone, systemic cyclosporine, anti-androgen treatment in women, systemic dapsone, systemic retinoids, and metformin), surgical treatments (eg, radical excision, marsupialization, and deroofing), and laser treatment (Naldi, 2006; Jemec, 2010; Zouboulis et al, 2015b).

Adalimumab is the only approved medicinal product for the treatment of moderate to severe HS with an inadequate response to conventional systemic HS therapy (approved in Sep 2015). However, 2 randomized, double-blind, placebo-controlled studies of adalimumab in a total of 633 adult subjects with moderate to severe HS indicated that only around 50% of subjects achieved a clinical response at Week 12. During the second part of both studies (up to 36 week treatment duration), approximately 40% of subjects who initially responded to adalimumab weekly therapy continued to benefit from this drug (Kimball et al, 2016a).

In summary, there is still a significant unmet medical need for additional therapies to treat this condition. In addition, given the significant reduction in QOL and functional impairment experienced by patients diagnosed with HS, there is an unmet need for medical therapies that can have a substantial impact on improving a patient's QOL.

2.2 Bimekizumab

Bimekizumab is an engineered, humanized full-length mAb of immunoglobulin G1 subclass of approximately 150,000 Daltons which is expressed in a genetically engineered Chinese Hamster Ovary (CHO) cell line. Bimekizumab has high affinity for human IL-17A and human IL-17F and selectively and potently inhibits the activity of both isoforms in vitro. Interleukin-17A and IL-17F are key pro-inflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases. Bimekizumab is being developed for the treatment of patients with inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), PSO, and axial spondyloarthritis. While anti-IL-17A antibodies have demonstrated efficacy in patients with PSO, PsA, and ankylosing spondylitis, as yet, no therapeutic approach is available that fully inhibits the activity of IL-17F. Bimekizumab selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro. Therefore, it permits an evaluation of the potential for additional efficacy that may be conferred by dual inhibition of both cytokines, in patients suffering from diseases in which both cytokines are active.

Published data and immunohistochemistry studies performed by UCB have shown that expression of both IL-17A and IL-17F are present in HS lesions and there are a number of published reports highlighting the potential for IL-17A and IL-17F to drive HS disease pathology (see Section 2.1.1). This supports the hypothesis that the IL-17 cytokine family is a potential therapeutic target in HS. Therefore, bimekizumab is hypothesized to demonstrate a treatment response in HS subjects because it selectively and potently inhibits the activity of both IL-17A and IL-17F isoforms in vitro.

2.2.1 Clinical

Currently, 4 clinical studies of bimekizumab (with a total of 134 subjects; 106 subjects exposed to bimekizumab) have been completed: RA0124 in 30 healthy volunteers, UP0031 in 12 healthy volunteers, UP0008 in 39 subjects with mild to moderate plaque PSO, and PA0007 in 53 subjects with PsA.

UP0008 was a Phase 1, single ascending dose study in adults with mild to moderate PSO affecting ≤5% body surface area. In this blinded study, single doses of up to 640mg (approximately 9mg/kg in a 70kg adult) were evaluated without any safety concerns. A total of 26 subjects with PSO with <5% of body surface involvement were treated with a range of single iv doses from 8 to 640mg. There were no clinically relevant safety findings identified at any dose and all doses were well tolerated. The prespecified exploratory assessment of disease activity showed clinically relevant and statistically significant improvements at the higher doses studied.

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

UP0031 was a Phase 1, open-label, parallel-group, single-dose level study in healthy subjects. The primary objective of this study was to determine the relative BA of a 160mg sc dose of bimekizumab, given as 2x80mg [redacted] or 1x160mg [redacted], in healthy subjects. The secondary objective of this study was to assess safety and tolerability of a single sc dose of bimekizumab in healthy subjects. In UP0031, the administration of bimekizumab demonstrated similar BA between the 2x80mg and 1x160mg treatment groups (geometric mean AUC values were 653.8day*µg/mL and 628.3day*µg/mL, respectively). Single sc doses of bimekizumab as Formulation A [redacted] and Formulation B [redacted] were demonstrated to be [redacted] and well tolerated in healthy subjects; no new safety issues were observed.

Bimekizumab has also been investigated in a Phase 1b, proof of concept, randomized, placebo-controlled, multiple-dose study (PA0007). The primary objective of PA0007 was to assess the safety and PK of multiple dose administration of iv bimekizumab in subjects with PsA. Four active doses (38 subjects) and placebo (14 subjects) were tested. Drug was administered as a loading dose at Week 0, and additional doses were administered at Week 3 and Week 6. In each treatment group, subjects received a total of 3 doses of bimekizumab, administered every 3 weeks as shown below:

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

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

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

Several additional studies of bimekizumab are ongoing in various patient populations (RA, ulcerative colitis, PSO, ankylosing spondylitis, and PsA).

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

2.2.2 Nonclinical

Parallel inhibition of IL-17A and IL-17F has shown potent effects in a variety of animal models of inflammatory disease. Intravenously administered bimekizumab was well tolerated in repeat dose toxicology studies in Cynomolgus monkeys with a no adverse effect level of 200mg/kg/week. The findings of note in toxicity studies were diarrhea related to infectious enteritis (observed in the single-dose study) and asymptomatic mild colonic ulceration in a proportion of animals (in the repeat-dose study); this latter finding was not associated with hematology abnormalities. Data suggest that bimekizumab has induced primary lesions to the mucosa-associated lymphoid tissue via a pharmacologically-related mechanism. In a second repeat-dose study, none of the minor apoptosis/necrosis findings observed in gut-associated lymph nodes were revealed. In animals given the highest dose of bimekizumab in the study (20mg/kg/week), a slightly higher number of protozoa (*Balantidium coli*) was observed in the cecum and colon as compared to the control animals and low dose animals. Therefore, the gut-associated lymph node lesions observed in the first study are considered to be accidental and/or linked to exaggerated pharmacology and proliferation of *Balantidium coli* and are considered to be the result of a change in local mucosal immunity. To date, similar findings have not been seen in studies in humans.

Additional information on the nonclinical data for bimekizumab is available in the current version of the IB.

The dose of bimekizumab used in this study is supported by nonclinical data and clinical data (see Section 5.4).

3 STUDY OBJECTIVES

3.1 Primary objective

The primary objective of this study is to evaluate the efficacy of bimekizumab in subjects with moderate to severe HS.

3.2 Secondary objective

The secondary objective of this study is to assess the safety, tolerability, immunogenicity, and PK of bimekizumab in subjects with moderate to severe HS.

3.3 Exploratory objective

The exploratory objective of the study is to further assess the efficacy of bimekizumab and to explore the effect of bimekizumab on gene and protein expression, and to explore the relationship between PD, nonhereditary pharmacogenomics, pharmacogenetic, and imaging biomarkers and HS disease biology, drug treatment, and inflammatory and immune responses.

4 STUDY VARIABLES

4.1 Efficacy variables

4.1.1 Primary efficacy variable

The primary efficacy variable is the clinical response as measured by HiSCR (defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining fistula count) at Week 12.

4.1.2 Exploratory efficacy variables

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

- Proportion of subjects with a total abscess and inflammatory nodule count of 0, 1, or 2 at Week 12
- Proportion of subjects with at least a 30% reduction and at least 1 unit reduction from Baseline in the PGA of Skin Pain (based on the subject's worst pain over the previous 24 hours) at Week 12
- Change from Baseline in modified Sartorius score at Week 12
- Change and percentage change from Baseline in lesion count (abscess count, inflammatory nodule count, abscess and inflammatory nodule count, and draining fistula count)
- Change from Baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) over time
- Change from Baseline in erythema assessment
- Change from Baseline in Hurley Stage
- Change and percentage change from Baseline in PGA of Skin Pain (pain at its worst and pain on average over the last 24 hours)
- Change from Baseline in the HS-Physician's Global Assessment 6-point scale
- Change from Baseline in the Dermatology Life Quality Index (DLQI)
- Change from Baseline in EQ-5D (index and visual analogue scale)
- Change from Baseline in Hospital Anxiety and Depression Scale (HADS) HADS-Anxiety (A) and HADS-Depression (D) scores

4.2 Pharmacokinetic, pharmacodynamic, pharmacogenomic, and pharmacogenetic variables

4.2.1 Secondary pharmacokinetic variable

Blood samples will be collected for the measurement of plasma bimekizumab concentrations at scheduled visits in accordance with the schedule of assessments in Table 5–1.

4.2.2 Exploratory pharmacodynamic variables

The PD variables assessed at time points specified in Table 5–1 are the blood or blood derivative (eg, plasma) concentrations of cytokines and chemokines of relevance to IL-17A/F signaling pathway and HS biology. Additional variables may include, but will not be limited to, serum complement concentrations and mononuclear cell subtypes.

4.2.3 Exploratory nonhereditary pharmacogenomic variables

Where local regulations permit, blood, urine and tissue biopsy samples will be collected at specific time points specified in Table 5–1 and stored for up to 20 years to allow for potential exploratory analyses of ribonucleic acid (RNA), proteins, and metabolites biomarkers relevant to HS and the inflammatory and immune response processes. The nature and format of these tentative analyses will be determined at a later stage.

4.2.4 Exploratory pharmacogenetic variables

Additional blood samples will be collected from subjects who consent to participate in the pharmacogenetic substudy at specific time points specified in Table 5–1 and stored at -80°C for up to 20 years. Pharmacogenetic biomarkers may be measured to evaluate the relationship with response to treatment with bimekizumab or adalimumab, HS disease biology, and inflammatory and immune response processes. The nature and format of these tentative substudy analyses will be determined when the results of the main study are made available.

4.3 Safety variables

4.3.1 Secondary safety variables

Safety variables to be assessed are:

- Frequency and severity of AEs and SAEs
- Withdrawal due to AEs
- Change from Baseline in vital signs (blood pressure [BP] and pulse rate) and body weight
- Changes from Baseline in ECG parameters
- Change from Baseline in clinical laboratory parameters (hematology, biochemistry, and urinalysis)
- Change from Baseline in physical examination

4.4 Immunological variables

4.4.1 Secondary immunological variable

Blood samples will be collected for the measurement of anti-drug antibody (ADA) at scheduled visits in accordance with the schedule of assessments Table 5–1.

4.5 Imaging variables

4.5.1 Exploratory imaging variables

Imaging biomarkers will be assessed by means of medical infrared imaging (thermography) and photography in specific centers with technological capabilities. Subjects who consent to participate in the imaging substudy at specific timepoints are specified in Table 5–1. Imaging biomarkers may be measured to evaluate the relationship with response to treatment with bimekizumab or adalimumab, HS disease biology, and inflammatory and immune response processes.

5 STUDY DESIGN

5.1 Study description

HS0001 is a Phase 2 multicenter, randomized, Investigator-blind, subject-blind, placebo-controlled, active reference arm study to assess the efficacy, safety, and PK of bimekizumab in eligible adult subjects with moderate to severe HS. To be eligible to participate in this study, subjects must be adults with a diagnosis of moderate to severe HS for at least 1 year prior to Screening (lesions present in at least 2 distinct anatomic areas [1 of which must be at least Hurley Stage II or III] and a total abscess and inflammatory nodule count ≥3) that has been stable for at least 2 months prior to Screening with an inadequate response to at least a 3-month study of an oral antibiotic treatment for HS (or exhibited recurrence after discontinuation to, or demonstrated intolerance to, or have a contraindication to oral antibiotics for treatment of their HS).

5.1.1 Study periods

This study will include 3 periods: a Screening Period (≥2 weeks up to a maximum of 4 weeks prior to randomization), a Treatment Period (12 weeks), and a SFU Period (20 weeks after the last dose of IMP).

Screening Period

The Screening Period will last ≥2 weeks up to a maximum of 4 weeks prior to randomization (dosing cannot occur earlier than 2 weeks after Screening due to IMP shipping timelines). During this time, laboratory data (hematology, urine, and biochemistry tests) will be obtained, and other information will be collected to confirm subject eligibility for this study.

Treatment Period

During the Treatment Period, eligible subjects will be randomized 2:1:1 (bimekizumab to placebo to adalimumab, stratified by Baseline Hurley Stage) to receive blinded IMP (all administered by sc injection by unblinded study personnel).

- Subjects randomized to receive bimekizumab will receive the following:
  - 640mg at Baseline (loading dose)
  - 320mg at Weeks 2, 4, 6, 8, and 10
- Subjects randomized to receive adalimumab will receive the following:
  - 160mg at Baseline (loading dose)

  - 80mg at Week 2
  - 40mg at Weeks 4, 5, 6, 7, 8, 9, and 10
- Subjects randomized to receive placebo will receive placebo at Baseline (loading dose) and at Weeks 2, 4, 5, 6, 7, 8, 9, and 10

Because of differences in the dosing schedule between bimekizumab and adalimumab, placebo injections will be administered along with active drug such that all subjects will receive the same number of injections at each corresponding visit. The number of placebo and active injections will vary by visit and treatment group, as described in Section 7.2 and Table 7–1.

A sufficient number of subjects will be screened in order to have 80 subjects randomized in the study. There will be approximately 40 subjects in the bimekizumab treatment group, 20 subjects in the placebo group, and 20 subjects in the adalimumab group. The primary efficacy variable will be assessed at Week 12 (Visit 11).

Subjects who withdraw early from the study for any reason, including those withdrawn from IMP, will be asked to return for study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and for an Early Withdrawal Visit that will comprise the same assessments as planned for the SFU Visit (Visit 12; 20 weeks after the last dose of IMP).

A Data Monitoring Committee (DMC) will review the data on an ongoing basis, as detailed in Section 11.5.

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

Safety Follow-Up Period

All subjects, including those withdrawn from IMP, will have a SFU Visit (Visit 12; 20 weeks after the last dose of IMP).

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

5.1.2 Study duration per subject

For each subject, the study will last a maximum of 34 weeks. This includes the following study period durations:

- Screening Period: ≥2 weeks up to a maximum of 4 weeks, from the time of informed consent up to randomization and administration of IMP at Baseline (Visit 2).
- Treatment Period: Up to 12 weeks, from the administration of IMP at Baseline (Visit 2) to the assessment of the primary efficacy variable at Week 12 (Visit 11).
- SFU Period: Up to 20 weeks, from the last dose of IMP at Week 10 (Visit 10) to the SFU Visit at Week 30 (Visit 12).

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

5.1.3 Planned number of subjects and sites

A sufficient number of subjects will be screened in order to have 80 subjects randomized in the study at multiple sites in North America, Europe, and Asia-Pacific (APAC) regions.

5.1.4 Anticipated regions and countries

The regions planned for study conduct are North America, Europe, and APAC, with possible extension into other regions.

5.2 Schedule of study assessments

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

Table 5–1: Schedule of study assessments

Procedures	Screening Period	Treatment Period										SFU Period
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/ SFU Visit/EW Visit
	Scr. [a]	Baseline Day 1 [b]	Week 2 (±3 days)[c]	Week 4 (±3 days)[c]	Week 5 (±3 days)[c]	Week 6 (±3 days)[c]	Week 7 (±3 days)[c]	Week 8 (±3 days)[c]	Week 9 (±3 days)[c]	Week 10 (±3 days)[c]	Week 12 (±3 days)[c]	Week 30 (-3 to +7 days)[c]
Written informed consent	X											
Demographics and Baseline characteristics[d]	X											
Inclusion/exclusion criteria verification	X	X										
Significant past medical history and concomitant diseases	X	X[e]										
Hidradenitis suppurativa history	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination [f]	X	X	X	X		X		X		X	X	X
Body weight	X	X									X	X
Vital signs [g]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X		X				X			X	X
Pregnancy test [h]	X	X		X				X			X	X
Urine drug screen	X											
Hematology, biochemistry, urinalysis	X	X		X				X			X	X

Table 5–1: Schedule of study assessments

Procedures	Screening Period	Treatment Period										SFU Period
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/ SFU Visit/EW Visit
	Scr. [a]	Baseline Day 1 [b]	Week 2 (±3 days)[c]	Week 4 (±3 days)[c]	Week 5 (±3 days)[c]	Week 6 (±3 days)[c]	Week 7 (±3 days)[c]	Week 8 (±3 days)[c]	Week 9 (±3 days)[c]	Week 10 (±3 days)[c]	Week 12 (±3 days)[c]	Week 30 (-3 to +7 days)[c]
Serology (HIV, Hepatitis B and C virus) [i]	X											
Chest x-ray or CAT scan of chest [j]	X											
TB questionnaire	X	X									X	X
IGRA TB test [k]	X											X
Blood sampling for plasma PK levels of bimekizumab [l]		X	X	X				X			X	X
Blood samples for PD and nonhereditary pharmacogenomic variables [l m]		X						X			X	
Blood samples for pharmacogenetic variables [l n]		X									X	
Blood samples for plasma levels of bimekizumab ADA [l]		X	X	X				X			X	X
Urine samples for biomarker research		X									X	

Table 5–1: Schedule of study assessments

Procedures	Screening Period	Treatment Period									SFU Period
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/ SFU Visit/EW Visit
	Scr. [a]	Baseline Day 1 [b]	Week 2 (±3 days)[c]	Week 4 (±3 days)[c]	Week 5 (±3 days)[c]	Week 6 (±3 days)[c]	Week 7 (±3 days)[c]	Week 8 (±3 days)[c]	Week 9 (±3 days)[c]	Week 10 (±3 days)[c]	Week 12 (±3 days)[c]	Week 30 (-3 to +7 days)[c]
Lesional and nonlesional skin biopsy		X									X	
Photography and thermography [o]		X		X				X			X	
Lesion count (including Hurley Stage) [p]	X	X	X	X		X		X		X	X	X
Modified Sartorius score		X									X	
Erythema assessment	X	X	X	X		X		X		X	X	X
PGA of Skin Pain		X	X	X		X		X		X	X	X
Hidradenitis Suppurativa-Physician's Global Assessment		X	X	X		X		X		X	X	X
DLQI		X	X	X		X		X		X	X	X
EQ5D		X	X	X		X		X		X	X	X
HADS	X	X	X	X		X		X		X	X	X
C-SSRS	X	X	X	X		X		X		X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Subject identification number assigned [q]	X											

Table 5–1: Schedule of study assessments

Procedures	Screening Period	Treatment Period										SFU Period
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11	Visit 12/ SFU Visit/EW Visit
	Scr. [a]	Baseline Day 1 [b]	Week 2 (±3 days)[c]	Week 4 (±3 days)[c]	Week 5 (±3 days)[c]	Week 6 (±3 days)[c]	Week 7 (±3 days)[c]	Week 8 (±3 days)[c]	Week 9 (±3 days)[c]	Week 10 (±3 days)[c]	Week 12 (±3 days)[c]	Week 30 (-3 to +7 days)[c]
Randomization [r]		X										
IMP treatment [s]		X	X	X	X	X	X	X	X	X		

ADA=anti-drug antibody; BMI=body mass index; CAT=Computed Axial Tomography; C-SSRS= Columbia-Suicide Severity Rating Scale; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; EQ-5D=European Quality-of-Life 5 dimensions questionnaire; EW=Early Withdrawal; HADS=Hospital Anxiety and Depression Scale; HiSCR=Hidradenitis Suppurativa Clinical Response; HIV=human immunodeficiency virus; IGRA=interferon-gamma release assay; IMP=investigational medicinal product; PD=pharmacodynamics; PGA=Patient's Global Assessment; PK=pharmacokinetics; RNA=ribonucleic acid; Scr.=Screening; SFU=Safety Follow-Up; TB=tuberculosis

Note: For subjects who prematurely terminate or complete the study, final study disposition will be recorded at the Early Withdrawal Visit. All subjects who prematurely terminate the study, including those withdrawn from IMP, will be asked to return for study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and for an EW Visit that will comprise the same assessments as planned for the SFU Visit (Visit 12; 20 weeks after the last dose of IMP).

[a] The Screening Period will last ≥2 weeks up to a maximum of 4 weeks prior to randomization (dosing cannot occur earlier than 2 weeks after Screening due to IMP shipping timelines).

[b] Day 1 is defined as the first day of administration and Day −1 is defined as the day before Day 1. Baseline (Visit 2) will include a visit window of ±2 days for all assessments prior to the first dose of IMP.

[c] Visit windows of ±3 days from the first dose at all visits except SFU. The SFU Visit window is -3 and +7 days from last dose.

[d] Will include lifestyle, childbearing potential, as applicable, height, and BMI.

[e] Ensure no significant changes in medical history and concomitant disease.

[f] Will include an evaluation of signs and symptoms of active TB and risk of exposure to TB at Screening and the SFU Visit (Visit 12).

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

[h] Pregnancy testing will be serum testing at Screening and the SFU Visit (Visit 12). The pregnancy test will be urine at all other visits.

[i] Subjects with HIV infection or who have evidence of, or tested positive for hepatitis B or hepatitis C virus are excluded. A positive test for the 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 the hepatitis C virus is defined as: 1) positive for hepatitis C antibody, and 2) positive via a confirmatory test for hepatitis C virus (for example, hepatitis C virus polymerase chain reaction).

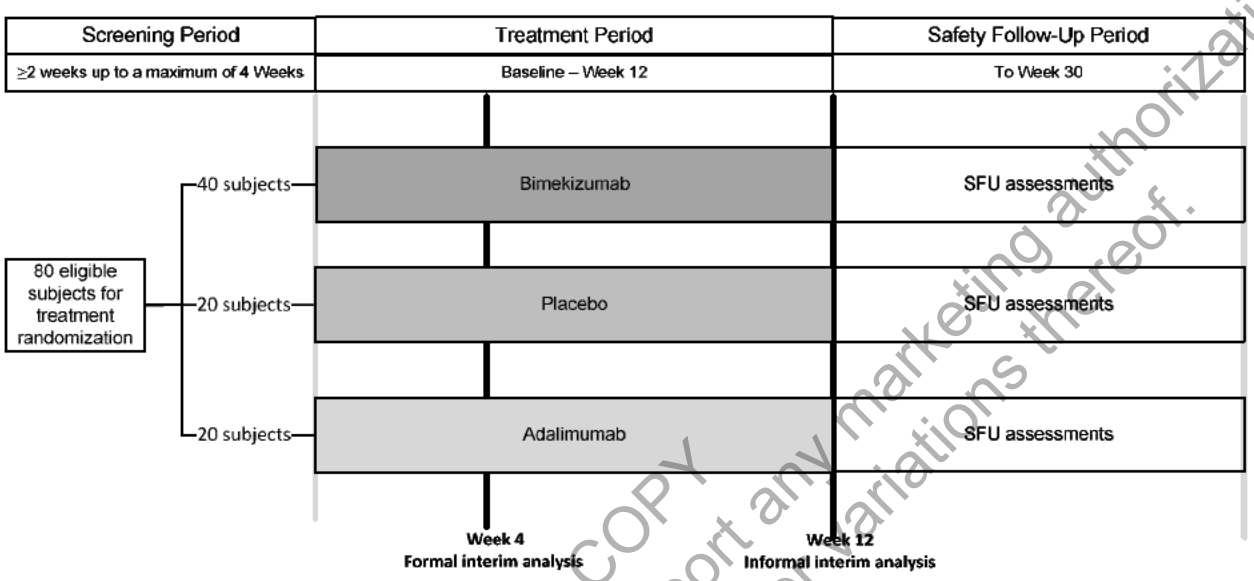
[j] A chest x-ray must be performed at Screening or must occur within 3 months prior to Screening and results must be available at Baseline. A CAT scan of chest at Screening or within 3 months prior to Screening is acceptable, if available.

[k] It is recommended that the QuantiFERON TB GOLD test be performed.
[l] All blood samples taken prior to dosing.
[m] The PD variables measured include: cytokines, complement, candidate biomarker analysis, and flow cytometry. The nonhereditary pharmacogenomics variables include RNA, proteins, and metabolites biomarkers.
[n] A separate Informed Consent Form will be required for subjects who decide to participate in the pharmacogenetic substudy. The Informed Consent Form must be signed prior to collecting any samples for the substudy.
[o] At certain sites, where feasible, representative photographs of the changes in skin will be captured. Photographs will be anonymized. Thermography (as described in Section 13) will also be performed at the same sites as photography.
[p] The lesion count will be performed at every study visit and must address all relevant anatomical regions in each subject; Hurley Stage is included as an assessment performed during the lesion count. See Section 9.3 for more details. The data collected from the lesion count will be used for the derivation of the HiSCR and International Hidradenitis Suppurativa Severity Score (see Section 9.1 and Section 9.2 for more details).
[q] The Investigator or designee will contact the Interactive Response Technology for the subject identification number.
[r] Randomization to IMP will occur at Baseline (Visit 2) and an Interactive Response Technology will be used for assigning eligible subjects to a treatment regimen. Subjects will be randomized 2:1:1 to bimekizumab, placebo, or adalimumab (stratified by Baseline Hurley Stage).
[s] Subjects will receive assigned IMP as described in Section 7.2 of the protocol. Because of differences in the dosing schedule between bimekizumab and adalimumab, a double-dummy approach will be applied such that all subjects receive 4 injections of IMP at Baseline; 2 injections of IMP at Weeks 2, 4, 6, 8, and 10; and 1 injection of IMP at Weeks 5, 7, and 9. The number of placebo and active injections will vary by visit and treatment group, as shown in Table 7–1.

5.3 Schematic diagram

A study schematic diagram of HS0001 is provided in Figure 5–1.

Figure 5–1: Schematic diagram



IMP=investigational medicinal product; sc=subcutaneous; SFU=Safety Follow-Up
Note: The first administration of IMP will occur at Baseline (Visit 2). The last dose of IMP will be at Week 10; the primary efficacy variable will be assessed at Week 12.
Note: In order to maintain the blind throughout the study, a double-dummy approach will be applied using placebo injections such that all subjects will receive the same number of injections at each corresponding visit. For a detailed description of IMP administration, see Section 7.2.

5.4 Rationale for study design and selection of dose

The inclusion criteria are selected to ensure all subjects have active moderate to severe HS. Some exclusion criteria are intended to exclude subjects who may present an unacceptable safety risk should they participate in this investigational study program. The full list of inclusion and exclusion criteria is provided in Section 6.

Dose selection and rationale:

The doses of bimekizumab used in this study include a 640mg loading dose administered sc at Baseline followed by a 320mg dose administered sc at Weeks 2, 4, 6, 8, and 10. The selection of the dose is founded on the principles described below.

The inflammatory burden in HS is greater than other auto-inflammatory conditions affecting the skin (ie, in PSO). Consistent with the recognition of the high inflammatory burden in HS, recent clinical studies of adalimumab in HS have shown the need for higher induction and maintenance doses in HS compared with PSO (Adalimumab European Public Assessment Report). Therefore, for bimekizumab, the dose required in HS subjects is expected to be higher than the maximum dose currently being explored in PSO (PS0010 and PS0016). The maximum dose that is being tested in Phase 2b studies in PSO is 480mg Q4W. The doses in the Phase 2b study in PSO were selected based on a PK-PD model that has been developed and is presented in the PK-PD report (CL0403, PK-PD report). The model simulation indicates that an increase in bimekizumab dose

leads to increased response and it is anticipated that a dose above 480mg Q4W is unlikely to lead to further clinical benefit in terms of PASI90 response; therefore, 480mg Q4W has been selected as the maximum dose in the study. The proposed dosage regimen in this study is predicted to achieve median trough concentrations >40µg/ml and is greater than those achieved with the 480 mg Q4W regimen in PSO. The 640mg dose administered at Baseline allows the predicted concentrations to be achieved rapidly, and 320mg Q2W is expected to maintain these concentrations over a period of 12 weeks.

The proposed dose of 640mg at Baseline is predicted to achieve 6.8-fold lower C_{max} (after first dose) compared to 640mg iv tested in mild PSO subjects due to a lower bioavailability following sc administration. Similarly, the predicted steady-state C_{max} following the proposed multiple dose regimen is 2-fold lower compared to the 560mg/320 mg Q3W regimen tested in PsA subjects, while the AUC_{τ} values are expected to be similar after accounting for differences in dosing interval. The predicted and observed PK parameters are shown in Table 5-2.

Table 5-2: Observed and model-predicted pharmacokinetic parameters for bimekizumab

Parameter	640mg iv (UP0008) Median (Geo CV%)	540/320mg Q3W iv (PA0007) Median (Geo CV%)	640/320mg Q2W sc (Model predicted) Median (90% PI)
C_{max} (µg/mL)	260 (21.40)	--	38 (23-70)
Steady-state C_{max} (µg/mL)	--	134.2 (22)	63 (37-121)
AUC_{τ} or AUC_{α} (µg*day/mL)	3787(39.034) [a]	1463 (18.9) [b]	823 (487-1588)

Geo CV=geometric coefficient of variation; iv=intravenous; PI=prediction interval; Q2/3W=every 2/3 weeks; sc=subcutaneous

[a] This value is for AUC_{α}.

[b] This value is for AUC_{τ}.

Current safety data from 106 subjects exposed to bimekizumab do not suggest dose dependency. Specifically, bimekizumab administered by iv infusion as a single ascending dose was tolerated at doses of up to 640mg in mild PSO subjects (UP0008). The MTD was not reached, and no safety issues were identified. No safety concerns were identified in PsA subjects (in PA0007), and bimekizumab was well tolerated at multiple dose administrations up to 560mg/320mg Q3W in subjects with PsA. There are multiple Phase 2b studies in PSO, PsA, and axial spondyloarthritis that are currently being conducted and the emerging data are not signaling any major safety concern. See Section 2.2.1 for further details on the clinical experience of bimekizumab.

Bimekizumab was well tolerated in the Cynomolgus monkey when administered iv or sc at doses up to 200mg/kg every week for up to 26 weeks; no treatment-related changes in clinical signs, clinical pathology, or histopathology indicative of toxicity were noted. No changes in BP or heart rate and no significant effects on ECG lead II parameters (PR, RR, QT, QT corrected for heart rate [QTc] intervals, and QRS duration) that could be ascribed to bimekizumab were noted. The only findings were related to decreased muco-epidermal immunity. These findings were variable from 1 study to the other, affected only some animals, occurred at doses exceeding largely those required for full IL-17A and IL-17F neutralization and translation to human was considered

unlikely. Additional information on the clinical and nonclinical data for bimekizumab is available in the current version of the IB.

The dose of bimekizumab used in this study supports the maximum likelihood of demonstrating the potential efficacy for bimekizumab in subjects with moderate to severe HS with an acceptable safety profile. Measures have also been taken to ensure the well-being of subjects by applying appropriate inclusion and exclusion criteria to recruit a target population that is most likely to benefit from treatment, while excluding subjects with an unacceptable risk to enter the study (see Section 6.2). Further, during the study, measures are in place to monitor the safety of subjects on a weekly basis, including assessment of cardiovascular risk factors as well as the potential risk of suicidal ideation and behavior. An independent DMC will also review the data on an ongoing basis, as detailed in Section 11.5.

Adalimumab will be administered at the approved dose for HS.

6 SELECTION AND WITHDRAWAL OF SUBJECTS

6.1 Inclusion criteria

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

1. An Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written Informed Consent Form (ICF) is signed and dated by the subject or by the legal representative.
2. Subject/legal representative is considered reliable and capable of adhering to the protocol (eg, able to understand and complete diaries), visit schedule, and medication intake according to the judgment of the Investigator.
3. Adult subjects (18 to 70 years of age, inclusive) must have a diagnosis of HS for at least 1 year prior to Baseline.
4. Hidradenitis suppurativa lesions must be present in at least 2 distinct anatomic areas, 1 of which must be at least Hurley Stage II or Hurley Stage III.
5. Subject must have stable HS for at least 2 months prior to Screening and also at the Baseline Visit as assessed by the Investigator through subject interview and review of medical history.
6. Subject must have had an inadequate response to at least a 3-month study of an oral antibiotic for treatment of HS (or exhibited recurrence after discontinuation to, or demonstrated intolerance to, or have a contraindication to oral antibiotics for treatment of their HS) as assessed by the Investigator through subject interview and review of medical history.
7. Subject must have a total abscess and inflammatory nodule count ≥3 at the Baseline Visit.
8. Subject must be considered, in the opinion of the Investigator, to be a suitable candidate for treatment with adalimumab per regional labeling.
9. Subject must have a C-reactive protein (CRP) level >3mg/L at the Baseline Visit.
10. Subject has a negative tuberculosis (TB) Screening assessment (including an interferon-gamma release assay [IGRA] test using QuantiFERON-TB Gold test, or equivalent) and negative posterior-anterior chest x-ray (CXR) or Computed Axial

Tomography (CAT) scan of chest at Screening or within 3 months prior to Screening (nuclear magnetic resonance films are not acceptable).

11. Subject must agree to daily use (and throughout the entirety of the study) of 1 of the following over-the-counter topical antiseptics on their HS lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater.
12. Subject is assessed to have no other medical condition that would preclude their participation in the study, as determined by the Principal Investigator based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead ECG performed during the Screening Period, and confirmed at Baseline.
13. **Female** subjects must be postmenopausal (at least 1 year; to be confirmed hormonally as part of the Screening process, if less than 2 years since last menstrual period), permanently sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) or, if of childbearing potential, must be willing to use a highly effective method of contraception up till 20 weeks after last administration of IMP, and have a negative pregnancy test at Visit 1 (Screening) and immediately prior to first dose. The following methods are considered highly effective when used consistently and correctly.
    - combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal).
    - progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).
    - intrauterine device (IUD).
    - intrauterine hormone-releasing system (IUS).
    - bilateral tubal occlusion.
    - vasectomized partner (where postvasectomy testing had demonstrated sperm clearance).
    - sexual abstinence if it is in accordance with a subject's preferred and common lifestyle. Subjects who use abstinence as a form of birth control must agree to abstain from heterosexual intercourse until 20 weeks after the last dose of IMP. Study personnel must confirm the continued use of abstinence is still in accordance with the subject's lifestyle at regular intervals during the study.

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

6.2 Exclusion criteria

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

1. Prior treatment with anti-IL17s or participation in an anti-IL17 study.
2. Subjects who previously received anti-TNFs.
3. Subjects participating in another study of a medication or a medical device under investigation within the last 3 months or at least 5 half-lives of the investigational product,

whichever is greater, or is currently participating in another study of a medication or medical device under investigation.

4. Subject has a known hypersensitivity to any excipient(s) of bimekizumab or adalimumab.
5. Subject is using concomitant oral analgesics for HS-related or non-HS-related pain at study entry:
   - Opioid analgesics within 14 days prior to the Baseline Visit.
   - Non-opioid oral analgesics ***unless*** at a stable dose for at least 14 days prior to the Baseline Visit (PRN use is not considered a stable dose).
6. Subject requires, or is expected to require, opioid analgesics for any reason (excluding tramadol).
7. Subject received prescription topical therapies for the treatment of HS within 14 days prior to the Baseline Visit.
8. Subject received systemic non-biologic therapies for HS with potential therapeutic impact for HS less than 28 days prior to Baseline Visit.
9. Subject has a draining fistula count >20 at the Baseline Visit.
10. Subjects with a diagnosis of inflammatory conditions other than HS, including but not limited to PSO, PsA, RA, sarcoidosis, or systemic lupus erythematosus. Subjects with a diagnosis of CD or ulcerative colitis are allowed as long as they have no active symptomatic disease at Screening or Baseline.
11. Subjects with a history of chronic or recurrent infections, or a serious or life-threatening infection within the 6 months prior to the Baseline Visit (including herpes zoster). Subjects with a high risk of infection in the Investigator's opinion (eg, subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections, prior prosthetic joint infection at any time, subjects who are permanently bedridden or wheelchair assisted).
12. Subject has any current sign or symptom that may indicate an active infection (except for common cold), or has had an infection requiring systemic antibiotics within 2 weeks of the Baseline Visit.
13. Any other active skin disease or condition (eg, bacterial, fungal or viral infection) that may interfere with assessment of HS.
14. Subject has history of or current clinically active infection with Histoplasma, Coccidiodes, Paracoccidioides, Pneumocystis, nontuberculous mycobacteria (NTMB), Blastomyces, or Aspergillus or current active Candidiasis (local or systemic).
15. Subject has acute or chronic viral hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) infection. Subjects who have evidence of, or tested positive for, hepatitis B or hepatitis C are excluded.
    - A positive test for the HBV is defined as: 1) positive for hepatitis B surface antigen; or, 2) positive for anti-hepatitis B core antibody.

- A positive test for the 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).

16. Subjects with known TB infection, at high risk of acquiring TB infection, with latent TB infection (LTB), or current or history of NTMB infection (refer to Section 11.3.1 for details on determining full TB exclusion criteria).
17. Subject has a primary immunosuppressive condition, including taking immunosuppressive therapy following an organ transplant, or has had a splenectomy.
18. Subjects with concurrent malignancy or history of malignancy (including surgically resected uterine/cervical carcinoma-in-situ) during the past 5 years will be excluded, with the following exceptions that may be included:
    a. ≤3 excised or ablated, basal cell carcinomas of the skin.
    b. One squamous cell carcinoma of the skin (stage T1 maximum) successfully excised, or ablated only (other treatments, ie, chemotherapy, do not apply), with no signs of recurrence or metastases for more than 2 years prior to Screening.
    c. Actinic keratosis(-es).
    d. Squamous cell carcinoma-in-situ of the skin successfully excised, or ablated, more than 6 months prior to Screening).
19. Subject has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
20. Subject has history of demyelinating disease (including myelitis) or neurologic symptoms suggestive of demyelinating disease.
21. Subjects with a current or recent history, as determined by the Investigator, of severe, progressive, and/or uncontrolled renal, hepatic, hematological, endocrine, pulmonary, cardiac (eg, congestive heart failure, New York Heart Association Grade 3 and 4), gastrointestinal (note: subjects with active peptic ulcer disease are excluded; subjects with a history of peptic ulcer disease are allowed), neurological disease, or inflammatory bowel disease.
22. Subject has a history of uncompensated heart failure, fluid overload, or myocardial infarction, or evidence of new onset ischemic heart disease or (in the opinion of the Investigator) other serious cardiac disease, within 12 weeks prior to the Baseline Visit.
23. Presence of active suicidal ideation, or positive suicide behavior using the "Baseline" version of the Columbia-Suicide Severity Rating Scale (C-SSRS) and the HADS with either of the following criteria:
    - Subject has a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response ("Yes") to either question 4 or question 5 of the "Screening/Baseline" version of the C-SSRS at Screening.
    - HADS-D score ≥10 and HADS-A score ≥15.

24. Subject has >2x upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), *alkaline phosphatase (ALP), or >ULN total bilirubin (≥1.5xULN total bilirubin if known Gilbert's syndrome). If subject has elevations only in total bilirubin that are >ULN and <1.5xULN, fractionate bilirubin to identify possible undiagnosed Gilbert's syndrome (ie, direct bilirubin <35%).

    *An isolated elevation between 2xULN and <3xULN of ALP is acceptable in the absence of an identified exclusionary medical condition.

    Tests that result in ALT, AST, or ALP up to 25% above the exclusion limit may be repeated once for confirmation during the Screening Period. Upon retesting, subjects whose ALT, AST, or ALP remain above the thresholds defined above, should not be randomized.

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

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

25. Subjects with clinically significant laboratory abnormalities (eg, creatinine >1.5xULN, neutropenia <1.5x10^9/L, hemoglobin <8.5g/dL, lymphocytes <1.0x10^9/L, platelets <100x10^9/L). 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 if they are within 25% of the exclusion limit. Upon retesting, subjects whose results remain outside this threshold should not be randomized.
26. Subject has 12-lead ECG with changes considered to be clinically significant upon medical review (eg, QTc using Fridericia's correction [QTcF] >450ms, bundle branch block, evidence of myocardial ischemia).
27. Subject has received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline Visit (eg, inactivated influenza and pneumococcal vaccines are allowed but nasal influenza vaccination is not permitted). Live vaccines are not allowed during the study or for 20 weeks after the last dose of IMP.
28. Subject has received Bacillus Calmette-Guerin vaccination within 1 year prior to IMP administration.
29. Subject has a history of chronic alcohol or drug abuse within the previous 6 months.
30. Subjects with any other condition which, in the Investigator's judgement, would make the subject unsuitable for inclusion in the study.
31. Subject has previous exposure to adalimumab.
32. Subjects are Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

33. Subjects are UCB employees or are employees of third-party organizations involved in the study.

6.3 Withdrawal criteria

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

Subjects should be withdrawn from the study and encouraged to come for the SFU Visit (20 weeks after the last dose of IMP) if any of the following events occur:

1. Subject withdraws his/her consent.
2. The Sponsor or a regulatory agency requests withdrawal of the subject.

Subjects should be withdrawn from all IMP and will be asked to return for the study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and for the SFU Visit (20 weeks after the last dose of IMP) if any of the following events occur:

1. There is confirmation of a pregnancy during the study, as evidenced by a positive pregnancy test.
2. Subject develops an illness that would interfere with his/her continued participation.
3. Subject considered to have either a suspected new LTB infection or who develops active TB or NTMB infection during the study (including but not limited to conversion demonstrated by IGRA or other diagnostic means) must be immediately discontinued from IMP and an Early Withdrawal Visit must be conducted as soon as possible, but not later than the next regular visit.

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

   Additional information on TB policies are provided in Section 11.3.1.
4. Subject is noncompliant with the study procedures or medications in the opinion of the Investigator.
5. Subject uses prohibited concomitant medications, with the exception of topicals, as defined in this protocol (Section 7.8.2), that may present a risk to the safety of the subject in the opinion of the Investigator and/or the Medical Monitor and/or UCB Study Physician.
6. Subject develops total bilirubin >2xULN (except Gilbert's); neutropenia <1.0x10^9/L; lymphopenia <0.5x10^9/L.
7. Subject has active suicidal ideation as indicated by a positive response ("Yes") to questions 4 or 5 or to the suicidal behavior questions of the "Since Last Visit" version of the self-rated C-SSRS. The subject should be referred immediately to a Mental Healthcare Professional and must be withdrawn from the study.
8. Subjects with a HADS-D score ≥15 must be withdrawn. Any subject who has a HADS-D score of ≥10 should be referred immediately to a Mental Healthcare Professional for further evaluation and potential withdrawal by the Investigator.

9. Subject experiences an AE as described below:
   - Any Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above AE that is assessed as related to study drug in the opinion of the Investigator.
     - If the event is deemed to be not related to study drug by the Investigator, the subject may remain in the study after approval by the Medical Monitor and/or UCB Study Physician.
   - Any CTCAE Grade 2 event that is evaluated as related to study drug in the opinion of the Investigator, is persistent, and falls into any of the following System Organ Classes: "Blood and lymphatic disorders," "Cardiac disorders," or "Vascular disorders."
     - Persistent is defined as lasting 28 days or more, which spans at least 2 bimekizumab dosing visits.
10. Subject has a clinical laboratory value meeting the following criteria:
    - CTCAE Grade 3 and above: subject must be withdrawn regardless of relationship to study drug or duration of event, unless the abnormal laboratory value is a natural variation of a condition pre-existing before Baseline (eg, hypercholesterolemia).
    - CTCAE Grade 2
      - Subject may remain in the study if the event is transient. If a subject has a Grade 2 laboratory abnormality that is not an expected natural variation of a condition present before Baseline, a retest is required within 1 to 2 weeks at a scheduled or unscheduled visit. If the repeat value is below Grade 2, the subject may receive the next scheduled study treatment. If the value on the repeat is still Grade 2 or above, a second repeat test must be performed and results made available prior to the next scheduled study treatment. If this second repeat value is still Grade 2 or above, the subject must be withdrawn.
11. Subjects with newly diagnosed Inflammatory Bowel Disease (IBD) or with IBD flares during the study must:
    - Be referred, as appropriate, to a healthcare professional treating IBD, such as a gastroenterologist
    - Discontinue the IMP and be followed-up until resolution of active IBD symptoms

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

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

Investigators should contact the Medical Monitor and/or UCB Study Physician, whenever possible, to discuss the withdrawal of a subject in advance.

6.3.1 Potential drug-induced liver injury investigational medicinal product discontinuation criteria

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

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

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

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

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

Evaluation of PDILI must be initiated as described in Section 11.2.1. If subjects are unable to comply with the applicable monitoring schedule, IMP must be discontinued immediately.

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

6.4 Study stopping rules

Reasons for suspension or discontinuation of the study can fall into 1 of the following 2 principal categories: safety and other reasons.

6.4.1 Safety

Should a critical safety issue or signal be identified during the study, then planned dosing and procedures may be discontinued or suspended for subjects in any part of the study and appropriate follow up procedures established.

Where an individual Investigator believes such a safety issue or signal has been identified in one or more of the subjects under their care, further dosing of those subjects may be suspended, but this action should be discussed with the UCB Study Physician prior to its implementation, unless any delay incurred would materially threaten the safety of those subjects.

Any decision to suspend or terminate dosing across the whole study should be taken by the Sponsor after consultation with DMC, following full review of the relevant data.

However, where any delay incurred in convening a DMC meeting might materially threaten the safety or well-being of subjects, the Sponsor (in the person of the Study Physician or the Patient Safety Physician) will make the decision whether or not to suspend dosing until the DMC can meet.

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

Whenever a pattern of AEs occurs that may contraindicate the further dosing of enrolled or additional subjects, including (but not limited to) more than 1 subject meeting any individual Withdrawal Criteria 3, 7, 8, 9, or 10 (as provided in Section 6.3), regardless of whether they met the same or different criteria; the DMC will meet as soon as possible. The DMC will determine whether discontinuation or suspension of the study should occur, and will determine what investigations, analyses, procedural amendments, or other actions should occur, before making any recommendation regarding the possibility of recommencing the study. Once a second subject meets any of those criteria, referral to the DMC may not be delayed while awaiting the outcome of either case.

Further details on the role of the DMC are provided in 11.1.7 and Section 11.5.

6.4.2 Other reasons

The study may be discontinued for any medical, safety, regulatory, or any other reasons that the Sponsor or its designees judge necessary, where consistent with applicable laws, regulations, and Good Clinical Practice (GCP).

6.5 Retesting/rescreening

In the event of an isolated laboratory value outside the laboratory's normal range, the evaluation may be repeated on 1 occasion during the Screening Period. If a value from the repeated test is within the Screening-specified ranges, the subject may be enrolled. Subjects whose Screening Period expires may be rescreened.

7 STUDY TREATMENTS

7.1 Description of investigational medicinal products

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

Bimekizumab will be supplied as a clear to opalescent, colorless to slightly brown, sterile, preservative-free solution in 2mL Type I, colorless glass vials (1.0mL extractable volume) closed with a rubber stopper and sealed with an aluminum cap overseal. [redacted]

Adalimumab is commercially available and will be supplied as a prefilled syringe for injection (40mg/0.8mL for US sites and 40mg/0.4mL for all other sites) in a single-use, 1mL glass syringe with a fixed 27 gauge, 0.5 inch needle. Each syringe contains 40mg adalimumab in 1.04mg citric acid monohydrate, 1.22mg dibasic sodium phosphate dihydrate, 9.6mg mannitol, 0.69mg monobasic sodium phosphate dihydrate, 0.8mg polysorbate 80, 4.93mg sodium chloride, 0.24mg sodium citrate, and water for injection (US Pharmacopeia).

Placebo will be supplied as 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (US Pharmacopoeia/European Pharmacopoeia) quality appropriate for injection.

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

7.2 Treatments to be administered

Subjects will be randomized in a 2:1:1 ratio to bimekizumab, placebo, or adalimumab (stratified by Baseline Hurley Stage).

- Subjects randomized to receive bimekizumab will receive the following:
  - 640mg at Baseline (loading dose)
  - 320mg at Weeks 2, 4, 6, 8, and 10
- Subjects randomized to receive adalimumab will receive the following:
  - 160mg at Baseline (loading dose)
  - 80mg at Week 2
  - 40mg at Weeks 4, 5, 6, 7, 8, 9, and 10
- Subjects randomized to receive placebo will receive placebo at Baseline, and Weeks 2, 4, 5, 6, 7, 8, 9, and 10

Because of differences in the dosing schedule between bimekizumab and adalimumab, placebo injections will be administered along with active drug such that all subjects will receive the same number of injections at each corresponding visit. The number of placebo and active injections will vary by visit and treatment group, as shown in Table 7–1.

Table 7–1: Administration of investigational medicinal product

Visit	Treatment group		
	Adalimumab [a] **(Total # injections, # of placebo injections)**	**Bimekizumab** [b] **(Total # injections, # of placebo injections)**	**Placebo**
Baseline	160mg (4 active injections, no placebo injections)	640mg (4 active injections, no placebo injections)	4 placebo injections
Week 2	80mg (2 active injections, no placebo injections)	320mg (2 active injections, no placebo injections)	2 placebo injections
Weeks 4, 6, 8, and 10	40mg (1 active injection, 1 placebo injection)	320mg (2 active injections, no placebo injections)	2 placebo injections
Weeks 5, 7, and 9	40mg (1 active injection, no placebo injection)	NA (no active injection, 1 placebo injection)	1 placebo injection

Table 7–1: Administration of investigational medicinal product

Visit	Treatment group		
	Adalimumab [a] **(Total # injections, # of placebo injections)**	**Bimekizumab** [b] **(Total # injections, # of placebo injections)**	**Placebo**
Baseline	160mg (4 active injections, no placebo injections)	640mg (4 active injections, no placebo injections)	4 placebo injections

NA=not applicable
Note: All treatments will be administered as subcutaneous injections.
[a] Each individual adalimumab injection will be 40mg.
[b] Each individual bimekizumab injection will be 160mg.

Bimekizumab will be supplied in vials, placebo will be supplied as a 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (US Pharmacopoeia/European Pharmacopoeia) quality appropriate for injection, and commercially available adalimumab will be supplied in prefilled syringes. Thus, in order to maintain the treatment blind the dosing solution will be prepared by the unblinded pharmacist and administered by unblinded study personnel (see Section 7.9). The unblinded study personnel will not have any other involvement in the study, and subject assessments will be performed by blinded study personnel.

Injections will be administered sc to the lateral abdominal wall or upper outer thigh. Investigational medicinal product will be administered by unblinded, qualified study personnel at the study site.

The injection should last approximately 20 seconds. The time of administration, volume, and injection site will be documented in the eCRF.

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

7.3 Packaging

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

7.4 Labeling

Clinical drug supplies will be labeled in accordance with the current International Council for Harmonisation (ICH) guidelines on GCP and GMP and will include any locally required statements. If necessary, labels will be translated into the local language. If necessary, labels will be translated into the local language as appropriate. Details on labeling will be provided in the IMP Handling Manual.

7.5 Handling and storage requirements

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

The Investigator (or designee) is responsible for the safe and proper storage of IMP at the site. Investigational medicinal product stored by the Investigator is to be kept in a secured area with limited access according to the storage conditions mentioned on the label. Appropriate storage conditions must be ensured either by controlling the temperature (eg, room, refrigeration unit) or by completion of a temperature log in accordance with local requirements on a regular basis (eg, once a week), showing actual and minimum/maximum temperatures reached over the time interval. In case an out-of-range temperature is noted, it must be immediately reported as per instructions contained in the IMP Handling Manual.

The IMP will be shipped to the study sites in temperature controlled containers. Out-of-range shipping or storage conditions must be brought to the attention of the Sponsor or designee, immediately. Authorization to use any out-of-range IMP must be documented and received prior to dispensing or administering the IMP at the study site.

7.6 Drug accountability

A Drug Accountability form will be used to record IMP dispensing and return information on a by-subject basis and will serve as source documentation during the course of the study. Details of any IMP lost, damaged (due to breakage or wastage), not used, partially used, disposed of at the study site, or returned to the Sponsor or designee must also be recorded on the appropriate forms. All supplies and pharmacy documentation must be made available throughout the study for UCB (or designee) to review.

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

Only unblinded study staff may be involved in the receipt, inventory, and destruction of the used, partially used, damaged, or unused kits since the packaging is unblinding. Unblinded study staff will be responsible for preparation (breaking tamper proof sticker on kit, etc) of the IMP, including recording the administration information on source document. Designated, unblinded site personnel must be appropriately trained and licensed (per country guidelines) to administer injections.

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

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

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

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

7.7 Procedures for monitoring subject compliance

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

7.8 Concomitant medications/treatments

7.8.1 Permitted concomitant treatments (medications and therapies)

The following concomitant medications/treatments are permitted during the study:

- Antiseptic Therapy
  - Subjects are required to use a daily antiseptic wash on their HS lesions. Allowable antiseptic washes are limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater.
- Wound Care
  - Concomitant use of wound care dressings on HS wounds is allowed; however, options are limited to alginates, hydrocolloids, and hydrogels.
- Analgesic Therapy
  - Most subjects will be required to washout all analgesics for 14 days prior to Baseline. This includes analgesics for HS-related pain and other pain (non-HS-related). However, if a subject is on a stable dose of a non-opioid analgesic (PRN is not considered stable) for HS-related pain or for a non-HS medical condition (eg, osteoarthritis), the subject may continue the analgesic, provided the dose is stable for 14 days prior to Baseline and is anticipated to remain stable throughout study participation.
  - If a subject's pain (HS-related or non-HS-related) worsens after Baseline, they may initiate analgesic therapy at any time as follows: For HS-related pain, permitted analgesics are limited to: ibuprofen (at a dose of up to 800 mg po every 6 hours) not to exceed 3.2 grams/per 24 hours; AND/OR acetaminophen/paracetamol as per local labeling. If HS-related pain is uncontrolled with ibuprofen or acetaminophen/paracetamol at the above dosing regimens after the Baseline Visit (Visit 2), subjects can be prescribed tramadol (at a dose of up to 100mg po every 4 hours), not to exceed 400mg per 24 hours.
- Antibiotic Therapy
  - Concomitant use of oral antibiotic therapy for treatment of HS is allowed provided the dosing regimen (dose and frequency) has been stable for at least 4 consecutive weeks (28 days) prior to Baseline. The dosing regimen must remain stable throughout study participation. Antibiotics taken on an "as needed" (PRN) basis are not considered a stable dose.
  - Permitted oral concomitant antibiotics include:
    - Oral: doxycycline (at a dose of up to 100 mg po bid); minocycline (at a dose of up to 100 mg po bid)

- If another Baseline oral concomitant antibiotic for HS is medically necessary, the UCB Study Physician must be contacted for approval. If systemic antibiotics are used concomitantly, the dose should remain stable and constant.

7.8.2 Prohibited concomitant treatments (medications and therapies)

The following concomitant medications are prohibited during the study:

- Any other immunomodulatory therapy, including systemic steroids
- Any analgesics other than those specified in Section 7.8.1
- Medications contraindicated for administration with adalimumab (per the regional approved labelling), including, but not limited to, abatacept, anakrina, and other TNF-blocking agents
- All other biologics

7.8.3 Rescue medication

There are no absolute restrictions on the use of concomitant medications to "rescue" subjects whose HS deteriorates during the course of the study. While the objectives of the study should be protected as much as possible through observance of the restrictions detailed in Section 7.8.2, the well-being of the subject will always take priority, and subjects should be managed as deemed appropriate by the Investigator. If use of any prohibited medications is anticipated, this should be discussed with the Medical Monitor and/or UCB Study Physician first, whenever possible.

If a subject should require emergency treatment for an uncontrolled flare(s) (defined as a ≥25% increase and an absolute increase in ≥2 in total abscess and inflammatory nodule count from Baseline) that includes development of a painful abscess (with purulent exudate and inflammation) during the study, rescue treatment will be allowed. This can include some form of analgesic for a limited period, incision and drainage of the abscess, and may also include a limited number of intralesional injections of triamcinolone. The need for these procedures should be discussed with the Medical Monitor and/or UCB Study Physician first, whenever possible.

7.9 Blinding

The IMP handling manual describes the handling of bimekizumab, adalimumab, and placebo. Appropriate training will be given to the site personnel to avoid the unblinding of blinded personnel and subjects. In case the Investigator becomes unblinded for any subject, another assessor will do the remaining evaluations for that subject.

Due to differences in presentation between the bimekizumab and adalimumab, unblinded study personnel appropriately delegated by the Investigator will be required to prepare and administer the IMP in order to maintain the blind. The unblinded study personnel will not have any other involvement in the study and will not be allowed to reveal a subject's allocated treatment to study personnel or to the subject. Blinded staff will not be involved in any activities pertaining to the receipt, storage, handling, or administration of IMP. All IMP documentation (eg, shipping receipts, accountability logs, IVRS randomization materials) will be maintained by unblinded staff only. Designated, unblinded study personnel will be appropriately trained and licensed (per country guidelines) to administer injections. Each site will have a written blinding plan signed by

the Investigator, which details the site's steps for ensuring that the Investigator-blind, subject-blind nature of the study is maintained.

All Sponsor and Investigator site personnel involved in the study will be blinded to the randomized IMP (bimekizumab, adalimumab, or placebo) assignment with the following exceptions:

- Sponsor clinical trial supply and qualified study personnel
- Sponsor Patient Safety (PS) staff reporting SAEs to the regulatory authorities
- Site pharmacist involved in IMP preparation and study personnel who administer IMP
- Monitor who reviews the IMP related documentation and drug accountability
- Bioanalytical staff analyzing blood samples for bimekizumab and anti-bimekizumab antibody determination
- DMC members (unblinded safety data)
- Any Sponsor staff and/or designee who is responsible for data analyses for the unblinded DMC and interim analyses. These individuals will be separate from the main blinded study team.

If necessary, the results of any planned DMC and/or interim analysis may be shared with key Sponsor's personnel in order to facilitate additional Clinical Planning or Portfolio Management decisions. The results will include both individual and summary results, and will be presented unblinded. All individuals seeing unblinded data will be documented in the Trial Master File.

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

7.9.1 Procedures for maintaining and breaking the treatment blind

7.9.1.1 Maintenance of study treatment blind

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

7.9.1.2 Breaking the treatment blind in an emergency situation

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

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

7.10 Randomization and numbering of subjects

An IRT will be used for assigning eligible subjects to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by UCB (or

designee). The randomization schedule will be stratified by Baseline Hurley Stage and will be produced by an independent biostatistician with the Contract Research Organization (CRO) who is otherwise not involved in this study. The IRT will generate individual assignments for subject kits of IMP, as appropriate, according to the visit schedule.

To enroll a subject at Screening (Visit 1), the Investigator or designee will contact the IRT and provide brief details about the subject to be enrolled. Each subject will receive a 5-digit number assigned at Screening that serves as the subject identifier throughout the study. The subject number will be required in all communication between the Investigator or designee and the IRT regarding a particular subject. Subject numbers and kit numbers will be tracked via the IRT.

To randomize a subject at Baseline (Visit 2), the Investigator or designee will contact the IRT and provide brief details about the subject to be randomized along with the subject's Baseline Hurley Stage (stratification factor). The IRT will automatically inform the Investigator or designee of the subject's randomization number. The IRT will allocate kit numbers to the subject based on the subject number during the course of the study. The randomization number must be incorporated into the eCRF.

8 STUDY PROCEDURES BY VISIT

Table 5–1 (schedule of study assessments) provides a general overview of study assessments. A list of procedures to be completed at each visit is described below.

- Visit windows of ±3 days on either side of the scheduled dosing are permitted; however, the Investigator should try to keep the subjects on the original dosing schedule. The window of ±3 days is relative to Baseline and applicable for all subsequent visits. Changes to the dosing schedule outside of the 3-day window must be discussed with the Medical Monitor and/or UCB Study Physician.
- The minimum of time between doses should be no less than 12 days and no more than 18 days.
- For the SFU Visit (20 weeks after the last dose of IMP), the visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

8.1 Screening Visit (Visit 1)

The Screening Period will last ≥2 weeks up to a maximum of 4 weeks prior to randomization (dosing cannot occur earlier than 2 weeks after the Screening Visit due to IMP shipping timelines).

Prior to any study specific activities, subjects will be asked to read, sign, and date an ICF that has been approved by the Sponsor and an IEC/IRB, and that complies with regulatory requirements. Subjects will be given adequate time to consider any information concerning the study given to them by the Investigator or designee. As part of the informed consent procedure, subjects will be given the opportunity to ask the Investigator any questions regarding potential risks and benefits of participation in the study.

Where local regulations permit, all subjects will also be given the option to participate in an imaging substudy (select sites) and a pharmacogenetic substudy. Subjects agreeing to participate in the pharmacogenomic substudy will be required to complete a separate ICF. The

pharmacogenomic substudy ICF must be signed prior to collecting any samples for the substudy. The pharmacogenomic substudy will only be conducted where ethically accepted and authorized by the regulatory agencies. Refusal to participate in either substudy will not affect a subject's ability to participate in the main HS0001 study.

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

- Obtain written informed consent
- Contact the IRT/Subject identification number assigned
- Verification of inclusion/exclusion criteria
- Demographics and Baseline characteristics (will include lifestyle, childbearing potential [as applicable], height, weight, and body mass index [BMI])
- Significant past medical history and concomitant diseases
- HS history
- Prior and concomitant medications
- Physical examination
- Vital signs (BP, pulse rate, and temperature)
- Record 12-lead ECG
- C-SSRS
- CXR or CAT scan of chest (not necessary if performed within 3 months prior to Screening Visit and report is available)
- TB questionnaire
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Erythema assessment
- Obtain blood sample(s) for:
  - TB test (IGRA; it is recommended that the QuantiFERON TB GOLD test be performed)
  - Serum pregnancy test for women of childbearing potential
  - Standard safety laboratory tests (hematology and biochemistry)
  - HBV and HCV virus testing
  - HIV
- Obtain urine sample for:
  - Standard safety laboratory tests

  - Urine drug screen
- Record AEs

Individual Screening tests for which the results are borderline for inclusion in the study may be repeated if necessary without complete rescreening of all tests.

8.2 Baseline Visit (Visit 2; Day 1)

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

- Confirm inclusion/exclusion criteria
- Contact the IRT for randomization
- Ensure no significant changes in medical history and concomitant disease
- Physical examination
- Body weight
- Concomitant medications
- Vital signs (BP, pulse rate, and temperature)
- Record 12-lead ECG
- C-SSRS
- TB questionnaire
- Photography and thermography (for subjects participating in the substudy)
- PGA of Skin Pain
- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Modified Sartorius score
- Erythema assessment
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - PD and nonhereditary pharmacogenomic variables
  - Pharmacogenetic variables (for subjects participating in the substudy)

  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
  - Biomarker research
- Obtain skin biopsy samples for:
  - lesional and nonlesional skin biopsy
- Record AEs
- IMP administration (after all other visit assessments completed)

8.3 Visit 3; Week 2 (±3 days)

The following procedures or assessments will be performed/recorded:

- Physical examination
- Concomitant medications
- Vital signs (BP, pulse rate, and temperature)
- C-SSRS
- PGA of Skin Pain
- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Erythema assessment
- Obtain blood sample(s) for:
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Record AEs
- IMP administration (after all other visit assessments completed)

8.4 Visit 4; Week 4 (±3 days)

The following procedures or assessments will be performed/recorded:

- Physical examination
- Concomitant medications

- Vital signs (BP, pulse rate, and temperature)
- Record 12-lead ECG
- C-SSRS
- Photography and thermography (for subjects participating in the substudy)
- PGA of Skin Pain
- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Erythema assessment
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Record AEs
- IMP administration (after all other visit assessments completed)

8.5 Visits 5, 7, and 9; Weeks 5, 7, and 9 (±3 days)

The following procedures or assessments will be performed/recorded:

- Concomitant medications
- Vital signs (BP, pulse rate, and temperature)
- Record AEs
- IMP administration (after all other visit assessments completed)

8.6 Visit 6; Week 6 (±3 days)

The following procedures or assessments will be performed/recorded:

- Physical examination
- Concomitant medications
- Vital signs (BP, pulse rate, and temperature)

- C-SSRS
- PGA of Skin Pain
- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Erythema assessment
- Record AEs
- IMP administration (after all other visit assessments completed)

8.7 Visit 8; Week 8 (±3 days)

The following procedures or assessments will be performed/recorded:

- Physical examination
- Concomitant medications
- Vital signs (BP, pulse rate, and temperature)
- Record 12-lead ECG
- C-SSRS
- Photography and thermography (for subjects participating in the substudy)
- PGA of Skin Pain
- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Erythema assessment
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - PD and nonhereditary pharmacogenomic variables
  - Anti-bimekizumab antibodies

- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
- Record AEs
- IMP administration (after all other visit assessments completed)

8.8 Visit 10; Week 10 (±3 days)

The following procedures or assessments will be performed/recorded:

- Physical examination
- Concomitant medications
- Vital signs (BP, pulse rate, and temperature)
- C-SSRS
- PGA of Skin Pain
- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Erythema assessment
- Record AEs
- IMP administration (after all other visit assessments completed)

8.9 Visit 11; Week 12 (±3 days)

The following procedures or assessments will be performed/recorded:

- Physical examination
- Body weight
- Concomitant medications
- Vital signs (BP, pulse rate, and temperature)
- Record 12-lead ECG
- C-SSRS
- TB questionnaire
- Photography and thermography (for subjects participating in the substudy)
- PGA of Skin Pain

- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Modified Sartorius score
- Erythema assessment
- Obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - PD and nonhereditary pharmacogenomic variables
  - Pharmacogenetic variables (for subjects participating in the substudy)
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests
  - Urine pregnancy test for women of childbearing potential
  - Biomarker research
- Obtain skin biopsy samples for:
  - Lesional and nonlesional skin biopsy
- Record AEs

8.10 Safety Follow-Up Visit (Visit 12; Week 30; 20 weeks after the last dose of IMP) (-3 to +7 days)

All subjects, including those withdrawn from IMP, will have a SFU Visit at 20 weeks after their last dose of IMP.

The SFU Visit should occur no more than 3 days prior to the scheduled visit date and within 7 days after the scheduled visit date (-3 days/+7 days).

The following procedures or assessments will be performed at the SFU Visit:

- Final subject disposition determination
- Physical examination
- Body weight
- Concomitant medications

- Vital signs (BP, pulse rate, and temperature)
- Record 12-lead ECG
- C-SSRS
- TB questionnaire
- PGA of Skin Pain
- HS-Physician's Global Assessment
- DLQI
- EQ5D
- HADS
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Erythema assessment
- Obtain blood sample(s) for:
  - TB test (IGRA; it is recommended that the QuantiFERON TB GOLD test be performed)
  - Serum pregnancy test for women of childbearing potential
  - Standard safety laboratory tests (hematology and biochemistry)
  - Bimekizumab plasma concentration
  - Anti-bimekizumab antibodies
- Obtain urine sample for:
  - Standard safety laboratory tests
- Record AEs

8.11 Early Withdrawal Visit

Subjects who withdraw early from the study for any reason, including those withdrawn from IMP (see Section 6.3), will be asked to return for the study assessments 12 weeks after the first dose (ie, the Week 12 Visit) and will then enter the SFU Period and will undergo the same assessments performed at the SFU Visit (20 weeks after the last dose of IMP) (see Section 8.10).

8.12 Unscheduled Visit

At the Investigator's discretion, an Unscheduled Visit may be completed at any time during the study but prior to the SFU Visit, if deemed necessary for the subject's safety and well-being.

If an Unscheduled Visit is conducted due to safety or efficacy reasons, a C-SSRS assessment will be performed with the subject during the visit. If an Unscheduled Visit is conducted for reasons other than safety or efficacy concerns (eg, replacement of lost medication, repeated collection of

a laboratory specimen due to collection or analysis issues), a C-SSRS will not be required at these visits.

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

- Vital signs
- C-SSRS
- Physical examination
- Lesion count (including Hurley Stage); note that data collected from the lesion count will be used for the derivation of the HiSCR and IHS4
- Record 12-lead ECG
- If medically indicated, obtain blood sample(s) for:
  - Standard safety laboratory tests (hematology, biochemistry)
  - The blood sample may also be used for PK assessments, if needed
- Obtain urine sample for standard safety laboratory tests (including urine pregnancy test)
- Record concomitant medications
- Record AEs

9 ASSESSMENT OF EFFICACY

The timing for all assessments described below is specified in Table 5–1.

9.1 Hidradenitis Suppurativa Clinical Response

The HiSCR was developed to address issues with available HS scoring systems and is a validated variable that is responsive to improvement in disease activity, simplifies the scoring process, and increases the sensitivity to detect HS-specific lesions (Kimball et al, 2014; Kimball et al, 2016b).

The HiSCR is defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining fistula count.

9.2 International Hidradenitis Suppurativa Severity Score System

The IHS4 is a validated tool to dynamically assess HS severity to be used both in real-life and the clinical trials setting (Zouboulis et al, in press). The determination of IHS4 requires counting the nodules, abscesses and draining fistulas/sinus tracts, making it straightforward to apply in both research and clinical practice and easy to use in conjunction with the HiSCR.

9.3 Lesion count

The lesion count is defined as a broad assessment of all the various skin “appearances” that are termed “lesions” in HS subjects. The lesion count must address all relevant anatomical regions in each subject. 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)
- Non-inflammatory fistulas (a fistula is a pathologic passageway connecting to the skin surface from dermis or sc tissue. A non-inflammatory fistula is a non-tender or minimally tender, non-erythematous fistula.)
- Draining fistulas (fistulas that drain serous or purulent fluid, either spontaneously or by gentle palpation)
- Fistulas/sinus tracts (a fistula with sinus tracts is a pathologic passageway that has developed into a channel to the skin surface)
- Non-inflammatory nodules (non-tender or minimally tender, non-erythematous 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.)
- Hypertrophic scars (enlargement or overgrowth of a scar so that it extends above the surrounding skin surface)
- Hurley Stage assessment (see Section 9.9)

The longest distance between 2 relevant lesions (if only one lesion, measure diameter of lesion) and whether the lesions are clearly separated by normal-appearing skin (yes/no) will be measured.

9.4 Patient's Global Assessment of Skin Pain

The PGA of Skin Pain is a unidimensional numeric rating scale (NRS) that allows for rapid (often 1 item) measures of pain that can be administered multiple times with minimal administrative burden. The NRS consists of scores from 0 to 10 (or 0 to 100) with 0 indicating "no skin pain" and 10 (or 100) indicating "worst skin pain imaginable".

The PGA of Skin Pain NRS will be administered verbally. The pain will be described as "pain at its worst during the last 24 hours" and "pain on average in the last 24 hours".

9.5 Modified Sartorius score

The Sartorius scale was created as a more detailed and dynamic HS severity scale and was modified in order to further develop and simplify this assessment for the clinical setting (Sartorius et al, 2003; Sartorius et al, 2009; Sartorius et al, 2010). The modified Sartorius score was the first disease-specific instrument for dynamically measuring clinical severity.

The main parameter in the modified Sartorius score is the counting of individual nodules and fistulas. The modified Sartorius score includes an assessment of the anatomical regions involved, the numbers and scores of lesions for each region, the longest distance between 2 relevant regions (or size of a single lesion), and whether all lesions are separated by normal skin (yes or no).

9.6 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 fistulas (Kimball et al, 2012; Zouboulis et al, 2015b). The HS-Physician's Global Assessment scale is defined by the following:

- Clear: No inflammatory or non-inflammatory nodules
- Minimal: Only the presence of non-inflammatory nodules
- Mild: <5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules
- Moderate: <5 inflammatory nodules or 1 abscess or draining fistula and 1 or more inflammatory nodules or 2 to 5 abscesses or draining fistulas and less than 10 inflammatory nodules
- Severe: 2 to 5 abscesses or draining fistulas and 10 or more inflammatory nodules
- Very severe: >5 abscesses or draining fistulas

9.7 Dermatology Life Quality Index

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

9.8 European Quality-of-Life 5 dimensions questionnaire

The EQ-5D 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). A summary index with a maximum score of 1 can be derived from these 5 dimensions by conversion with a table of scores. The maximum score of 1 indicates the best health state, by contrast with the scores of individual questions, where higher scores indicate more severe or frequent problems. In addition, there is a visual analogue scale to indicate the general health status with 100 indicating the best health status.

9.9 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). Stage I HS is the most common (68% of patients), while Stage II occurs in about 28% of patients and Stage III only occurs in about 4% of patients.

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.

9.10 Erythema assessment

The erythema assessment is a scoring system used to assess the overall degree of erythema in the HS lesions. This assessment uses a 4-point ordinal scale ranging between 0 (no redness) for no erythema and 3 (very red or bright red coloration) for severe erythema. A score of 1 (faint but discernible pink coloration) or 2 (moderate red coloration) indicates a moderate degree of erythema.

9.11 Hospital Anxiety and Depression Scale

The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with other inflammatory skin diseases (Dauden et al, 2009; Langley et al, 2010). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating worse state. A score below 8 is considered to be normal whereas a score of 15 and above is considered severe (Snaith and Zigmond, 1994). A score of 11 to 14 is considered moderate.

10 ASSESSMENT OF PHARMACOKINETICS PHARMACODYNAMIC, NONHEREDITARY PHARMACOGENOMICS, AND PHARMACOGENETICS

10.1 Pharmacokinetic variables

Blood samples for measurement of the PK variables (see Section 4.2.1) will be collected at the time points specified in the schedule of study assessments (Table 5–1).

At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analysis will be provided in a bioanalytical report.

10.2 Pharmacodynamic variables

Blood samples for measurement of PD variables (see Section 4.2.2) will be collected at the time points specified in the schedule of study assessments (Table 5–1). Flow cytometry by fluorescence-activated cell sorting analysis might include, but is not limited to: CD3, CD19, CD4, CD8, and CD69. Candidate biomarkers might include, but are not limited to: IL-17A/IL17-F pathway signaling and HS (eg, IL-17A, IL-17F, IL-23, IL-6, TNF, DC-STAMP, and circulating osteoclast precursors). At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. Detailed information on sample analysis will be provided in a bioanalytical report.

10.3 Nonhereditary pharmacogenomic variables

Where local regulations permit, blood samples will be drawn for exploratory RNA, proteins and metabolites biomarker analysis at the time points specified in the schedule of study assessments (Table 5–1). Where local regulations permit, lesional and nonlesional skin biopsies for exploratory RNA, proteins, and metabolites biomarker analysis will be taken at the time points specified in the schedule of study assessments. Where local regulations permit, urine samples will be drawn for exploratory proteins and metabolites biomarker analysis at the time points specified in the schedule of study assessments. Collection of these samples will enable evaluation of biomarkers relative to disease biology and progression, drug treatment and inflammatory and immune response processes.

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.

10.4 Pharmacogenetic variables

For individuals consenting to the pharmacogenetic substudy, blood samples will be drawn for exploratory genetic/epigenetic analyses at the time points specified in the schedule of study assessments (Table 5–1). 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 subjects 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 subject'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.

11 ASSESSMENT OF SAFETY

11.1 Adverse events

11.1.1 Definitions

11.1.1.1 Adverse Events

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

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

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

11.1.1.2 Serious adverse event

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

- Death
- Life-threatening

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

  (Important medical events may include, but are not limited to, potential Hy's Law [see Section 11.1.1.3], allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

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

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

this would then qualify as an AE and, if necessary, the seriousness of the event would need to be determined.)

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

11.1.1.2.1 Anticipated serious adverse events

The following list of Anticipated SAEs (Table 11–1) has been identified, as these events are anticipated to occur in the population studied in this protocol at some frequency that is independent of drug exposure. This original list will remain in effect for the duration of the protocol. Note that listed events will not be regarded as anticipated SAEs if they are life threatening or if they result in the death of the study subject.

This list does not change the Investigator's obligation to report all SAEs (including Anticipated SAEs) as detailed in Section 11.1.2.3.

Table 11–1: Anticipated serious adverse events for the population of subjects with hidradenitis suppurativa

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

MedDRA=Medical Dictionary for Regulatory Activities; SAE=serious adverse event
Note: Exception: Listed events will not be regarded as anticipated SAEs if they are life threatening or if they result in the death of the study subject.

11.1.1.3 Adverse events of special interest

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

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

must ALWAYS be reported to UCB as an AESI (ie, without waiting for any additional etiologic investigations to have been concluded). Follow-up information should then be reported if an alternative etiology is identified during investigation and monitoring of the subject.

11.1.1.4 Adverse events for special monitoring

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

Adverse events for special monitoring for this study include: serious infections (including opportunistic infections and TB, see Section 11.3.1), cytopenias, hypersensitivities, suicide ideation or behavior (assessed using the C-SSRS), depression and anxiety (assessed using the HADS, see Section 9.11), major cardiovascular events and liver function test changes/enzyme elevations (ALT, AST, and bilirubin; see Section 11.2.1), malignancies, and inflammatory bowel diseases.

11.1.2 Procedures for reporting and recording adverse events

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

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

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

11.1.2.1 Description of adverse events

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

When recording the intensity of an AE in the eCRF (ie, mild, moderate, or severe), the Investigator should use the following criteria:

- Mild: the subject is aware of the sign or symptom (syndrome), but it does not interfere with his/her usual activities and/or is of no clinical consequence
- Moderate: the AE interferes with the usual activities of the subject or it is of some clinical consequence
- Severe: the subject is unable to work normally or to carry out his/her usual activities, or the AE is of definite clinical consequence

Details for completion of the AE eCRF (including judgment of intensity and relationship to IMP) are described in the eCRF Completion Guidelines.

11.1.2.2 Rule for repetition of an adverse event

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

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

11.1.2.3 Additional procedures for reporting serious adverse events

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

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

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

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

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

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

11.1.2.4 Immediate reporting of adverse events

The following AEs must be reported immediately:

- SAE: AE that the Investigator classifies as serious by the definitions in Section 11.1.1.2, regardless of causality
- Suspected transmission of an infectious agent via a medicinal product
- AESIs as defined in Section 11.1.1.3.

- Suspected transmission of an infectious agent via a medicinal product

11.1.3 Follow up of adverse events

An AE should be followed until it has resolved, has a stable sequelae, the Investigator determines that it is no longer clinically significant, or the subject is lost to follow up. This follow-up requirement applies to AEs, SAEs, and AESIs; further details regarding follow up of PDILI events is provided in Section 11.2.1.5.

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

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

11.1.4 Pregnancy

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

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

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

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

In cases where the partner of a male subject enrolled in a clinical study becomes pregnant, the Investigator or designee is asked to contact the subject to request consent of the partner via the Partner Pregnancy Consent form that has been approved by the responsible IRB/IEC and should be available in the Investigator site file. In case of questions about the consent process, the Investigator may contact the UCB/CRO contract monitor for the study. The Investigator will complete the Pregnancy Report and Outcome form and send it to UCB's PS department (for

contact details see SAE reporting information at the beginning of this protocol) only after the partner has agreed that additional information can be captured and has provided the signed Partner Pregnancy Consent form. UCB's PS department is also the primary contact for any questions related to the data collection for the partner pregnancy, eventual birth, and follow up.

A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion (elective or spontaneous), unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used), ectopic pregnancy, fetal demise, or any congenital anomaly/birth defect of the baby. Those SAEs must be additionally reported using the Investigator SAE Report form.

11.1.5 Suspected transmission of an infectious agent via a medicinal product

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

11.1.6 Overdose of investigational medicinal product

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

11.1.7 Safety signal detection

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

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

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

In addition, an independent DMC will periodically review and monitor the safety data from this study and advise UCB. Details will be provided in the DMC Charter.

11.2 Laboratory measurements

Clinical laboratory assessments consist of biochemistry, hematology, and urinalysis. A centralized laboratory will be used to supply all laboratory test supplies and analyze all blood samples for hematology, biochemistry, and urinalysis measurements. Any unscheduled laboratory testing should also be collected using the central laboratory. Testing to rule out HBV, HCV, and HIV (see Exclusion Criteria, Section 6.2) will be performed at the Screening Visit in addition to those measurements listed in Table 11-2.

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

The following laboratory parameters will be measured:

Table 11-2: Laboratory measurements

Hematology	Chemistry	Urinalysis	Serology
Basophils	Bicarbonate	Albumin	HIV
Eosinophils	Calcium	Bacteria	HLA-B27
Lymphocytes	Chloride	Crystals	Hepatitis B
Atypical lymphocytes	Creatinine	Glucose	Hepatitis C
Monocytes	hsCRP	pH	
Neutrophils	Magnesium	RBC	
Hematocrit	Potassium	WBC	
Hemoglobin	Sodium	Urine dipstick for pregnancy testing [a]	
MCH	Glucose	Urine drug screen	
MCHC	BUN		
MCV	ALP		
Platelet count	AST		
RBC count	ALT		
WBC count	GGT		
	Total bilirubin [b]		
	Uric acid		
	LDH		
	Total cholesterol		
	Serum pregnancy testing		
	Serum FSH [c]		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; GGT=gamma glutamyltransferase; hsCRP= high sensitivity C-reactive protein; HLA=human leukocyte antigen; HIV=human immunodeficiency virus; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; RBC=red blood cell; WBC=white blood cell

[a] Pregnancy testing will be done in all women of childbearing potential and will consist of serum testing at Screening and at the Safety Follow-Up Visit and urine testing at all other visits.

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

[c] The serum FSH test (at Screening only) should only be performed on postmenopausal females who have been postmenopausal for ≥1 year and last menstrual cycle occurred <2 years ago.

11.2.1 Evaluation of potential drug-induced liver injury

The PDILI IMP discontinuation criteria for this study are provided in Section 6.3.1, with the accompanying required follow-up investigation and monitoring detailed below. All PDILI events must be reported as an AE and reported to the study site and Sponsor within 24 hours of learning of their occurrence. Any PDILI event that meets the criterion for potential Hy's Law must be reported as an AESI (see Section 11.1.1.3), and, if applicable, also reported as an SAE (see Section 11.1.1.2).

Evaluation of PDILI consists of the diagnostic testing and continued monitoring included in Table 11-3 (specific tests dependent on laboratory results and corresponding symptoms) and consultation with a local hepatologist (if applicable; discussed in Section 11.2.1.1). The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. Additional investigation and monitoring may be required and adapted based on the diagnosis after the cause of the liver injury/abnormality is confirmed (details in Section 11.2.1.5).

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.

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

Table 11-3 summarizes the approach to investigate PDILI.

Table 11-3: Required investigations and follow-up for PDILI

Laboratory value			Immediate		Follow-up	
ALT or AST	**Total bilirubin**	**Symptoms [a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN	≥2xULN[b]	NA	Hepatology consult [c] Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.	Essential: Must have repeat liver chemistry values and additional testing completed ASAP (see Section 11.2.1.4); recommended to occur at the site with HCP.	Monitoring of liver chemistry values at least twice per week until values normalize, stabilize, or return to within Baseline values. [d]
≥3xULN	NA	Yes				
≥5xULN	NA	NA	Need for hepatology consult to be discussed.(required if ALT or AST ≥8xULN) Medical Monitor must be notified within 24 hours (eg, by laboratory alert) and subject discussed with Medical Monitor ASAP.	Immediate, permanent IMP discontinuation.		

Table 11-3: Required investigations and follow-up for PDILI

Laboratory value			Immediate		Follow-up	
ALT or AST	**Total bilirubin**	**Symptoms [a] of hepatitis of hypersensitivity**	**Consultation requirements**	**Actions**	**Testing**	**Evaluation**
≥3xULN (and ≥2x Baseline) and <5xULN (and ≥2x Baseline)	<2xULN	No	Discussion with Medical Monitor required. Consider need for hepatology consult if there is no evidence of resolution (see Follow-up requirements). [c]	Further investigation – immediate IMP discontinuation not required (see Section 11.2.1.2). IMP discontinuation required if any of the following occur: • Subject cannot comply with monitoring schedule. • Liver chemistry values continue to increase during 2 week monitoring period. • Liver chemistry values remain ≥3xULN (and ≥2x Baseline) after 2 weeks of monitoring without evidence of resolution.	Essential: Every attempt must be made to have repeat liver chemistry values and additional testing completed within 48 hours at the site with HCP (see Section 11.2.1.4).	Monitoring of liver chemistry values at least twice per week for 2 weeks. [d] • Immediate IMP discontinuation required if liver chemistry values continue to increase. After 2 weeks of monitoring liver chemistry values: • Discontinue IMP if levels remain ≥3xULN (and ≥2x Baseline) without evidence of resolution. [d] Continue to monitor until values normalize, stabilize, or return to within Baseline values. [d]

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

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

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

[c] Details provided in Section 11.2.1.1. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist.

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

11.2.1.1 Consultation with Medical Monitor and local hepatologist

Potential drug-induced liver injury events require notification of the Medical Monitor within 24 hours (eg, by laboratory alert), and the subject must be discussed with the Medical Monitor as soon as possible. If required, the subject must also be discussed with the local hepatologist. The local hepatologist is the expert usually consulted by the treating physician for assessment and management of potential hepatic disease. This would usually be a hepatologist, but may be a gastroenterologist. If determined necessary, this discussion should be followed by a full hepatology assessment (see Section 11.2.1.4) and SAE report (if applicable).

11.2.1.2 Immediate action: determination of investigational medicinal product discontinuation

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

The immediate action is dependent on the laboratory values and symptoms of hepatitis or hypersensitivity and ranges from continuation of IMP (followed by immediate investigation) to immediate and permanent discontinuation (see Section 6.3.1 and Table 11-3 for details).

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

11.2.1.3 Investigational medicinal product restart/rechallenge

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

11.2.1.4 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 11–4 (laboratory measurements) and Table 11–5 (additional information). Results of the laboratory measurements and information collected are to be submitted to the Sponsor on the corresponding eCRF. If the medical history of the subject indicates a requirement for other assessments not included below, these additional assessments should be completed and submitted, as applicable.

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

The measurements to be assessed are detailed in Table 11–4.

Table 11–4: PDILI laboratory measurements

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

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

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

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

The following additional information is to be collected (Table 11–5).

Table 11–5: PDILI information to be collected

New or updated information
Concomitant prescription and over-the-counter medications (eg, acetaminophen/paracetamol, 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

11.2.1.5 Follow-up evaluation

Potential drug-induced liver injury events require follow-up monitoring as described in Table 11-3. Monitoring should continue until liver chemistry values normalize, stabilize, or return to Baseline. Determination of stabilization is at the discretion of the Investigator in consultation with the hepatologist (as applicable) and UCB responsible physician, as needed.

11.3 Other safety measurements

11.3.1 Assessment and management of tuberculosis and tuberculosis risk factors

All subjects will be assessed for TB prior to administration of IMP and at the time points specified in the Schedule of Assessments (Table 5–1) through physical examination for signs and symptoms of TB, laboratory testing (Section 11.3.1.1), CXR (Section 11.3.1.2), and subject questionnaire (Section 11.3.1.3).

Prior to administration of IMP, subjects will have an IGRA test (QuantiFERON TB GOLD is recommended), a CXR or CAT scan of chest (unless already performed within 3 months of Screening), and examination for signs and symptoms of TB unless an IGRA negative result is

available less than 4 weeks prior to the first dose of IMP. In addition, each subject will complete a TB questionnaire with questions directed at symptoms of TB and potential exposure to TB.

Test Conversion

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

Latent TB

In case the evaluation by the appropriate specialist indicates a new LTB infection during the study, a prophylactic TB treatment should be initiated and the IMP can be continued no sooner than 4 weeks after start of prophylactic TB treatment, if it is deemed likely by the Investigator that prophylactic TB treatment is continued to completion.

If prophylaxis is not initiated, the subject must be withdrawn.

Every related action should be discussed in advance with the Medical Monitor and/or UCB Study Physician.

Once withdrawn from IMP, subjects should return for the Early Withdrawal Visit and complete a SFU Visit (20 weeks after the last dose of IMP).

Active TB or NTMB infection

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

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

11.3.1.1 Tuberculosis assessment by interferon-gamma release assay

During conduct of the study, the TB assessment by IGRA (QuantiFERON TB GOLD is recommended) will be performed at study entry (unless an IGRA negative result is available less than 4 weeks prior to the first dose of IMP). The test results will be reported as positive, negative, or indeterminate. UCB also recommends that a TB specialist be consulted where TB (latent or active) is suspected or if there are doubts regarding test results. If latent or active TB is identified, subject must undergo appropriate study-specified withdrawal procedures.

11.3.1.2 Chest x-ray for tuberculosis

A plain posteroanterior CXR must be performed in the Screening Period unless one has been performed within 3 months prior to the Screening Visit. The CXR (or, if done, CAT of the chest) must be clear of signs of TB infection (previous or current) before first IMP administration. All chest imaging (particularly x-rays) should be available for review by the Investigator before randomization of the subject. The CXR should be repeated only if the TB test was confirmed positive or any further evidence is suggestive of potential lung TB infection (eg, exposure). Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

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

11.3.1.3 Tuberculosis questionnaire

The questionnaire "Evaluation of signs and symptoms of tuberculosis" should be used as a source document. The questionnaire will be completed at study entry and at all visits specified in Table 5–1. The questionnaire will assist with the identification of subjects who may require therapy for TB. A subject who answers "Yes" to the question [redacted] at HS0001 entry is excluded. A "Yes" response to any of the other questions within the questionnaire at HS0001 entry should trigger further careful assessment to determine if subject has LTB or active TB. A "Yes" response to any of the questions during the study should trigger further assessments to determine if the subject has either LTB or active TB infection.

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

11.3.1.4 Tuberculosis management

LTB infection and active TB identified during study

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

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

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

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

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

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

11.3.2 Pregnancy testing

Pregnancy testing will consist of serum testing at the Screening and SFU Visits. The pregnancy test will be urine at all other visits.

The Screening Visit serum pregnancy testing results must be negative and received and reviewed prior to randomization. A negative urine pregnancy test result should be obtained immediately prior to each administration of IMP and at all subsequent post-dosing visits. Pregnancy tests should be administered to all female subjects of childbearing potential, regardless of their use of birth control.

11.3.3 Vital signs

Vital signs will be collected at the visits specified in Table 5–1 and will include systolic and diastolic BP, pulse rate, and body temperature (oral, axillary, or otic). Subjects should be sitting for 5 minutes before and during vital signs assessments.

Vital signs are to be measured prior to blood sampling, and prior to dosing, where applicable.

11.3.4 12-lead electrocardiograms

Twelve-lead standard ECGs will be recorded at the visits specified in Table 5–1.

A standard 12-lead ECG will be recorded after >10 minutes of rest in the supine position and prior to taking blood samples. The following ECG variables will be recorded: heart rate, PR interval, QRS duration, QT interval, QTcF, and the Investigator's interpretation of the ECG profile.

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

11.3.5 Physical examination

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

11.3.6 Body weight

Body weight, including height and BMI, will be collected at the visits specified in Table 5–1. The same scale for measuring body weight should be utilized throughout the study where possible.

11.3.7 Assessment of suicidal ideation and behavior

Suicidal ideation and behavior will be assessed during the study by trained study personnel using the C-SSRS. The visits at which the C-SSRS assessments will be performed are specified in the schedule of study assessments (Table 5–1).

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

11.4 Other study measurements

11.4.1 Demographic and Baseline information

Demographic and Baseline information will be collected in all subjects and will include age, gender, race, and ethnicity along with lifestyle, childbearing potential (as applicable), height, weight, and BMI. Information on demographics will be collected according to local rules and regulations. Demographic and Baseline information will be recorded in the eCRF.

11.4.2 Medical history

A complete medical history will be collected as part of the Screening assessment (and any changes will be collected at Baseline [Visit 2]) and include all clinically relevant past or coexisting medical conditions and surgeries. Findings will be recorded in the eCRF.

11.4.3 Hidradenitis suppurativa history

Detailed information of each subject's HS history will be collected at Screening and will include, but will not be limited to, the following:

- The date of initial onset of HS
- The date, onset, and duration of past treatments for HS
- The date of any prior surgeries for HS

11.5 Data Monitoring Committee

The DMC membership includes experienced clinicians and a statistician, all of whom have expertise in clinical trials. Board members may not participate in the study as principal or co-Investigators, or as study subject care physicians. The duration of membership for the DMC will be inclusive of planned analyses for HS0001. The DMC may also be asked to provide a review of final study results, as deemed appropriate.

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

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

12 ASSESSMENT OF IMMUNOLOGICAL VARIABLES

Blood samples for the measurement of ADA will be collected at the visits specified in the schedule of assessments (Table 5–1).

At dosing visits, blood samples will be drawn prior to dosing, and will be drawn at the same time of the sampling for clinical laboratory tests. The time and date of collection will be recorded in the eCRF.

Instructions pertaining to sample collection, processing, storage, labeling, and shipping are provided in the laboratory manual for this study. The presence of ADA will be determined using a validated bioanalytical method. Detailed information on sample analysis will be provided in a bioanalytical report.

13 ASSESSMENT OF IMAGING VARIABLES

At certain sites, where feasible, representative imaging of the changes in skin will be captured through photography and thermography.

Subjects will have full body (anterior and posterior views, below neck) photographs taken. Photographs will be anonymized. Study sites able to perform photography will be trained and receive standardized photographic equipment.

Thermography, a non-invasive and radiation-free imaging method, has been used in research medicine to detect temperature changes in tissue abnormalities beneath the skin or on the skin's surface in specific areas (Langemo and Spahn, 2017; Sagaidachnyi et al, 2017; Sun et al, 2017). At the same sites, Scout (WoundVision LLC, Indianapolis, Indiana), an FDA-approved visual and thermal imaging device and software analysis tool, will be used for the procedure. This device can provide clinicians with a reliable and reproducible way to incorporate long-wave infrared thermography and relative temperature differential into clinical lesions assessment by consistently identifying control areas against which to measure lesion temperature.

14 STUDY MANAGEMENT AND ADMINISTRATION

14.1 Adherence to protocol

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

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

14.2 Monitoring

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

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

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

14.2.1 Definition of source data

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

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

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

14.2.2 Source data verification

Source data verification ensures accuracy and credibility of the data obtained. During monitoring visits, reported data are reviewed with regard to being accurate, complete, and verifiable from source documents (eg, subject files, recordings from automated instruments, tracings [ECG], x-ray films, laboratory notes). All data reported on the eCRF should be supported by source documents, unless otherwise specified in Section 14.2.1.

14.3 Data handling

14.3.1 Case Report Form completion

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

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

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

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

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

14.3.2 Database entry and reconciliation

Case Report Forms/external electronic data will be entered/loaded into a validated electronic database using a clinical data management system (CDMS). Computerized data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data. The data will be entered into the electronic eCRFs once and will be subsequently verified.

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

14.3.3 Subject Screening and Enrollment log/Subject Identification Code list

The subject's screening and enrollment will be recorded in the Subject Screening and Enrollment Log.

The Investigator will keep a Subject Identification Code list. This list remains with the Investigator and is used for unambiguous identification of each subject.

The subject's consent and enrollment in the study must be recorded in the subject's medical record. These data should identify the study and document the dates of the subject's participation.

14.4 Termination of the study

UCB reserves the right to temporarily suspend or prematurely discontinue this study either at a single site, multiple sites, or at all sites at any time for reasons including, but not limited to, safety or ethical issues, inaccurate or incomplete data recording, noncompliance, or unsatisfactory enrollment with respect to quality or quantity.

If the study is prematurely terminated or suspended, UCB (or its representative) will inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The IRB/IEC should also be informed and provided with reason(s) for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the return of all unused IMP and other material in accordance with UCB procedures for the study.

14.5 Archiving and data retention

The Investigator will maintain adequate records for the study, including eCRFs, medical records, laboratory results, Informed Consent documents, drug dispensing and disposition records, safety reports, information regarding participants who discontinued, and other pertinent data.

All essential documents are to be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or by an agreement with UCB (CPMP/ICH/135/95, 2002 [Section 4.9.5]). The Investigator will contact UCB for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify UCB should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's Trial Master File.

14.6 Audit and inspection

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

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

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

14.7 Good Clinical Practice

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

15 STATISTICS

A description of statistical methods follows and further detail will be included in the statistical analysis plan (SAP). Deviations from the original SAP will be documented in the clinical study report (CSR).

15.1 Definition of analysis sets

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

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

The Safety Set (SS) will consist of all subjects who receive at least 1 dose of the IMP.

The Full Analysis Set (FAS) will consist of all randomized subjects who receive at least 1 dose of the IMP and have a valid measurement of the primary efficacy variable at Baseline and at least one post baseline efficacy assessment.

The Per-Protocol Set (PPS) will consist of all subjects in the FAS who have no important protocol deviation affecting the primary efficacy variable. The subjects with important protocol deviations will be predefined and evaluated during a data evaluation meeting prior to unblinding of the data.

The Pharmacokinetics Per-Protocol Set (PK-PPS) will consist of all randomized subjects who received at least 1 dose of the IMP and have at least 1 quantifiable post-dose plasma concentration.

15.2 General statistical considerations

Statistical evaluation will be performed by PAREXEL and supervised by the Exploratory Statistics and Global Statistical Sciences Departments of UCB.

All analyses will be performed using SAS® version 9.2 or later (SAS Institute, Cary, NC, US), R Version 2.10.1 (R Development Core Team) or later, or OpenBUGS Version 3.0.6 or later.

Descriptive statistics will be used to provide an overview of the Baseline, efficacy, and safety results. For categorical parameters, the number and percentage of subjects in each category will be presented by treatment group. The denominator for the percentages will be based on the number of subjects 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 (Visit 2) or the last available value obtained prior to treatment administration at Screening (Visit 1) (details to be specified in the SAP).

Formal statistical testing will be conducted for this study for the primary efficacy variable. Exploratory efficacy variables will be summarized descriptively by treatment arm. Additionally, exploratory 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.

15.3 Subject disposition

The number of subjects who were screened, subjects included in each analysis set, and subjects who completed/prematurely discontinued the study, as well as the primary reason for discontinuation, will be presented by treatment group and overall using frequency counts and percentages.

15.4 Subject characteristics

The following subject characteristics will summarized and listed, as appropriate:

- Demographics (including gender, age, race, and ethnicity)

- Baseline characteristics (including lifestyle, childbearing potential, height, weight, and BMI)
- Medical/procedure history
- Prior and concomitant medications/medical procedures
- Baseline disease characteristics

15.5 Planned efficacy analyses

The primary efficacy analyses will be based on the PPS.

15.5.1 Analysis of the primary efficacy variable

The primary efficacy analysis will be the comparison between bimekizumab and placebo in the proportion of subjects achieving HiSCR at Week 12, although the model used will analyze data from all three treatment groups. The number and percentage of subjects who achieved HiSCR at Week 12 will be presented by treatment group and the statistical analysis of this variable will be conducted following a Bayesian paradigm utilizing an informative prior on both the placebo and adalimumab group response rates where these informative priors were derived from published summary data (Clinical Study Protocol M11-810 - PIONEER II). A vague prior will be assumed for the bimekizumab treatment group.

The Bayesian analysis of HiSCR at Week 12 will employ a logistic regression model including treatment group (placebo, adalimumab, and bimekizumab) and adjusting for Baseline Hurley Stage.

The posterior distributions of the treatment group response rates together with 95% credible intervals for all three treatment group response rates, and of the difference in response rates between the treatment groups will be summarized. A 95% credible interval will be presented for the bimekizumab versus placebo comparison and a 60% credible interval will be presented for the bimekizumab versus adalimumab comparison. This latter comparison of bimekizumab with adalimumab is an informal one to assess whether any improvements in response rate observed with bimekizumab (over placebo) are comparable to the current standard of care and will be used for internal decision making on the future development of the compound. This comparison will not be part of the evaluation of Proof of Concept for this study. The posterior probability that the difference in response rates between the placebo and bimekizumab treatment groups is greater than zero will also be presented.

The study will be considered a success if the posterior probability that the difference in response rates between the placebo and bimekizumab groups being greater than zero is at least 97.5% (ie, the lower bound of the 95% credible interval of the difference between bimekizumab and placebo in HiSCR rates is greater than or equal to zero).

If further information (independent to this study) regarding the placebo and/or adalimumab treatment group response rates comes to light subsequent to writing this protocol then this study may be updated prior to study unblinding, and details of this will be supplied in the SAP and the CSR. Note that the informative priors for the placebo and adalimumab treatment group response rates may be updated based upon any observed differences in the proportions of Baseline Hurley Stage II and III subjects as long as no response rate data from the current study, blinded or un-blinded, have been taken into consideration. For example, if updated, these priors may be fitted by Baseline Hurley Stage if the relative proportions of Baseline Hurley Stage II and III subjects

within the current study differ substantially from those reported in the historical data. In this case the priors will still be based only on historic response data, but using the Hurley-stage specific information rather than the average information.

15.5.2 Supportive analysis of the primary efficacy variable

A sensitivity analysis of the choice of the prior distribution for the placebo treatment group will be conducted by repeating the primary efficacy analysis assuming vague priors for all parameters of the model. The priors will be fully documented in the SAP and in the interim analysis SAP.

Additional sensitivity analyses will assess the primary efficacy variable for the FAS.

Further analyses of the primary efficacy variable may be performed adjusting for other Baseline covariates (to be defined in the SAP). Results from any additional analyses will not be used as a substitute for the planned analyses, but may be used as supplemental information for the CSR.

15.5.3 Analysis of the exploratory efficacy variables

The exploratory efficacy variables are listed in Section 4.1.2.

Actual values and changes (including percentage changes, where applicable) from Baseline in the continuous exploratory efficacy variables will be listed and summary statistics will be presented by treatment group and time point. Changes from Baseline in the categorical exploratory variables will summarized in shift tables presented by treatment group and time point. Any formal statistical analyses of the exploratory efficacy variables will be described in more detail in the SAP.

15.6 Planned pharmacokinetic analyses

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

Bimekizumab trough plasma concentrations will be summarized by treatment group at each time point using descriptive statistics.

15.7 Planned immunological analyses

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

Anti-bimekizumab antibody data will be summarized for each treatment group at each scheduled visit, and the rate of ADA positive subjects for each treatment group will be calculated.

15.8 Planned safety analyses

All safety variables will be analyzed for all subjects in the SS.

Adverse events will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA®). The incidence of treatment-emergent adverse events (TEAEs) will be summarized descriptively by MedDRA system organ class, preferred term, and treatment group. Additional tables will summarize TEAEs by intensity and relationship to IMP, TEAEs leading to withdrawal from the study, serious TEAEs, and deaths. All AE information will be listed.

Laboratory values, ECGs, vital signs, physical examination, and extent of exposure will be presented descriptively by treatment group. The C-SSRS data will be listed only.

15.9 Handling of protocol deviations

After all data have been verified/coded/entered into a database, a data review will be performed. The purpose of this review will be to check all protocol deviations, define the PPS, and check the quality of the data. The review will also help decide how to manage problems in the subjects' data (eg, missing values, withdrawals, dropouts, and protocol deviations).

Accepted deviations from theoretical time points will be described in the appropriate documents and included in the Trial Master File. After the pre-analysis review, resolution of all issues, and documentation of all decisions, the database will be locked.

15.10 Handling of dropouts or missing data

For the analysis of the primary efficacy variable, non-responder imputation will be used to impute missing data for subjects who have missing data at a specific visit and for subjects who discontinue early from the study during the Treatment Period for any reason. These subjects will be defined as non-responders at all subsequent visits after the time of study discontinuation. In additional sensitivity analyses, subjects who receive specific rescue therapy may also be considered a non-responder from the time that the rescue therapy was taken to the end of the Treatment Period.

Further details on all methods to be used for missing data imputation in the analysis of the efficacy variables will be included in the SAP.

15.11 Planned interim analysis and data monitoring

This study will include two unblinded interim analyses, the first after approximately 45 subjects have completed 4 weeks of the study and the second when the last randomized subject for this study has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely. The purpose of these interim analyses is for sponsor key personnel to review results from the primary efficacy analysis and a subset of the analyses of exploratory efficacy and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions; consequently, neither analysis and will lead to any formal decision to alter or terminate the trial. Interim analyses will be conducted by an unblinded study team and will follow internal SOPs for the formal process to control the unblinding of the study for interim analysis purposes. This process will ensure that no unnecessary or unintentional unblinding occurs. The unblinded team will not disclose any unblinded information to the blinded study team and the storage of all unblinded documentation will be held securely and separately from the rest of the study documentation and outputs up until the end of the study. All analyses and unblinding instructions will be prespecified in the interim SAP and SAP.

The conduct of the study and monitoring of the safety data will be supervised by an independent DMC to optimize subjects' safety and to identify any safety signals. Full details of the DMC composition and roles will be described in a separate DMC Charter.

15.12 Determination of sample size

The predefined success criterion for declaring a positive study requires a posterior probability of at least 97.5% that the HiSCR rate at Week 12 for bimekizumab will be higher than that for placebo.

Additionally, the study has an exploratory objective to informally compare bimekizumab against the current standard of care for HS (adalimumab) using the 60% credible interval for the treatment difference.

Sample size calculations are based on the number of subjects required to meet the above success criterion assuming a true underlying HiSCR rate at Week 12 of 70% for bimekizumab. Published data from the PIONEER I and II studies (Kimball et al, 2016a) indicate that, when antibiotic therapy is allowed, the response rates for placebo and adalimumab at Week 12 are 27.6% and 58.9% respectively.

Using simulation, it was estimated that with data from 40 subjects on bimekizumab, 20 subjects on placebo and 20 subjects on adalimumab (80 subjects total), the study will provide at least an 85% probability of meeting the success criterion and an 80% probability of meeting the exploratory criterion under the assumptions described below.

These simulations were based upon Bayesian augmented control models in which the published summary data were used to construct informative priors for the placebo and adalimumab treatment arms in the current study. Based on historic data, the Bayesian model assumes an informative prior distribution for the placebo group HiSCR rate to be β (5.52,14.48). This prior distribution contributes an approximate effective sample size of 20 subjects for the placebo treatment group. Similarly, the Bayesian model assumes an informative prior distribution for the adalimumab group HiSCR rate to be β (11.78,8.22), which, with the parameterization in the model, is equivalent to an adalimumab response rate of 58.9%. This prior distribution contributes an approximate effective sample size of 20 subjects for the adalimumab group. For the bimekizumab HiSCR rate, a vague prior probability distribution N (0,1E4) was assumed.

16 ETHICS AND REGULATORY REQUIREMENTS

16.1 Informed consent

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

A separate ICF will be required for subjects participating in the pharmacogenetic substudy.

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

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

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

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

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

16.2 Subject identification cards

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

16.3 Institutional Review Boards and Independent Ethics Committees

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

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

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

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

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

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

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

Investigators are to provide the Sponsor (or its representative) with evidence of such IRB/IEC notification.

16.4 Subject privacy

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

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

16.5 Protocol amendments

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

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

17 FINANCE, INSURANCE, AND PUBLICATION

Insurance coverage will be handled according to local requirements.

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

18 REFERENCES

Adalimumab (Humira) European Public Assessment Report.

Alikhan A, Lynch PJ, Eisen DB. Hidradenitis suppurativa: a comprehensive review. J Am Acad Dermatol. 2009;60(4):539-61.

Baroja-Mazo A, Martin-Sánchez F, Gomez AI, Martinez CM, Amores-Iniesta J, Compan V, et al. The NLRP3 inflammasome is released as a particulate danger signal that amplifies the inflammatory response. Nat Immunol. 2014;15(8):738-48.

Basra MK, Chowdhury MM, Smith EV, Freemantle N, Piquet V. A review of the use of the dermatology life quality index as a criterion in clinical guidelines and health technology assessments in psoriasis and chronic hand eczema. Dermatol Clin. 2012;30(2):237-44.

Cho KA, Suh JW, Lee KH, Kang JL, Woo SY. IL-17 and IL-22 enhance skin inflammation by stimulating the secretion of IL-1β by keratinocytes via the ROS-NLRP3-caspase-1 pathway. Int Immunol. 2012;24(3):147-58.

Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. Int J Dermatol. 1983;22(5):325-8.

CPMP/ICH/135/95 Note for guidance on Good Clinical Practice (EMEA) Jul 2002.

Danby FW, Margesson LJ. Hidradenitis suppurativa. Dermatol Clin. 2010;28(4):779-93.

Dauden E, Griffiths CE, Ortonne JP, Kragballe K, Molta CT, Robertson D, et al. Improvements in patient-reported outcomes in moderate-to-severe psoriasis patients receiving continuous or paused etanercept treatment over 54 weeks: the CRYSTEL study. J Eur Acad Dermatol Venereol. 2009;23(12):1374-82.

Ehrchen JM, Sunderkötter C, Foell D, Vogl T, Roth J. The endogenous Toll-like receptor 4 agonist S100A8/S100A9 (calprotectin) as innate amplifier of infection, autoimmunity, and cancer. J Leukoc Biol. 2009;86(3):557-66.

Esmann S, Dufour DN, Jemec GB. Questionnaire-based diagnosis of hidradenitis suppurativa: specificity, sensitivity and positive predictive value of specific diagnostic questions. Br J Dermatol. 2010;163(1):102-6.

Fimmel S, Zouboulis CC. Comorbidities of hidradenitis suppurativa (acne inversa). Dermatoendocrinol. 2010;2(1):9-16.

Finlay AY. Quality of life assessments in dermatology. Semin Cutan Med Surg. 1998;17(4):291-6.

Hotz C, Boniotto M, Guguin A, Surenaud M, Jean-Louis F, Tisserand P, et al. Intrinsic Defect in Keratinocyte Function Leads to Inflammation in Hidradenitis Suppurativa. 2016;136(9):1768-80.

Hurley H. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial benign pemphigus: surgical approach. In: Dermatologic surgery. Roenigh R, Roenigh H, editors. Marcel Dekker. 1989:729-39.

Jemec GB. Treatment of Skin Disease, 3rd ed. Lebwohl MG et al, editors. Saunders. 2010: Chapter 97.

Kimball AB, Kerdel F, Adams D, Mrowietz U, Gelfand JM, Gniadecki R. Adalimumab for the treatment of moderate to severe Hidradenitis suppurativa: a parallel randomized trial. Ann Intern Med. 2012;157(12):846-55.

Kimball AB, Jemec GB, Yang M, Kageliery A, Signorovitch JE, Okun MM, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol. 2014;171(6):1434-42.

Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, et al. Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa. N Engl J Med. 2016a;375(5):422-34.

Kimball AB, Sobell JM, Zouboulis CC, Gu Y, Williams DA, Sundaram M, et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. J Eur Acad Dermatol Venereol. 2016b;30(6):989-94.

Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, Hsu MC, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in

patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. J Am Acad Dermatol. 2010;63(3):457-65.

Langemo DK, Spahn JG. A reliability study using a long-wave infrared thermography device to identify relative tissue temperature variations of the body surface and underlying tissue. Adv Skin Wound Care. 2017;30(3):109-19.

McMillan, K. Hidradenitis suppuratica: number of diagnosed patients, demographic characteristics, and treatment patterns in the United States. Am J Epidemiol. 2014;179(12):1477-83.

Mundt JC, Greist JH, Gelenberg AJ, Katzelnick DJ, Jefferson JW, Modell JG. Feasibility and Validation of a Computer-Automated Columbia-Suicide severity Rating Scale Using Interactive Voice Response Technology. J Psychiatr Res. 2010;44(16):1224-8.

Naldi L. Epidemiology. In: Hidradenitis Suppurativa. Chapter 8. Jemec GB, Revuz J, Leyden J, editors. Springer-Verlag. 2006:58-64.

Nikolakis G, Join-Lambert O, Karagiannidis, Guet-Revillet H, Zouboulis CC, Nassif A. Bacteriology of hidradenitis suppurativa/acne inversa: A review. J Am Acad Dermatol. 2015;73(5 Suppl 1):D12-8.

Nikolakis G, Liakou AI, Bonovas S, Seltman H, Bonitsis N, Join-Lambert O, et al. Bacterial colonization in Hidradenitis Suppurativa/Acne Inversa: A Cross-sectional Study of 50 patients and Review of Literature. Acta Derm Venereol. 2016;Nov 24:doi 10.2340/00015555-2591. [Epub ahead of print].

Posner K, Brown GK, Stanley B, Brent DA, Yershova KV, Oquendo MA, et al. The Columbia-Suicide Severity Rating Scale: Initial Validity and Internal Consistency Findings From Three Multisite Studies With Adolescents and Adults. Am J Psychiatry. 2011;168(12):1266-77.

Revuz JE, Canoui-Poitrine F, Wolkenstein P, Vialette C, Gabison G, Pouget F, et al. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol. 2008;59(4):596-601.

Riis PT, Vinding GR, Ring HC, Jemec GB. Disutility in patients with hidradenitis suppurativa: a cross-sectional study using EuroQoL-5D. Acta Derm Venereol. 2016;96(2):222-6.

Sagaidachnyi AA, Fomin AV, Usanov DA, Skripal AV. Thermography-based blood flow imaging in human skin of the hands and feet: a spectral filtering approach. Physiol Meas. 2017;38(2):272-88.

Sartorius K, Lapins J, Emtestam L, Jemec GB. Suggestions for uniform outcome variables when reporting treatment effects in hidradenitis suppurativa. Br J Dermatol. 2003;149(1):211-3.

Sartorius K, Emtestam L, Jemec GB, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. Br J Dermatol. 2009;161(4):831-9.

Sartorius K, Killasli H, Heilborn J, Jemec GB, Lapins J, Emtestam L. Interobserver variability of clinical scores in hidradenitis suppurativa is low. Br J Dermatol. 2010;162(6):1261-8.

Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/TH17 pathway in lesions of hidradenitis supprativa. J Am Acad Dermatol. 2011;65(4):790-8.

Snaith RP, Zigmond AS. The hospital anxiety and depression scale, with the irritability-depression-anxiety scale and the Leeds situational anxiety scale manual. 1994.

Sun G, Nakayama Y, Dagdanpurev S, Abe S, Nishimura H, Kirimoto T, et al. Remote sensing of multiple vital signs using a CMOS camera-equipped infrared thermography system and its clinical application in rapidly screening patients with suspected infectious diseases. Int J Infect Dis. 2017;55:113-7.

Tzellos T, Zouboulis CC, Gulliver W, Cohen AD, Wolkenstein P, Jemec GB. Cardiocascular disease risk factors in patients with hidradenitis suppurativa: a systemic review and meta-analysis of observational studies. Br J Dermatol. 2015;173(5):1142-55.

van der Zee HH, van der Woude CJ, Florencia EF, Prens EP. Hidradenitis suppurativa and inflammatory bowel disease: are they associated? Results of a pilot study. Br J Dermatol. 2010;162:195-7.

van der Zee HH, de Ruiter L, Boer J, van den Broecke DG, den Hollander JC, Laman JD, et al. Alterations in leucocyte subsets and histomorphology in normal-appearing perilesional skin and early and chronic hidradenitis suppurativa lesions. Br J Dermatol. 2012;166(1):98–106.

von der Werth JM, Jemec GB. Morbidity in patients with hidradenitis suppurativa. Br J Dermatol. 2001;144:809-13.

Wolkenstein P, Loundou A, Barrau K, Auquier P, Revuz J; Quality of Life Group of the French Society of Dermatology. Quality of life impairment in hidradenitis suppurativa: a study of 61 cases. J Am Acad Dermatol. 2007;56:621–623.

Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GB. Hidradenitis suppurativa/acne inversa: criteria for diagnosis, severity assessment, classification and disease evaluation. Dermatology. 2015a;231(2):184-90.

Zouboulis CC, Desai N, Emtestam L, Hunger RE, Loannides D, Juhász I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol. 2015b;29(4):619-44.

Zouboulis CC, Kyrgidis A, Jemec GBE, Bechara FG, Giamarellos-Bourboulis EJ, Ingram JR, et al. Development and validation of IHS4, a novel dynamic scoring system to assess hidradenitis suppurativa/acne inversa severity. *Submitted to the British Journal of Dermatology*.

19 APPENDICES

19.1 Protocol Amendment 1

Rationale for the amendment

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

The statistical analysis section of the protocol was also updated to include text describing the planned analysis of the primary efficacy variable, and text describing the planned interim analyses and sample size re-estimation was revised. The rationale for this is that the observed pattern of subject recruitment is not as expected at the time of study planning. Consequently, an insufficient number of subjects will have completed the Week 12 visit and be evaluable for response at the time of the first interim analysis. The risk of performing an analysis with a very small amount of data is that the estimates obtained from the analysis will be unstable and the risk of committing a Type II error will be inflated. To mitigate these risks it was decided to remove the formal futility and sample size re-estimation aspects from the first interim analysis.

Minor formatting corrections were also made.

Modifications and changes

Specific changes

Change #1

Sponsor Study Physician

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

Was changed to:

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

Change #2

List of Abbreviations

Inflammatory Bowel Disease (IBD) was added to the list

Change #3

Section 5.1.1 Study periods

The following paragraph was deleted:

A formal, unblinded interim analysis will be conducted when approximately 45 subjects have completed 4 weeks of the study. During this interim analysis, the sample size assumptions will be checked and the final sample size may be modified or the study may be stopped for futility. An informal, unblinded interim analysis will be performed when the last randomized subject for this study has completed the Week 12 Visit or the subject's participation has ended prematurely

Change #4

Section 6.3 Withdrawal criteria

The following was added to the withdrawal criteria:

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

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

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

Change #5

Section 6.4 Study stopping rules

Reasons for suspension or discontinuation of the study can fall into 1 of the following 3 principal categories: safety, futility, and other reasons.

Was changed to:

Reasons for suspension or discontinuation of the study can fall into 1 of the following **2** principal categories: safety and other reasons.

Change #6

Section 6.4.2 Futility

The following section was deleted:

6.4.2 Futility

A formal, unblinded interim analysis will be conducted when approximately 45 subjects have completed 4 weeks of the study, and the study may be stopped for futility (see Section 15.11).

Change #7

Section 15.5.1 Analysis of the primary efficacy variable

The primary efficacy analysis will be the comparison between bimekizumab and placebo in the proportion of subjects achieving HiSCR at Week 12.

The number and percentage of subjects who achieved HiSCR at Week 12 will be presented by treatment group and the statistical analysis of this variable will be conducted following a Bayesian paradigm utilizing an informative prior on the placebo group response rate where the informative prior was derived from published summary data (Clinical Study Protocol M11 810 PIONEER II). A vague prior is assumed for the bimekizumab treatment arm.

The Bayesian analysis of HiSCR at Week 12 will employ a logistic regression model including treatment group and adjusting for Baseline Hurley Stage.

The posterior distributions of the placebo and bimekizumab group response rates, and of the difference in response rates between the treatment groups will be summarized including 95% credible intervals. The posterior probability that the difference in response rates between the placebo and bimekizumab groups is greater than zero (ie, bimekizumab demonstrates a greater response compared with placebo) will also be presented.

The study will be considered a success if this posterior probability is at least 97.5% (ie, the lower bound of the 95% credible interval of the difference between treatment groups (bimekizumab placebo) in HiSCR rates is greater than zero).

If further information (independent to this study) regarding the placebo group response comes to light subsequent to writing this protocol then this study may be updated prior to study unblinding, and details of this will be supplied in the SAP and the CSR. Note that the prior for the placebo response rate may be updated based upon any observed differences in the response rate between Hurley Stages. If updated, priors will be fitted by Hurley Stage taking into account the relative proportions of Hurley Stage II and III subjects within the current study. In this case the priors will still be based upon the historic data.

Was changed to:

The primary efficacy analysis will be the comparison between bimekizumab and placebo in the proportion of subjects achieving HiSCR at Week 12, **although the model used will analyze data from all three treatment groups**. The number and percentage of subjects who achieved HiSCR at Week 12 will be presented by treatment group and the statistical analysis of this variable will be conducted following a Bayesian paradigm utilizing an informative prior on **both** the placebo **and adalimumab** group response rate**s** where the**se** informative prior**s** w**ere** derived from published summary data (Clinical Study Protocol M11 810 PIONEER II). A vague prior **will be** assumed for the bimekizumab treatment **group**.

The Bayesian analysis of HiSCR at Week 12 will employ a logistic regression model including treatment group **(placebo, adalimumab, and bimekizumab)** and adjusting for Baseline Hurley Stage.

The posterior distributions of the treatment group response rates together with 95% credible intervals for all three treatment group response rates, and of the difference in response rates between the treatment groups will be summarized. A 95% credible interval will be presented for the bimekizumab versus placebo comparison and a 60% credible

interval will be presented for the bimekizumab versus adalimumab comparison. This latter comparison of bimekizumab with adalimumab is an informal one to assess whether any improvements in response rate observed with bimekizumab (over placebo) are comparable to the current standard of care and will be used for internal decision making on the future development of the compound. This comparison will not be part of the evaluation of Proof of Concept for this study. The posterior probability that the difference in response rates between the placebo and bimekizumab treatment groups is greater than zero will also be presented.

The study will be considered a success if the posterior probability that the difference in response rates between the placebo and bimekizumab groups being greater than zero is at least 97.5% (ie, the lower bound of the 95% credible interval of the difference between bimekizumab and placebo in HiSCR rates is greater than or equal to zero).

If further information (independent to this study) regarding the placebo and/or adalimumab treatment group response rates comes to light subsequent to writing this protocol then this study may be updated prior to study unblinding, and details of this will be supplied in the SAP and the CSR. Note that the informative priors for the placebo and adalimumab treatment group response rates may be updated based upon any observed differences in the proportions of Baseline Hurley Stage II and III subjects as long as no response rate data from the current study, blinded or un-blinded, have been taken into consideration. For example, if updated, these priors may be fitted by Baseline Hurley Stage if the relative proportions of Baseline Hurley Stage II and III subjects within the current study differ substantially from those reported in the historical data. In this case the priors will still be based only on historic response data, but using the Hurley-stage specific information rather than the average information.

Change #8

Section 15.5.2 Supportive analysis of the primary efficacy variable

The following paragraph was deleted:

In addition to the primary comparison of the bimekizumab and placebo treatment groups, an additional comparison between bimekizumab and adalimumab in HiSCR at Week 12 will be performed using the methods as described above in Section 15.5.1 for the primary efficacy analysis. This will be an informal comparison to assess whether any improvements in response rate observed with bimekizumab (over placebo) are comparable to the current standard of care (adalimumab) and will be used for internal decision making on the future development of the compound.

Change #9

Section 15.11 Planned interim analysis and data monitoring

A formal unblinded non-binding interim analysis will be conducted when approximately 45 subjects have completed 4 weeks of the study. During this interim analysis, the sample size assumptions will be checked and the final sample size may be modified if the sample size assumptions at study planning are no longer accurate. Also, at this interim analysis, the study may be stopped for futility. Sample size re-estimation criteria and methods along with futility

rules and operating characteristics will be detailed in the interim SAP. The futility rule will be chosen such that the overall power of the study remains high.

An informal, unblinded interim analysis will be performed when the last randomized subject for this study has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely. The purpose of this informal interim analysis is for the Sponsor key personnel to review the results of the primary efficacy analysis and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions.

All analyses and unblinding instructions will be prespecified in the interim SAP and SAP.

Was changed to:

This study will include two unblinded interim analyses, the first after approximately 45 subjects have completed 4 weeks of the study and the second when the last randomized subject for this study has completed the Week 12 Visit at the end of the Treatment Period or this subject's participation has ended prematurely. The purpose of these interim analyses is for sponsor key personnel to review results from the primary efficacy analysis and a subset of the analyses of exploratory efficacy and safety outcomes to facilitate additional Clinical Planning or Portfolio Management decisions; consequently, neither analysis and will lead to any formal decision to alter or terminate the trial. Interim analyses will be conducted by an unblinded study team and will follow internal SOPs for the formal process to control the unblinding of the study for interim analysis purposes. This process will ensure that no unnecessary or unintentional unblinding occurs. The unblinded team will not disclose any unblinded information to the blinded study team and the storage of all unblinded documentation will be held securely and separately from the rest of the study documentation and outputs up until the end of the study. All analyses and unblinding instructions will be prespecified in the interim SAP and SAP.

Change #10

Section 15.12 Determination of sample size

The predefined success criterion for declaring a positive study requires a posterior probability of at least 97.5% that the HiSCR rate at Week 12 for bimekizumab will be higher than that for placebo.

Additionally, the study has an exploratory objective to informally compare bimekizumab against the current standard of care for HS (adalimumab) using the 60% posterior distribution of the treatment difference.

Sample size calculations are based on the number of subjects required to meet the above success criterion assuming a true underlying HiSCR rate at Week 12 of 64% for bimekizumab. Published data from the PIONEER I and II studies (Kimball et al, 2016a) indicate that, when antibiotic therapy is allowed, the response rates for placebo and adalimumab at Week 12 are 27.6% and 58.9% respectively.

Using simulation, it was estimated that with data from 40 subjects on bimekizumab, 20 subjects on placebo and 20 subjects on adalimumab (80 subjects total), the study will provide at least an 85% probability of meeting the success criterion and an 80% probability of meeting the exploratory criterion under the assumptions described below.

These simulations were based upon Bayesian augmented control models in which the published summary data were used to construct informative priors for the placebo and adalimumab treatment arms in the current study. Based on historic data, the Bayesian model assumes an informative prior distribution for the placebo group HiSCR rate to be β (5.52,14.48). This prior distribution contributes an approximate effective sample size of 20 subjects for the placebo treatment group. Similarly, the Bayesian model assumes an informative prior distribution for the adalimumab group HiSCR rate to be β (15.83,4.17), which, with the parameterization in the model, is equivalent to an adalimumab response rate of 58.9%. This prior distribution contributes an approximate effective sample size of 20 subjects for the adalimumab group. For the bimekizumab HiSCR rate, a vague prior probability distribution N (0,1E4) was assumed.

Was changed to:

The predefined success criterion for declaring a positive study requires a posterior probability of at least 97.5% that the HiSCR rate at Week 12 for bimekizumab will be higher than that for placebo.

Additionally, the study has an exploratory objective to informally compare bimekizumab against the current standard of care for HS (adalimumab) using the 60% **credible interval** for the treatment difference.

Sample size calculations are based on the number of subjects required to meet the above success criterion assuming a true underlying HiSCR rate at Week 12 of **70**% for bimekizumab. Published data from the PIONEER I and II studies (Kimball et al, 2016a) indicate that, when antibiotic therapy is allowed, the response rates for placebo and adalimumab at Week 12 are 27.6% and 58.9% respectively.

Using simulation, it was estimated that with data from 40 subjects on bimekizumab, 20 subjects on placebo and 20 subjects on adalimumab (80 subjects total), the study will provide at least an 85% probability of meeting the success criterion and an 80% probability of meeting the exploratory criterion under the assumptions described below.

These simulations were based upon Bayesian augmented control models in which the published summary data were used to construct informative priors for the placebo and adalimumab treatment arms in the current study. Based on historic data, the Bayesian model assumes an informative prior distribution for the placebo group HiSCR rate to be β (5.52,14.48). This prior distribution contributes an approximate effective sample size of 20 subjects for the placebo treatment group. Similarly, the Bayesian model assumes an informative prior distribution for the adalimumab group HiSCR rate to be β (**11.78,8.22**), which, with the parameterization in the model, is equivalent to an adalimumab response rate of 58.9%. This prior distribution contributes an approximate effective sample size of 20 subjects for the adalimumab group. For the bimekizumab HiSCR rate, a vague prior probability distribution N (0,1E4) was assumed.

20 DECLARATION AND SIGNATURE OF INVESTIGATOR

I confirm that I have carefully read and understood this protocol and agree to conduct this clinical study as outlined in this protocol, according to current Good Clinical Practice and local laws and requirements.

I will ensure that all subinvestigators and other staff members read and understand all aspects of this protocol.

I have received and read all study-related information provided to me.

The objectives and content of this protocol as well as the results deriving from it will be treated confidentially, and will not be made available to third parties without prior authorization by UCB.

All rights of publication of the results reside with UCB, unless other agreements were made in a separate contract.

Investigator:

Printed name	Date/Signature

21 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.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Approval Date (dd-mon-yyyy (HH:mm))
[redacted]	Clinical Approval	09-Mar-2018 11:57 GMT+01
[redacted]	CMC Technical Lead Approval	09-Mar-2018 14:27 GMT+01
[redacted]	Clinical Approval	09-Mar-2018 14:40 GMT+01