Trial Protocol

A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

SPONSOR

XBiotech USA Inc

22 January 2020

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Basic Information

STUDY TITLE: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

INVESTIGATIONAL PRODUCT:	Bermekimab
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SPONSOR:	XBiotech USA, Inc. 5217 Winnebago Lane Austin, Texas 78744 U.S.A. Phone: 512-386-2900
SPONSOR'S MEDICAL OFFICER:	PPD
STUDY CHAIR:	PPD

Investigator/Sponsor Signatures

STUDY TITLE: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

PROTOCOL VERSION / DATE: 2.0 / 22 January 2020

STUDY INVESTIGATOR SIGNATURE:

I have read the protocol and appendices. I understand the contents and intend to comply fully with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorization by XBiotech USA, Inc., in the form of a protocol amendment.

INVESTIGATOR SIGNATURE:

_____
Printed name of Investigator

_____
Signature

_____
Date

SPONSOR SIGNATURE:

XBiotech USA, Inc.

_____
Printed Name

_____
Signature

_____
Date

Clinical Protocol Synopsis

Study Title: A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

Sponsor:
XBiotech USA, Inc.

Study Chair:
PPD

Sample Size:
Approximately 150 patients will be enrolled in the USA.

Approximate Duration:
The duration of subject participation in the randomized, double-blind, placebo-controlled portion of the trial is approximately 40 weeks: including a screening period of up to 30 days, a 32-week treatment period, and 4-week follow-up period.

Study Objectives:
Primary Endpoint:

- Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12

Secondary Endpoints:

- Change from baseline to week 32 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score
- Change from baseline to week 16 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score
- Change from baseline to week 12 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score
- Change from baseline to week 8 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score

- Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at week 32
- Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at week 16
- Change in Modified Hidradenitis Suppurativa Score (mHSS), Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) and Hurley Stage from baseline to week 32
- Change in Modified Hidradenitis Suppurativa Score (mHSS), Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) and Hurley Stage from baseline to week 16
- Change in Modified Hidradenitis Suppurativa Score (mHSS), Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) and Hurley Stage from baseline to week 12
- Change in patient reported outcomes from baseline to week 32, including: Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI), Health Status Questionnaire (EQ-5D-3L), Patient Global Impression of Change (PGI-c), Patient Global Impression of Severity (PGI-s) and Hidradenitis Suppurativa Symptom Diary (HSSD) HS related Pain Symptom Score in the past 24 hours and total symptom score
- Change in patient reported outcomes from baseline to week 16, including: Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI), Health Status Questionnaire (EQ-5D-3L), Patient Global Impression of Change (PGI-c), Patient Global Impression of Severity (PGI-s) and Hidradenitis Suppurativa Symptom Diary (HSSD) HS related Pain Symptom Score in the past 24 hours and total symptom score
- Change in patient reported outcomes from baseline to week 12, including: Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI), Health Status Questionnaire (EQ-5D-3L), Patient Global Impression of Change (PGI-c), Patient Global Impression of Severity (PGI-s) and Hidradenitis Suppurativa Symptom Diary (HSSD) HS related Pain Symptom Score in the past 24 hours and total symptom score
- Assessment of Pharmacokinetics (PK)
- Reduction in serum IL-6 from baseline to week 32
- Reduction in serum IL-6 from baseline to week 16
- Reduction in serum IL-6 from baseline to week 12
- Reduction in serum IL-6 from baseline to week 8

Exploratory Endpoints:

- Change from baseline to week 32 in International Hidradenitis Suppurativa Severity Score System (IHS4)

- Change from baseline to week 16 in International Hidradenitis Suppurativa Severity Score System (IHS4)
- Change from baseline to week 32 in Hidradenitis Suppurativa Quality of Life Measure (HiSQOL)
- Change from baseline to week 16 in Hidradenitis Suppurativa Quality of Life Measure (HiSQOL)
- Change from baseline to week 32 in Physician's Global Assessment of Inflammatory Skin Disease (PGA-ISD)
- Change from baseline to week 16 in Physician's Global Assessment of Inflammatory Skin Disease (PGA-ISD)

Trial Design*

This is a randomized, double-blind, placebo-controlled study to further establish the efficacy and safety and explore dose effects for bermekimab monotherapy in adults with moderate-to-severe HS. Approximately 50% of patients enrolled will have failed prior targeted biologic therapy(ies) and approximately 50% will be naïve to these forms of biologic therapy in each arm. Patients will be assessed for study eligibility at the initial screening visit after providing informed consent. Thirty days are allowed in the screening window to complete all screening procedures and randomize the subject. During the screening period, certain treatments will be washed out, as applicable, according to eligibility requirements. Patients who fail initially may be re-screened once based on the investigator discretion but only if inclusion criteria are met at time of re-screening.

The study is approximately 40 weeks (30 day screening period, 32-week treatment period and a 4-week follow-up period) for all subjects.

Patients who meet eligibility criteria at screening will be randomized in a 1:1:1 fashion to one of three treatment arms:

- Arm 1: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and 1 followed by weekly (qw) subcutaneous (SC) injections of 400 mg bermekimab through week 31
- Arm 2: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and

1 followed by subcutaneous (SC) injections of 400 mg bermekimab every other week (q2w) alternating with matching placebo q2w through week 31.

- Arm 3: 4mL loading dose of placebo (2 x 2mL SC injections) at weeks 0 and 1 followed by weekly placebo injections from weeks 2 through week 15. Patients in Arm 3 will begin to receive weekly (qw) blinded subcutaneous (SC) injections of 400 mg bermekimab beginning at week 16 through week 31.

In order to maintain blinding, all patients will receive two injections at week 0 and 1, followed by weekly injections from weeks 2 to 31. Additionally, at least one qualified individual will be designated at each study site to perform all preparation and injection of the investigational product. The designated injector(s) should have no other contact with the participant during the study, should not discuss the participant's treatment with the participant, participant's caregiver, or other site personnel at any time, and will not be permitted to review the participant's medical records, questionnaires, or the electronic CRF prior to each injection. The designated injector(s) should be documented in the source documents at each visit.

Study treatment will be administered weekly in the clinic for 31 weeks with weekly office visits for 32 weeks. Patients will remain at the study site for a minimum of 30 minutes (+/- 10 minutes) after injections at weeks 0, 1, 2, 16, 17 and 18 injections for safety monitoring.

During the 32-week treatment period, patients will attend weekly clinical study visits. Clinical assessments, collection of samples for bermekimab concentrations, and safety testing will be performed at specified clinic visits. The primary endpoint data will be collected at week 12. After completion of the 36-week study period, data will be locked and analyzed for safety and efficacy endpoints for all arms. In addition to the analyses that will be performed following the formal database lock at the end of the study at Week 36, an additional database lock may be performed at Week 16, and interim analyses utilizing unblinded efficacy data available as the study progresses, may also be conducted to help plan potential future development activities. An internal interim analysis committee (IAC) will be established to review the interim data and formulate recommended decisions/actions. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in study conduct or compound development), one of whom will chair the committee, and may also include other members as required by the nature of the IAs. Details will be provided in a separate IAC charter, which will define the organization and roles and responsibilities of the committee, possible

recommendations or requests, and the communication process following IA reviews. Results from the Week 16 database lock and/or interim analyses will not be disseminated to investigators or subjects participating in the study. In addition, results of the interim analyses will not be disseminated to individuals associated with the conduct of the study.

Patients will be monitored at a follow up visit (visit 34/week 36) for safety and clinical assessments after completing the 32 week treatment period.

Figure 1. Study Flow Diagram

	Screening	Treatment Period			Follow-up
		Baseline	Weekly Dosing	Endpoint Assessment	
Visit (V)	D -30 to -1	V1	V2 to V32	V33	V34
Week (W)		W0	W1 to W31	W32	W36
Day (D)		D0	D7 to D217	D224	D252

Inclusion Criteria:

No waivers/exemptions will be granted for protocol inclusion/exclusion criteria.

Subjects are included in the study if they meet all of the following criteria:

- Written informed consent provided by the patient.
- Male or female, age ≥18 years.
- Naïve to OR failure of prior targeted biologic therapy for HS (including anti-TNF, anti-IL-17, or JAK inhibitor therapy).
- Must agree to daily use (throughout the entirety of the study) of one of the following over-the-counter treatments to the body areas affected with HS lesions: either soap and water, or a topical antiseptic wash containing chlorhexidine gluconate, triclosan, or benzoyl peroxide, or a dilute bleach bath.
- Diagnosis of HS for at least 1 year prior to screening.
- HS affecting at least two distinct anatomic areas, one of which is Hurley II or III stage.
- A total body count of abscesses and inflammatory nodules (A+N) of at least 3.

- Full understanding of the procedures of the study protocol and willingness to comply with them.
    - In case of female patients of childbearing potential, willingness to use one method of contraception of high efficacy during the entire study period. This method can be hormonal contraceptives or one of the following: condoms, diaphragm, or an intrauterine device. Women of non-childbearing potential include those considered to have a medical history that indicates that pregnancy is not a reasonable risk, including post-menopausal women and those with a history of hysterectomy or surgically sterilized.
- If you are a male participating in this clinical research study, you should not get a sexual partner pregnant during your participation in this research study as the effect of the study drug on sperm is not known.

Exclusion Criteria:
Subjects with ANY of the following will be excluded from the study:

- Age below 18 years.
- History of treatment with bermekimab for any reason.
- Receipt of oral antibiotic treatment for HS within 28 days prior to baseline.
- Receipt of prescription topical therapies for the treatment of HS within 14 days prior to baseline
- Receipt of systemic non-biologic therapies for HS (immunosuppressants, corticosteroids, retinoids, or hormonal therapies) within 28 days prior to screening.
- Subject has been treated with any drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to baseline.
- History of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies.
- Has received a live (attenuated) vaccine over the 28 days prior to screening.
- If entering the study on a dose of opioid analgesics that has not been stable for at least 14 days prior to baseline visit (PRN is not considered a stable dose).
- Subject received non-opioid analgesics within 24 hours of baseline visit.
- Subject has a draining fistula count of greater than 20 at baseline.
- Major surgery (requiring general anesthesia or respiratory assistance) within 28 days prior to Day 0 of start of study drug.

- Hepatic dysfunction defined as any value of transaminases, of γ-glutamyl transpeptidase (γGT) or of total bilirubin > 3x upper normal limit.
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g. tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution.
- Stage C Child-Pugh liver cirrhosis.
- History of human immunodeficiency virus (HIV) or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
- Neutropenia defined as <1,000 neutrophils/mm^3.
- Pregnancy or lactation.

Abbreviations

ADA	Anti-Drug Antibody
AE	Adverse event
ALT	Alanine aminotransferase (ALT, SGPT)
PT/aPTT	Prothrombin Time/Activated Partial Thromboplastin Time
ALP	Alkaline phosphate
BMI	Body mass index
BP	Blood pressure
BSA	Body Surface Area
CBC	Complete blood count
CI	Confidence interval
CH	Heavy chain constant region
CL	Light chain constant region
eCRF	Electronic Case report form
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CTCAE	Common terminology criteria for adverse events
DLQI	Dermatology Life Quality Index
EC	Ethics Committee
ELISA	Enzyme-linked immunosorbent assay
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HADS	Hospital Anxiety Depression Scale
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HiSCR	Hidradenitis Suppurativa Clinical Response Score
HiSQOL	Hidradenitis Suppurativa Quality of Life Measure
HIV	Human immunodeficiency virus
HS	Hidradenitis Suppurativa
HS-PGA	Hidradenitis Suppurativa Physicians Global Assessment
IDEOM	International Dermatology Outcome Measures
IFN-□	Interferon Gamma
IHS4	International Hidradenitis Suppurativa Severity Score System
IgG	Immunoglobulin G
IL-6	Interleukin-6
IL-1α	Interleukin-1 α
IL-1β	Interleukin-1 β
IL-1RA	Interleukin-1 receptor antagonist
IRB	Institutional review board
mHSS	Modified Hidradenitis Suppurativa Score
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-inflammatory Drug
PD	Pharmacodynamics
PK	Pharmacokinetics
PGA-ISD	Physician's Global Assessment of Inflammatory Skin Disease
PGI-c	Patient's Global Impression of Change
PGI-s	Patient's Global Impression of Severity
pI	Isoelectric Point
SAE	Serious Adverse Event
TNF	Tumor Necrosis Factor
ULN	Upper limit of normal
UV	Ultraviolet
VAS	Visual Analog Scale
WOCBP	Women of childbearing potential

1. BACKGROUND

1.1 OVERVIEW

XBiotech USA, Inc. has developed a True Human monoclonal antibody, Bermekimab, that binds the cytokine IL-1α with high affinity and is an effective blocker of IL-1α biological activity. IL-1α is a key mediator of sterile inflammatory responses and has been implicated in the pathology of advanced cancer, cardiovascular disease, and rheumatologic disease. Clinical evidence generated to date suggests that targeting IL-1α may be an effective treatment in undermining the inflammatory process that drives a wide array of diseases, including dermatologic conditions.

The active ingredient in the drug product bermekimab is MABp1, a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α). The entire bermekimab heavy and light chain sequences are identical to those found in naturally-occurring human IgG1κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual. No *in vitro* affinity maturation or modifications have been made to improve its natural binding affinity (211 +/- 31 pM). We believe that a true human antibody should be effectively non-immunogenic in humans and thus exhibit optimal activity and pharmacokinetics. XBiotech has conducted 10 clinical studies to date using the bermekimab antibody. These studies have been conducted in a wide range of therapeutic areas, from cancer to healthy volunteers, and have included a several different dose levels and dosing schedules. Both intravenous and subcutaneous formulations have been explored for safety and evidence of efficacy.

Five phase 2 studies sponsored by XBiotech have been completed in dermatologic indications (psoriasis [NCT01384630], acne vulgaris [NCT01474798], pyoderma gangrenosum [NCT01965613], atopic dermatitis [NCT03496974], and hidradenitis suppurativa [NCT03512275]), along with one investigator sponsored study in Hidradenitis Suppurativa[1,2,3]. Subjects with moderate to severe psoriasis experienced a rapid reduction in their psoriasis area and severity index (PASI), and subjects with acne vulgaris experienced reductions of inflammatory lesion counts, as well as reduced hospital anxiety and depression scores (HADS). Similar preliminary treatment efficacy was demonstrated for atopic dermatitis, with patients experiencing rapid reduction in pain and itch, as well as improved quality of life. In all of these trials, there were

few adverse events, most of which were grade 1 (mild) and the only events that appeared to be related to therapy were mild injection site reactions in two patients.

The investigator-initiated phase II RCT trial among patients not eligible for adalimumab (EudraCT number 2015-002321-20; ClinicalTrials.gov NCT02643654) was recently completed and showed promising results for activity of bermekimab in HS. Twenty patients with severe HS and with either primary or secondary failure of previous anti-TNF agents, or who were unwilling to receive subcutaneous adalimumab treatment, were randomly allocated (1:1) to receive, in a blinded fashion, every other week treatment with placebo or bermekimab at a dose of 7.5 mg/kg IV. Treatment was administered intravenously for 12 weeks. The primary efficacy endpoint was the positive HiSCR score, that was achieved among 10% of patients allocated to placebo and 60% of patients allocated to bermekimab. The odds ratio for positive HiSCR after 12 weeks of treatment was 13.50 (95% confidence intervals 1.19-152.51, p: 0.035). Analysis of the secondary endpoints showed some remarkable advantages of bermekimab treatment versus placebo treatment: a) blind follow-up for 12 weeks after stopping treatment showed that clinical efficacy was sustained, in that a positive HiSCR score was found in 40% of the treatment group and 0% of patients receiving placebo (p: 0.043); b) positive patient reported outcomes were found at week 12 in 70% and 30% respectively (p: 0.010); c) the median time to new HS flare-up was prolonged to 11 weeks and 7 weeks respectively; d) with the use of dermal ultrasound at week 12, a 20% or more decrease in total depth of involved skin lesions was found in 77.8% and 22.2%, respectively (p: 0.029); and e) serum IL-8 was decreased at week 12 in 90% and 40% respectively (p: 0.029)[4].

Data from XBiotech's recent 2018-PT045 open-label Phase 2 study of bermekimab treating HS corroborated the positive results generated from the investigator led study. 18 patients with no prior treatment with anti-TNF treatment (Group B) and 24 whom had failed previous anti-TNF treatment (Group A) were enrolled into the study. A positive HiSCR was again used as the primary efficacy endpoint. A positive HiSCR after 12 weeks was found in 63% of patients in Group A, and 61% of in group B. In addition to patients achieving a meaningful clinical response, patients also experienced a marked reduction in pain, with Group A patients reporting a 54% reduction in pain ($p < .0001$) and Group B Patients reports a 64% reduction in pain ($p < .0001$).

1.2 RATIONALE

Hidradenitis suppurativa/acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions (Dessau definition, 1st International Conference on Hidradenitis suppurativa/Acne inversa, March 30–April 1, 2006, Dessau, Germany)[5]. The clinical course is characterized by exacerbations and remissions of flare-ups. During these flare-ups, hair follicles in the affected regions become occluded, leading to tissue inflammation and the formation of lesions[6]. The duration of a flare-up is typically 3-5 days and is characterized by pain and difficulty in movement. Emotional stress is commonly associated with flare-ups, and flare-ups are commonly present in women before menses[7]. As the disease progresses, fistulas are formed under the dermis. These fistulas often suppurate continuously[8]. This chronic inflammation and the accompanying pain account for the fact that HS is ranked first among skin disorders in terms of adversely affecting quality of life[9]. In addition to the well understood comorbidity of pain, the often-overlooked comorbidity of pruritus further diminishes patient quality of life. A possible explanation for HS associated pruritus is the degranulation of tryptase-positive mast cells, found in high densities in HS affected anatomical regions. This degranulation is thought to release histamine and other mediators of pruritus. 211 patients in a recent cross sectional- study of reported an average Pruritus NRS score of 6.1 +/- 2.0, with 121 patients reporting a baseline pruritus NRS score of >3. Of these 121 patients, 70% reported pruritus at least occasionally affected their sleep, while 53% reported it occasionally affected activities of daily living[10]. Although HS is commonly understood to be an extremely painful disease, the quality of life impairments brought about by HS associated pruritus highlight the importance of assessing improvements in patient reported pruritus levels.

HS reportedly has an overall disease prevalence in the United States of 0.10%, reaching nearly 3 times that amount in African Americans[11]. The average disease prevalence in Europe is an order of magnitude higher, estimated at 1.0%[6]. A recent review of electronic records in the United States revealed an incidence of 11.4 per 100,000 in the general population[12]. The incidence was 2.5 times higher among African Americans than among white Americans[13]. The reported disease incidence in Europe is roughly half of that seen in the USA, with mean incidence found to be 6 cases in 100,000 person-years[11].

Based on findings showing high expression of tumor necrosis factor-alpha (TNFα) in the lesions of patients[14], the fully humanized monoclonal anti-TNF antibody adalimumab was studied for treatment of HS. Two large-scale randomized clinical studies (RCT) were conducted, designated PIONEER I and PIONEER II, which shared a common study design. Following an initial loading dose of 160 mg and a second 80 mg dose after two weeks, adalimumab was administered subcutaneously at a dose of 40 mg every week, and efficacy was compared to that in placebo-treated patients. The primary efficacy endpoint for both PIONEER studies was set at 12 weeks of treatment. This efficacy endpoint was the achievement of a positive hidradenitis suppurativa clinical response (HiSCR) score. After the initial 12-week treatment course, patients allocated to placebo were maintained to placebo whereas patients allocated to adalimumab were either switched to an open label extension (OLE) arm, or were further randomized to placebo, adalimumab 40 mg every other week or adalimumab 40 mg every week. Results showed that a positive HiSCR was found in 28.6% of placebo-treated patients and in 41% of adalimumab-treated patients of the PIONEER I study and in 27.6% of placebo-treated patients and in 58.9% of adalimumab-treated patients in the PIONEER II study[15]. As stated above, after the first 12 weeks of treatment patients initially treated with adalimumab could be further randomized and received another 12 weeks of treatment with placebo, 40mg adalimumab weekly or every other week. Analysis showed that approximately half of patients showed a positive initial response to treatment, and half of these maintained this response long-term. As also stated above, after the first 12 weeks of treatment, 88 patients were switched to an OLE receiving 40 mg of adalimumab every week; positive HiSCR was achieved at weeks 120 and 168 in 56.8% and 52.3% respectively[16]. Adalimumab has been registered in both USA and Europe for moderate to severe HS based on the results of the two PIONEER studies.

Adalimumab is an important advance for the treatment of HS. However, there remains considerable unmet need for patients with HS, including 41% to 58% of patients who have primary response failures after 12 weeks of adalimumab treatment and the 30-50% patients that have a positive initial response to treatment but relapse after 12 weeks of therapy. These primary and secondary failures to adalimumab treatment may reflect the biological heterogeneity of the HS. About half of patients, for example, over-express TNFα in their lesions, whereas others have lesions better characterized by the production of cytokines like interleukin (IL)-1β and IL-1α[17]. In a small randomized study ten patients were allocated to treatment with placebo and nine patients to treatment with anakinra (IL-1 receptor antagonist targeting both IL-1β and IL-1α). A positive HiSCR score was achieved in 30% and 78% of patients, respectively (p: 0.039)[18]. These results suggested that inhibition of IL-

1 may be a promising treatment strategy, including that for patients evidencing primary or secondary failure of adalimumab. Interluekin-6 (IL-6) levels have shown to be correlated with disease severity in HS and potentially have a greater reliability for predicting response to HS treatment than CRP levels[19,20]. In previous clinical studies, decreased IL-6 levels have been demonstrated in patients receiving bermekimab therapy[21,22]. Therefore, IL-6 may be considered as a candidate pharmacodynamic measure of response to bermekimab in HS.

Endogenous anti-IL-1α antibodies are present in 5% to 28% of the general population[23,24,25,26]. No negative correlations with disease have been noted for these individuals. To the contrary, the presence of natural anti-IL-1α antibodies has been associated with favorable outcomes, both with respect to rheumatoid arthritis and ischemic heart disease. Animal studies also indicate that IL-1α loss or antagonism does not result in harm. Moreover, the well-tolerated use of other approved biological agents that employ alternative other strategies to block IL-1 activity suggest that bermekimab's targeting of IL-1α represents a safe treatment approach.

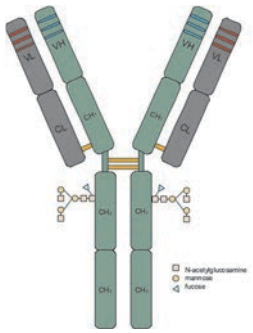
In previous dermatology studies bermekimab was well tolerated and showed impressive therapeutic activity.

2. INVESTIGATIONAL PRODUCT

2.1 ACTIVE INGREDIENT, PHARMACOLOGIC CLASS, STRUCTURE

The active ingredient in the drug product bermekimab is MABp1, a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α). The entire bermekimab heavy and light chain sequences are identical to those found in naturally-occurring human IgG1κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual.

Figure 1.0: Bermekimab Antibody



The bermekimab primary glycoform has a molecular weight of 148.1 kilodaltons. Like all IgG1 molecules, the heavy chains are joined at their hinge regions through two disulfide linkages, and each heavy chain is joined to one light chain through one disulfide linkage between their CH_1 and CL domains respectively.

The main isoform has a pI of about 9.2 and comprises about 70-80% of the total isoform population in all lots that have been manufactured to date, as determined by capillary isoelectric focusing. The heavy chain CH_2 domains are glycosylated primarily with the oligosaccharide structure shown in Figure 1.0, as determined by mass spectroscopy of the cleaved glycans. The glycosylated residue (Asn-302 as numbered from the N-terminus of bermekimab) has been determined by peptide mapping to be in the same highly conserved N-linked glycosylation site as found in endogenous IgG1 (Asn-297 according to the generic numbering system). Similarly, the primary glycan, commonly referred to as G0F, is the same as that found on about 22% of endogenous human IgG molecules[27].

The entire bermekimab heavy and light chain sequences are identical to those found in naturally-occurring human IgG1κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual.

Endogenous anti-IL-1α antibody has been reported in 5% to 28% of healthy serum or plasma samples[28,29]. It has been measured in cord blood, children and adults[30]. The anti-IL-1α antibodies measured in human plasma have been strictly of the IgG class, particularly IgG1, IgG2, and IgG4. Relatively equal distribution is seen in male and female plasma[31]. Binding affinities reported for endogenous anti-IL-1α antibodies, ranging from 4 to 16 pM.

It is important to point out that affinity maturation had already taken place in the human host, and therefore no *in vitro* affinity maturation was required to increase the natural binding affinity of bermekimab. Also important is the fact that, unlike most other therapeutic IgG products, for which the Fc regions are derived from a rare human allele, XBiotech's product includes a heavy chain in which the constant (CH) region represents an allele found in approximately 70% of the human population. These two features should make for a drug product with reduced potential for immunogenicity.

2.2 DRUG PRODUCT (BERMEKIMAB 200 MG/ML) DESCRIPTION

XBiotech's dosage form is a sterile liquid formulation of 200 mg/mL bermekimab in a stabilizing isotonic subcutaneous formulation buffer at pH 6.2-6.5 containing non-active ingredients of low concentrations of sodium phosphate, citric acid and trehalose. The drug product is packaged in pre-filled syringes. Drug product in syringes is stored at 2-8°C and is recommended to be protected from light.

2.3 STORAGE

The recommended storage condition is at 2-8°C.

2.4 STABILITY

The drug product is formulated in a buffer in which most of the tonicity comes from trehalose rather than salt. Trehalose is an effective stabilizer against oxidation, aggregation, thermal, and mechanical stress. Citrate was selected as the buffering agent due to its antioxidant properties.

Extensive stability data indicates that the drug product is very stable, even under thermally and mechanically stressed conditions. Short excursions to room temperature have shown no negative effect on the product. However, the study treatment products are not to be frozen at any time. The 200 mg/ml drug product is labeled with a 12-month retest date. Every lot of 200mg/ml dosage form is also subjected to ongoing stability analysis per ICH guidelines.

2.5 DESIGNATED INDIVIDUAL FOR DRUG ADMINISTRATION

To ensure that no unintentional unblinding occurs during study drug administration, at lease one qualified individual will be designated at each study site to perform all preparation and injection of the investigational product. The designated injector(s) should have no other contact with the participant during the study, should not discuss the participant's treatment with the participant, participant's caregiver, or other site personnel at any time, and will not be permitted to review the participant's medical records, questionnaires, or the electronic CRF prior to each injection. The designated injector(s) should be documented in the source documents at each visit.

2.6 METHOD OF ADMINISTRATION

Following two initial 800 mg loading doses of either bermekimab or placebo, patients in all arms will receive 400 mg of either bermekimab or placebo via subcutaneous injection administered weekly. Each injection should be administered at least one inch from previous injection sites.

*** At least 45 minutes prior to injection, remove the pre-filled syringe from refrigeration**

Lay the syringe on a flat surface and let it naturally warm to room temperature before injection. It may also be warmed by holding in hand. Do not heat the syringe.

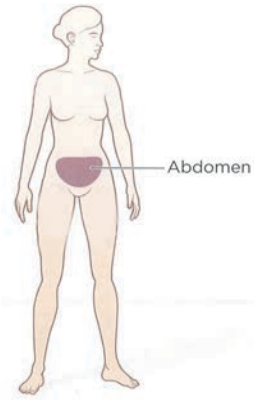
Materials

Bermekimab pre-filled syringe for injection, warmed to room temperature*
Sterile alcohol wipes
Band-aids, along with 2x2 gauze bandages and paper tape
Latex-free gloves

Injection Site

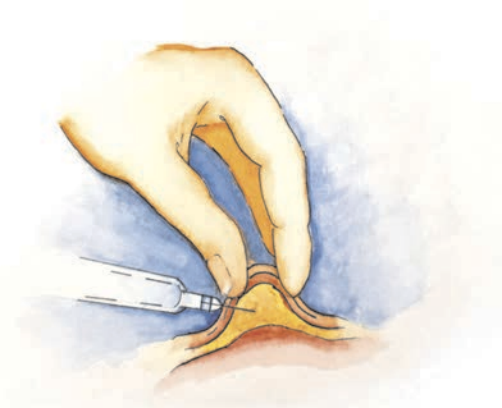
Abdomen, at least 2 inches away from the belly button

(Note: avoid areas where the skin is burned, scarred, hardened, inflamed, swollen, or damaged).



Injection

- Put on gloves
- Wipe injection site clean with alcohol pads
- Raise a fold of skin between the thumb and forefinger and insert needle as illustrated
- Insert needle as illustrated in adjacent diagram
- Inject drug slowly
- Withdraw needle. Place band-aid over injection site if necessary (*Note: If bleeding occurs, hold pressure on the injection site for 90 seconds or until bleeding stops, and then apply gauze bandage secured by tape*).



***Investigator may, at their judgement, administer antihistamines/NSAIDs to prevent or treat injection site reaction. This must be captured in eCRF.

2.7 AGENT ORDERING

The Responsible Investigational Pharmacy will order study drug from XBiotech's contract drug distributor as needed.

2.8 POTENTIAL DRUG INTERACTIONS

There are no known drug interactions reported with bermekimab.

2.9 PROHIBITED THERAPY

- Phototherapy (PUVA and/or UVB)
- All biologic therapy with a potential therapeutic impact on the HS presented by the patient, including but not limited to the following:
  - Abatacept (Orencia ®)
  - Anakinra (Kineret ®)
  - Belimumab (Benlysta ®)
  - Cetolizumab (Cimzia ®)
  - Efalizumab (Raptiva ®)
  - Etanercept (Enbrel ®)
  - Golimumab (Simponi ®)
  - Infliximab (Remicade ®)
  - Natalizumab (Tysabri ®)
  - Rituximab (Rituxan ®)
  - Tocilizumab (Actemra ®)
  - Ustekinumab (Stelara ®)
- Live virus vaccines (during the study and for 70 days after the last dose of study drug)
- Investigational agents other than bermekimab
- Oral or injectable corticosteroids for treatment of HS except those listed in section 2.11.3 Lesion Intervention
- Oral Analgesics not listed in Section 2.11.1 Analgesic Therapy
- New prescription topical therapies for HS
- Over-the-counter topical washes, creams, soaps, ointments, gels and liquids containing antibacterial agents to treat HS not listed in Section

- 2.10.2 Wound Care
- Surgical or laser intervention for an HS lesion except as outlined in Section 2.11.3 Lesion Intervention

2.10 CONCOMITANT THERAPY

2.10.1 Concomitant Corticosteroid use for Conditions Other than HS

The use of systemic corticosteroids for indications other than HS should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤2 weeks. Longer-term use of corticosteroids should be discussed with the medical monitor or designee and may require discontinuation of study drug. Inhaled, otic, ocular, nasal or other routes of mucosal delivery of corticosteroids are allowed throughout the study.

2.10.2 Wound Care

Subjects are required to use a daily antiseptic wash on their HS lesions. Allowable antiseptic washes are limited to one of the following: soap and water, chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater. Concomitant use of wound care dressings on HS wounds is allowed, however options are limited to alginates, hydrocolloids and hydrogels.

2.11 RESTRICTED THERAPY

2.11.1 Analgesic Therapy

Antihistamine/NSAID use is permitted in this study including those to prevent or treat injection site reaction(s). Most subjects will be required to washout of all opioid analgesics for 14 days prior to baseline or, in the case of non-opioid analgestics, for 24 hours prior to baseline. However, if a subject is on a stable dose of a opioid analgesic medication (PRN is not considered stable), 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:

- Ibuprofen (at a dose of up to 800 mg po every 6 hours) not to exceed 3.2 grams/24 hours; AND/OR acetaminophen as per local labeling.

- If pain is uncontrolled with ibuprofen or acetaminophen at the above dosing regimens after the baseline visit, subjects can be prescribed tramadol (at a dose of up to 100 mg po every 4 hours), not to exceed 400 mg/24 hours.

Dose adjustments of ibuprofen, acetaminophen, or tramadol, and use of these analgesics on an "as needed" (PRN) basis for HS-related pain up to the maximum permitted dose and frequency, are allowed during the study.

From Screening through the end of their study participation, subjects will be required to report to site staff any analgesics taken since their last visit . All analgesics and doses will be captured in the source and on the concomitant medications eCRF.

2.11.2 Antibiotic Rescue Therapy

Concomitant use of oral antibiotic therapy for treatment of HS is not allowed. At Week 4 or Week 8, if a subject experiences an increase in their AN count such that the total count is greaterthanor equalto 150% of their Baseline AN count, antibiotic rescue medication may be initiated. Subjects who qualify may initiate treatment with minocycline or doxycycline up to 100 mg bid. The dosing regimen must remain stable throughout study participation. Otherwise, concomitant use of oral antibiotic therapy for treatment of HS is not allowed. Rescue antibiotic therapy should be captured in the source and on the appropriate eCRF.

2.11.3 Lesion Intervention

In the event that an acutely painful lesion occurs that requires an immediate intervention, physicians will have the option to perform protocol-allowed interventions. Only two types of interventions are allowed: injection with intralesional triamcinolone acetonide suspension (at a concentration of up to 5 mg/mL, up to 1 cc) and incision and drainage.

If incision and drainage is performed, the required over-the-counter antiseptic wash should continue to be used. New systemic and topical therapies following incision and drainage (including antibiotics), are prohibited. Concomitant use of wound care dressings is allowed however options are limited to alginates, hydrocolloids, and hydrogels. Subjects should continue using any ongoing oral and topical therapies (with

the constraints as described in Section 2.11 RESTRICTED THERAPY during the study. See Section 9.8 TOXICITY MANAGEMENT for additional discussion on the use of concomitant medications if medically necessitated. Concomitant medications associated with the lesion intervention(s) must be captured in the source and on the appropriate eCRF.

A total of two protocol-allowed interventions are permissible. An intervention can occur on maximally two different lesions at the same visit or on the same lesion at two different study visits. The same lesion cannot be treated two times at the same visit. If a subject requires more than two interventions within the 32 week treatment period, then they must be discontinued from the study treatment.

All study visit evaluations must occur before any interventions are performed. Any lesion that undergoes an intervention will be documented in the source. The site will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention and must account for it in the source and on the appropriate eCRF.

3. STUDY DESIGN AND OBJECTIVES

This is a randomized, double-blind, placebo-controlled study to further establish the efficacy and safety and explore dose effects for bermekimab monotherapy in adults with moderate-to-severe HS. Approximately 50% of patients enrolled will have failed prior targeted biologic therapy(ies) and approximately 50% will be naïve to these forms of biologic therapy in each arm. Patients will be assessed for study eligibility at the initial screening visit after providing informed consent. Thirty days are allowed in the screening window to complete all screening procedures and randomize the subject. During the screening period, certain treatments will be washed out, as applicable, according to eligibility requirements. Patients who fail initially may be re-screened once based on the investigator discretion but only if inclusion criteria are met at time of re-screening.

The study is approximately 40 weeks (30 day screening period, 32-week treatment period and a 4-week follow-up period) for all subjects.

Patients who meet eligibility criteria at screening will be randomized in a 1:1:1 fashion to one of three treatment arms:

- Arm 1: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and 1 followed by weekly (qw) subcutaneous (SC) injections of 400 mg bermekimab through week 31
- Arm 2: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and 1 followed by subcutaneous (SC) injections of 400 mg bermekimab every other week (q2w) alternating with matching placebo q2w through week 31.
- Arm 3: 4mL loading dose of placebo (2 x 2mL SC injections) at weeks 0 and 1 followed by weekly placebo injections from weeks 2 through week 15. Patients in Arm 3 will begin to receive weekly (qw) blinded subcutaneous (SC) injections of 400 mg bermekimab beginning at week 16 through week 31.

In order to maintain blinding, all patients will receive two injections at week 0 and 1, followed by weekly injections from weeks 2 to 31. Additionally, at least one qualified individual will be designated at each study site to perform all preparation and injection of the investigational product. The designated injector should have no other contact with the participant during the study, should not discuss the participant's treatment with the participant, participant's caregiver, or other site personnel at any time, and will not be permitted to review the participant's medical records, questionnaires, or the electronic CRF prior to each injection. The designated injector should be documented in the source documents at each visit.

Study treatment will be administered weekly in the clinic for 31 weeks with weekly office visits for 32 weeks. Patients will remain at the study site for a minimum of 30 minutes (+/- 10 minutes) after injections at weeks 0, 1, 2, 16, 17 and 18 injections for safety monitoring.

During the 32-week treatment period, patients will attend weekly clinical study visits. Clinical assessments, collection of samples for bermekimab concentrations, and safety testing will be performed at specified clinic visits. The primary endpoint data will be collected at week 12. After completion of the 36-week study period, data will be locked and analyzed for safety and efficacy endpoints for all arms. In addition to the analyses that will be performed following the formal database lock at the end of the study at Week 36, an additional database lock may be performed at Week 16, and interim analyses utilizing unblinded efficacy data available as the study progresses, may also be conducted to help plan potential future development activities. An internal interim analysis committee (IAC) will be established to review the

interim data and formulate recommended decisions/actions. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in study conduct or compound development), one of whom will chair the committee, and may also include other members as required by the nature of the IAs. Details will be provided in a separate IAC charter, which will define the organization and roles and responsibilities of the committee, possible recommendations or requests, and the communication process following IA reviews. Results from the Week 16 database lock and/or interim analyses will not be disseminated to investigators or subjects participating in the study. In addition, results of the interim analyses will not be disseminated to individuals associated with the conduct of the study.

Patients will be monitored at a follow up visit (visit 34/week 36) for safety and clinical assessments after completing the 32 week treatment period.

The study protocol will be approved by the Institutional Review Board (IRB) or the Ethics Committee (EC) of the participating study sites. Depending on the participating countries both local and central IRB/EC approvals will be granted. The study will be registered at www.clinicaltrials.gov before the enrollment of the first patient. The trial will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

3.1 STUDY ENDPOINTS

Primary Endpoint:

- Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at week 12

Secondary Endpoints:

- Change from baseline to week 32 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score
- Change from baseline to week 16 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score
- Change from baseline to week 12 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score

- Change from baseline to week 8 in Numeric Rating Scale for Pain & Itch (NRS Pain & Itch) score
- Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at week 32
- Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at week 16
- Change in Modified Hidradenitis Suppurativa Score (mHSS), Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) and Hurley Stage from baseline to week 32
- Change in Modified Hidradenitis Suppurativa Score (mHSS), Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) and Hurley Stage from baseline to week 16
- Change in Modified Hidradenitis Suppurativa Score (mHSS), Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA) and Hurley Stage from baseline to week 12
- Change in patient reported outcomes from baseline to week 32, including: Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI), Health Status Questionnaire (EQ-5D-3L), Patient Global Impression of Change (PGI-c), Patient Global Impression of Severity (PGI-s) and Hidradenitis Suppurativa Symptom Diary (HSSD) HS related Pain Symptom Score in the past 24 hours and total symptom score
- Change in patient reported outcomes from baseline to week 16, including: Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI), Health Status Questionnaire (EQ-5D-3L), Patient Global Impression of Change (PGI-c), Patient Global Impression of Severity (PGI-s) and Hidradenitis Suppurativa Symptom Diary (HSSD) HS related Pain Symptom Score in the past 24 hours and total symptom score
- Change in patient reported outcomes from baseline to week 12, including: Hospital Anxiety and Depression Scale (HADS), Dermatology Life Quality Index (DLQI), Health Status Questionnaire (EQ-5D-3L), Patient Global Impression of Change (PGI-c), Patient Global Impression of Severity (PGI-s) and Hidradenitis Suppurativa Symptom Diary (HSSD) HS related Pain Symptom Score in the past 24 hours and total symptom score
- Assessment of Pharmacokinetics (PK)
- Reduction in serum IL-6 from baseline to week 32
- Reduction in serum IL-6 from baseline to week 16
- Reduction in serum IL-6 from baseline to week 12
- Reduction in serum IL-6 from baseline to week 8

Exploratory Endpoints:

- Change from baseline to week 32 in International Hidradenitis Suppurativa Severity Score System (IHS4)
- Change from baseline to week 16 in International Hidradenitis Suppurativa Severity Score System (IHS4)
- Change from baseline to week 32 in Hidradenitis Suppurativa Quality of Life Measure (HiSQOL)
- Change from baseline to week 16 in Hidradenitis Suppurativa Quality of Life Measure (HiSQOL)
- Change from baseline to week 32 in Physician's Global Assessment of Inflammatory Skin Disease (PGA-ISD)
- Change from baseline to week 16 in Physician's Global Assessment of Inflammatory Skin Disease (PGA-ISD)

4. ELIGIBILITY CRITERIA

4.1 INCLUSION CRITERIA

No waivers/exemptions will be granted for protocol inclusion/exclusion criteria.

Subjects are included in the study if they meet all of the following criteria:

- Written informed consent provided by the patient.
- Male or female, age ≥18 years.
- Naïve to OR failure of prior targeted biologic therapy for HS (including anti-TNF, anti-IL-17, or JAK inhibitor therapy).
- Must agree to daily use (throughout the entirety of the study) of one of the following over-the-counter treatments to the body areas affected with HS lesions: either soap and water, or a topical antiseptic wash containing chlorhexidine gluconate, triclosan, or benzoyl peroxide, or a dilute bleach bath.
- Diagnosis of HS for at least 1 year prior to screening.
- HS affecting at least two distinct anatomic areas, one of which is Hurley II or III stage.
- A total body count of abscesses and inflammatory nodules (A+N) of at least 3.
- Full understanding of the procedures of the study protocol and willingness to comply with them.

- In case of female patients of childbearing potential, willingness to use one method of contraception of high efficacy during the entire study period. This method can be hormonal contraceptives or one of the following: condoms, diaphragm, or an intrauterine device. Women of non-childbearing potential include those considered to have a medical history that indicates that pregnancy is not a reasonable risk, including post-menopausal women and those with a history of hysterectomy or surgically sterilized.
- Males participating in this clinical research study should not get a sexual partner pregnant during participation in this research study as the effect of the study drug on sperm is not known.

4.2 EXCLUSION CRITERIA

Subjects with ANY of the following will be excluded from the study:

- Age below 18 years.
- History of treatment with bermekimab for any reason.
- Receipt of oral antibiotic treatment for HS within 28 days prior to baseline.
- Receipt of prescription topical therapies for the treatment of HS within 14 days prior to baseline
- Receipt of systemic non-biologic therapies for HS (immunosuppressants, corticosteroids, retinoids, or hormonal therapies) within 28 days prior to screening.
- Subject has been treated with any drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to baseline.
- History of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies.
- Has received a live (attenuated) vaccine over the 28 days prior to screening.
- If entering the study on a dose of opioid analgesics that has not been stable for at least 14 days prior to baseline visit (PRN is not considered a stable dose).
- Subject received non-opioid analgesics within 24 hours of baseline visit.
- Subject has a draining fistula count of greater than 20 at baseline.
- Major surgery (requiring general anesthesia or respiratory assistance) within 28 days prior to Day 0 of start of study drug.
- Hepatic dysfunction defined as any value of transaminases, of γ-glutamyl transpeptidase (γGT) or of total bilirubin > 3x upper normal limit.

- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g. tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution.
- Stage C Child-Pugh liver cirrhosis.
- History of human immunodeficiency virus (HIV) or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
- Neutropenia defined as <1,000 neutrophils/mm^3.
- Pregnancy or lactation.

5. TREATMENT PLAN

5.1 STUDY PROCEDURES

PLACEBO-CONTROLLED PERIOD

Screening (maximum 30 days): The screening period begins once the informed consent is signed.

- Informed Consent
- Inclusion/ Exclusion
- Medical History/ Demographics
- Height, Weight, Body Mass Index (BMI) [BMI= weight (kg)/height (m2)]
- Concomitant Medications/treatments
- Provide subject copies of the patient take home diary, which will consist of NRS pain (worst moment, average & current) and itch (worst moment & average) assessments to be completed by patients daily.
- Lesion Counts (HiSCR), mHSS, HS-PGA, PGA-ISD, IHS4, Hurley Staging
- DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
- Physical Exam
- Electrocardiogram
- Vital Signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Urinalysis: pH, protein, glucose and blood cells (RBCs and WBCs)
- Blood Draw:
    - Chemistry panel: Albumin, Alkaline Phosphatase, ALT, AST, GGT,

Bicarbonate (CO2), Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen (BUN)

- Hematology Panel: Complete Blood Count (CBC) with differential and platelets
- Infectious disease panel: HIV antibody, Hepatitis C antibody, Hepatitis B panel (HBsAg, anti-HBc, anti-HBs), and interferon gamma release assay (IGRA) for TB
- Serum pregnancy test for WOCBP
- Inflammation Markers: CRP (C-Reactive Protein), ESR (Erythrocyte Sedimentation Rate)

- Randomization to study arm (once confirmed patient has passed screening requirements).

****Patients will be monitored at the study site at visits 1, 2, 3, 17, 18 & 19 (weeks 0, 1, 2, 16, 17 & 18) for a minimum of 30-minutes after study drug administration. Vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.****

Visit 1 (Week 0) (day 0, must occur within 30 days of signing informed consent):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Verify patient still meets inclusion/exclusion criteria
  - Height, Weight, Body Mass Index (BMI) [BMI= weight (kg)/height (m2)]
  - Patient Diary
  - Baseline Lesion Counts (for future HiSCR assessments), mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
  - DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
  - Physical Exam, Vital signs, Urine pregnancy
  - Urinalysis
  - Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Bermekimab/placebo subcutaneous injections (To deliver a loading dose to subjects in the bermekimab groups while maintaining blinding, all subjects will receive two injections)
- Post-injection
  - Adverse event monitoring

- Concomitant medications/treatments

Visit 2 (Week 1) (day 7 +/-3); Visit 4 (Week 3) (day 21 +/-3); Visit 6 (Week 5) (day 35 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Patient Diary
  - HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
  - DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
  - Physical Exam, Vital signs, Urine pregnancy
  - Blood draw for PK/ADA, IL-6, PD, biomarker and research analysis
- Bermekimab/placebo subcutaneous injections (To deliver a loading dose to subjects in the bermekimab groups while maintaining blinding, all subjects will receive two injections)
- Post-injection
  - Adverse event monitoring
  - Concomitant medications/treatments

Visit 3 (Week 2) (day 14 +/-3); Visit 5 (Week 4) (day 28 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Patient Diary
  - Vital signs, Urine pregnancy
  - Blood draw for PK/ADA, IL-6, PD, biomarker and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
  - Adverse event monitoring
  - Concomitant medications/treatments

Visit 7 (Week 6) (day 42 +/-3); Visit 11 (Week 10) (day 70 +/-3); Visit 14 (Week 13) (day 91 +/-3); Visit 15 (Week 14) (day 98 +/-3); Visit 16 (Week 15) (day 105 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection

    - Patient Diary
    - Vital signs, Urine pregnancy
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

Visit 8 (Week 7) (day 49 +/-3); Visit 10 (Week 9) (day 63 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
    - Patient Diary
    - HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
    - DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
    - Physical Exam, Vital signs, Urine pregnancy
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

Visit 9 (Week 8) (day 56 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
    - Patient Diary
    - Vital signs, Urine Pregnancy
    - Urinalysis
    - Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

Visit 12 (Week 11) (day 77 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
    - Patient Diary
    - Physical Exam, Vital signs, Urine pregnancy
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

Visit 13 (Week 12) (day 84 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
    - Patient Diary
    - HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
    - DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
    - Physical Exam, Vital signs, Urine pregnancy
    - Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

BLINDED ACTIVE DOSING PERIOD

Visit 17 (Week 16) (day 112 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
    - Patient Diary
    - HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
    - DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL

- Physical Exam, Vital signs, Urine pregnancy
- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Urinalysis

- Bermekimab/placebo subcutaneous injection
- Post-injection
  - Adverse event monitoring
  - Concomitant medications/treatments

Visit 18 (Week 17) (day 119 +/-3); Visit 19 (Week 18) (day 126 +/-3); Visit 20 (Week 19) (day 133 +/-3); Visit 22 (Week 21) (day 147 +/-3); Visit 23 (Week 22) (day 154 +/-3); Visit 24 (Week 23) (day 161 +/-3); Visit 26 (Week 25) (day 175 +/-3); Visit 27 (Week 26) (day 182 +/-3); Visit 28 (Week 27) (day 189 +/-3); Visit 30 (Week 29) (day 203 +/-3); Visit 31 (Week 30) (day 210 +/-3); Visit 32 (Week 31) (day 217 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Patient Diary
  - Vital signs
  - Urine pregnancy
- Bermekimab/placebo subcutaneous injection
- Post-injection
  - Adverse event monitoring
  - Concomitant medications/treatments

Visit 21 (Week 20) (day 140 +/-3); Visit 29 (Week 28) (day 196 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Patient Diary
  - HiSCR, mHSS, HS-PGA, PGA-ISD and IHS4
  - DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
  - Vital signs, Urine pregnancy
- Bermekimab/placebo subcutaneous injection
- Post-injection

- Adverse event monitoring
- Concomitant medications/treatments

Visit 25 (Week 24) (day 168 +/-3):

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Patient Diary
  - HiSCR, mHSS, HS-PGA, PGA-ISD and IHS4
  - DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
  - Vital signs, Urine pregnancy
  - Urinalysis
  - Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
  - Adverse event monitoring
  - Concomitant medications/treatments

Visit 33 (Week 32) (day 224 +/-3):

- Patient Diary
- HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
- DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
- Physical Exam, Vital signs, Urine pregnancy
- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Urinalysis
- Adverse event monitoring
- Concomitant medications/treatment

FOLLOW-UP PERIOD

Visit 34 (Week 36) (day 252 +/-3):

- HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
- DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
- Physical Exam, Vital signs, Urine pregnancy

- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Urinalysis
- Adverse event monitoring
- Concomitant medications/treatment

UNSCHEDULED VISIT (if applicable)

- Patient Diary
- HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
- DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
- Physical Exam, Vital signs, Urine or Serum pregnancy
- Electrocardiogram
- Blood draw for infectious disease panel, chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Urinalysis
- Adverse event monitoring
- Concomitant medications/treatment

EARLY TERMINATION VISIT (if applicable)

- Patient Diary
- HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4 and Hurley Staging
- DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL
- Physical Exam, Vital signs, Serum pregnancy
- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, IL-6, PD, biomarker and research analysis
- Urinalysis
- Adverse event monitoring
- Concomitant medications/treatment

5.2 STUDY CALENDARS

5.2.1 Placebo-controlled Period

Study Procedure	Screening	Baseline	Placebo-controlled Period															
Visit (V)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**
Week (W)		**W0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**
Day (D)	**-30 to -1**	**D0**	**D7**	**D14**	**D21**	**D28**	**D35**	**D42**	**D49**	**D56**	**D63**	**D70**	**D77**	**D84**	**D91**	**D98**	**D105**	**D112**
Visit Window (d)	+5d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:[1]																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Medical History/ Demographics	X																	
Height, Weight, BMI	X	X																
Randomization	X																	
Treatment:[2, 3, 5]																		
Administer Study Drug		X[6]	X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]
Con Meds/ Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[4]																		
Patient Diary (daily)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HiSCR, mHSS, HS PGA, PGA-ISD, IHS4	X	X	X		X		X		X		X			X				X
Hurley Stage	X	X	X		X		X		X		X			X				X
DLQI, HADS, PGI-C, PGI-S, EQ-5D-3L, HSSD, HiSQOL	X	X	X		X		X		X		X			X				X
Safety:[4]																		
Physical Examination	X	X	X		X		X		X		X		X	X				X
Electrocardiogram	X																	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[4]																		
Infectious Disease Panel	X																	
Hematology, Chemistry, Inflammation Markers	X	X								X				X				X
Urinalysis	X	X								X								X
Pregnancy Test (WOCBP only)	Serum	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD/ADA:[4]																		
PK/ADA, IL-6, PD, biomarker & research samples (serum/plasma)		X	X	X	X	X	X			X				X				X

[1] 30 days are allowed to complete all screening procedures and randomization.

[2] Patients will be monitored at the study site at visits 1, 2, 3, 17, 18 & 19 (weeks 0, 1, 2, 16 17 & 18) for a minimum of 30-minutes after study drug administration. Vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[3] Patients will be randomized to treatment arm 1, 2, or 3 and will follow the corresponding treatment plan.

[4] Assessments/procedures should be conducted in the following order: patient assessments, investigator assessments, safety and laboratory assignments, administration of the study drug.

[5] Concomitant medications within 30 days before screening until 7 days after the last administration of the study drug must be recorded for the purpose of drug-drug and drug-disease interaction evaluation and signal detection

[6] Loading Doses: Treatment arm 1: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and 1; Treatment arm 2: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and 1; Arm 3: 800 mg loading dose of placebo (2 x 400 mg SC injections) at weeks 0 and 1.

[7] Patients in Arm 3 will begin to receive active bermekimab therapy from visit 17 (week 16). Patients in all arms will remain blinded through end of study.

Blinded Active Dosing Period

Study Procedure			Blinded Active Dosing Period													
Visit (V)	**V18**	**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V26**	**V27**	**V28**	**V29**	**V30**	**V31**	**V32**	**V33**
Week (W)	**W17**	**W18**	**W19**	**W20**	**W21**	**W22**	**W23**	**W24**	**W25**	**W26**	**W27**	**W28**	**W29**	**W30**	**W31**	**W32**
Day (D)	**D119**	**D126**	**D133**	**D140**	**D147**	**D154**	**D161**	**D168**	**D175**	**D182**	**D189**	**D196**	**D203**	**D210**	**D217**	**D224**
Visit Window (d)	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Treatment:[2, 3, 5]																
Administer Study Drug	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Con Meds/ Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy:[4]																
Patient Diary (daily)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HiSCR, mHSS, HS PGA, PGA-ISD, IHS4				X				X				X				X
Hurley Stage																X
DLQI, HADS, PGI-C, PGI-S, EQ-5D-3L, HSSD, HiSQOL				X				X				X				X
Safety:[4]																
Physical Examination																X
Electrocardiogram																
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[4]																
Infectious Disease Panel																
Hematology, Chemistry, Inflammation Markers								X								X
Urinalysis								X								X
Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD/ADA:[4]																
PK/ADA, IL-6, PD, biomarker & research samples (serum/plasma)								X								X

[2] Patients will be monitored at the study site at visits 1, 2, 3, 17, 18 & 19 (weeks 0, 1, 2, 18, 19 & 20) for a minimum of 30 minutes after study drug administration. Vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

[3] Patients will be randomized to treatment arm 1, 2, or 3 and will follow the corresponding treatment plan.

[4] Assessments/procedures should be conducted in the following order: patient assessments, investigator assessments, safety and laboratory assignments, administration of the study drug.

[5] Concomitant medications within 30 days before screening until 7 days after the last administration of the study drug must be recorded for the purpose of drug-drug and drug-disease interaction evaluation and signal detection

[6] Loading Doses: Treatment arm 1: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and 1; Treatment arm 2: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at weeks 0 and 1; Arm 3: 800 mg loading dose of placebo (2 x 400 mg SC injections) at weeks 0 and 1

5.2.2 Follow-Up Period

Study Procedure	**Follow-up Period**	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V34**		
Week (W)	**W36**		
Day (D)	**D252**		
Visit Window (d)	±3d		
Treatment:[3]			
Con Meds/Treatments	X	X	X
Efficacy:[1]			
HiSCR, mHSS, HS-PGA, PGA-ISD, IHS4, Hurley Stage	X	X	X
DLQI, HADS, PGI-c, PGI-s, EQ-5D-3L, HSSD, HiSQOL	X	X	X
Patient Diary (daily)		X	X
Safety:[1]			
Vital Signs	X	X	X
Physical Examination	X	X	X
Electrocardiogram		X	
Adverse Events	X	X	X
Laboratory Testing:[1]			
Hematology, Chemistry, Inflammation Markers	X	X	X
Infectious Disease Panel		X	
Urinalysis	X	X	X
Pregnancy Test (WOCBP only)	Urine	Urine/Serum	Serum
PK/PD/ADA:[1]			
PK/ADA, IL-6, PD, biomarker & research samples (serum/plasma)	X	X	X

[1] Assessments/procedures should be conducted in the following order: patient assessments, investigator assessments, safety and laboratory assignments

[2] During an unscheduled visit, any of the study procedures noted may be performed, but not all are required.

[3] Concomitant medications within 30 days before screening until 7 days after the last administration of the study drug must be recorded for the purpose of drug-drug and drug-disease interaction evaluation and signal detection

5.3 DISCONTINUATION OF THERAPY

If a patient is discontinued from study, the reason for discontinuation/withdrawl must be clearly documented in the source documentation and the EDC. Every effort should be made by the investigative site to have subjects who discontinue early from study complete all assessments included in the Early Termination visit included in the study calendar provided in section 5. All subjects will be unblinded after clinical database lock.

Study therapy MUST immediately be discontinued for any the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- Any clinical adverse event, laboratory abnormality, inter-current illness, or clinical progression of disease which, in the opinion of the Principal Investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by the sponsor
- Imprisonment or the compulsory detention for medical treatment.
- Initiating treatment with prohibited therapies (see section 2.9)….

5.4 TRIAL STOPPING RULES

Sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to Sponsor in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If Sponsor terminates the study for safety reasons, Sponsor will immediately notify the investigator by phone and subsequently provide written instructions for study termination.

5.5 EMERGENCY UNBLINDING

Subjects and investigators will be unblinded to their treatment allocation after database lock. In the event of an emergency that would require the investigator to be aware of the treatment allocation prior to the end of the trial, the investigator can obtain this information, on a per subject basis, after consultation with the Sponsor's Medical Monitor, if possible. Every effort should be made to consult with the Medical Monitor prior to emergency unblinding. Events that qualify as emergencies are as follows:

- A grade 3 or greater AE which are "probably or definitely" related to study drug, and only if **treatment assignment information is essential for the management of the event**. This type of reaction would require that the patient receives no further doses, and is followed until the resolution of the toxicity.
- Any suspected, unexpected, serious adverse reaction (SUSAR)
- Pregnancy

6. CORRELATIVE STUDIES

6.1 PHARMACOKINETICS (PK)/ ANTI-DRUG ANTIBODY (ADA)/ PHARMACODYNAMICS (PD)/ BIOMARKER, RESEARCH SAMPLE COLLECTION

Patient blood will be drawn into blood collection tubes at each collection time point per the study protocol for PK/ADA/PD/research analysis. These samples will be processed by the collection lab per the study laboratory flowchart and the obtained plasma/serum will be sent to a central laboratory before being shipped to XBiotech in monthly batches for analysis.

An enzyme-linked immunosorbent assay (ELISA) has been developed and validated to specifically measure bermekimab levels (PK) in human plasma. The PK samples will also be used to test for the presence of treatment-emergent antibodies against bermekimab. XBiotech has developed and validated an ELISA method to measure treatment-emergent ADA. Additionally, samples will be used for pharmacodynamic analysis and exploratory research.

7. ASSESSMENT OF SAFETY

Safety will be assessed by monitoring adverse events, vital signs, and clinical laboratory measurements. Data from ECG will be included in safety analysis only when all of these measures are available for each subject (baseline and last visit). Adverse events will be monitored from visit 1 (week 0) (post-injection) through visit 33 (week 32) as well as during the 4-week follow up period (visit 34 at week 36). Any serious adverse events whether related or not to study drug will be followed up until resolution.

Study drug, bermekimab, will be administered under close observation in a facility equipped to handle anaphylaxis or injection site reactions. Subjects must be closely monitored at the study site at visits 1, 2, 3, 17, 18 & 19 (for the first three injections) until at least 30 minutes following the administration of the antibody. Vital signs and AE assessments will be done at 30 minutes (+/- 10 minutes) post-injection.

Any grade 3 or greater adverse event or injection site reaction must be reported to the sponsor within 24 hours of learning of the event.

8. STUDY VARIABLES

8.1 DEMOGRAPHIC AND DISEASE CHARACTERISTICS

Demographic characteristics will include standard demography (age, sex, race, height, weight, and BMI) medical history, medication history, and prior biologic use for each patient. Characteristics of the patients with hidradenitis suppurativa, including duration of disease, baseline disease severity scores (HiSCR, Modified Hidradenitis Suppurativa Score, Hurley Staging and Hidradenitis Suppurativa Physician's Global Assessment, Physician's Global Assessment of Inflammatory Skin Disease), and baseline patient reported outcomes (PGI-c, PGI-s, NRS Pain, NRS Itch, EQ-5D-3L, HADS, HSSD, HiSQOL, IHS4 and DLQI), will be collected. Baseline is defined as the visit 1 (week 0), pre-injection assessment.

8.2 STUDY ENDPOINTS

Primary Endpoint

- The proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR). For this score patients are defined as achievers or non-achievers. The positive HiSCR score is defined as a ≥ 50% reduction in inflammatory lesion AN count (sum of abscesses and inflammatory nodules), and no increase in abscesses or draining fistulas in HS compared with the lesions counted on visit 1 (week 0)[32].

Secondary Assessments

- Numerical Rating Scale (NRS) for Pain & Itch [take home patient diary]. Patients will be given a diary to complete each night before bed. Patients will be asked to report "average pain", and "worst moment pain" as well as "average itch" and "worst moment itch" on a 0-10 numeric rating scale.
- HS Related Pain Symptom Score in the past 24 hours based on Hidradenitis Suppurativa Symptom Diary (HSSD). HSSD is a 7-item patient self-reported questionnaire that assesses 5 HS-related symptoms including pain, tenderness, hot skin feeling, odor, and itchiness. The participants are asked to rate the severity of each symptom on a 0 to 10 numerical rating scale, with 0 indicating no symptom experience and 10 indicating the worst possible symptom experience.
- Pharmacokinetics (PK) and Interleukin-6 (IL-6). An enzyme-linked immunosorbent assay (ELISA) has been developed to specifically measure bermekimab levels in human plasma. Blood will be drawn into

three 6 ml collection tubes at each research draw collection time point. These samples will be collected per the study lab manual and shipped to the Sponsor for PK and IL-6 analyses. The samples will also be used for various pharmacodynamic (PD), biomarker, and general research analyses. The PK samples will also be used to test for the presence of antibodies against bermekimab. The IL-6 samples will be used to test for change in serum IL-6 levels in patients, which has shown to correlate with disease severity in HS and potentially a more reliable predictor of treatment response in HS patients than CRP[33,34].

- Hidradenitis Suppurativa Physician's Global Assessment (HS-PGA). This is defined as: a) clear when the total number of abscesses is 0, the total number of draining fistulas is 0, the total number of inflammatory nodules is 0 and the total number of non-inflammatory nodules is 0; b) minimal when the total number of abscesses is 0, the total number of draining fistulas is 0, the total number of inflammatory nodules is 0 and there is presence of non-inflammatory nodules; c) mild when the total number of abscesses is 0, the total number of draining fistulas is 0, and the total number of inflammatory nodules is 1-4, or when there is presence of one abscess or draining fistula and absence of any inflammatory nodules; d) moderate when the total number of abscesses is 0, the total number of draining fistulas is 0 and the total number of inflammatory nodules is at least 5; or when there is presence of one abscess or draining fistula and at least one inflammatory nodule; or when there are 2-5 abscesses or draining fistulas and fewer than 10 inflammatory nodules; e) severe when the total number of abscesses or draining fistulas is 2-5 and the total number of inflammatory nodules is at least 10; and f) very severe when there are more than 5 abscesses or draining fistulas[35].
- The modified Hidradenitis Suppurativa score (mHSS). The Sartorius Scale is used to quantify the severity of HS. Points are awarded for 12 body areas (left and right axillae, left and right sub/inframammary areas, intermammary area, left and right buttocks, left and right inguino-crural folds, perianal area, perineal area, and other): points were awarded for nodules (2 points for each); abscesses (4 points); fistulas (4 points); scars (1 point); other findings (1 point); and longest distance between two lesions (2-6 points, 0 if no lesions); and if lesions are separated by normal skin (yes-0 points; no-6 points). The total Sartorius score is the sum of the 12 regional scores.
- Hurley Stage. The Hurley stage is used to qualify the severity of HS. Affected anatomic regions are individually scored. Hurley Stage I is defined as localized formation of single or multiple abscesses without sinus tracts and scarring. Hurley Stage II is defined as recurrent abscesses with sinus tract formation and scarring; single or multiple lesions. Hurley Stage III is defined as diffuse involvement with interconnected tracts and abscesses.
- Dermatology Life Quality Index (DLQI). The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on

QOL. The format is a simple response (0 to 3 where 0 is “not at all” and 3 is “very much”) to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL.

- Hospital Anxiety Depression Scale (HADS). The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient’s emotional state. The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.
- Health Status Questionnaire (EQ-5D-3L). The EQ-5D-3L consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).The EQ-5D-3L descriptive system comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. The patient is asked to indicate his/her health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results into a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the patient’s health state. The EQ VAS records the patient’s self-rated health on a vertical visual analogue scale where the endpoints are labelled ‘Best imaginable health state’ and ‘Worst imaginable health state’. The VAS can be used as a quantitative measure of health outcome that reflects the patient’s own judgement.
- Patient Global Impression of Change (PGI-c). The PGI-c is a single item patient reported outcome that assesses change in severity of skin pain due to HS. Participants will rate how his/her HS has changed since the beginning of the study using a 7-point scale ranging from 1 which indicates "very much better" to 7 which indicates "very much worse" with a neutral center point 4 which indicates ("no change").
- Patient Global Impression of Severity (PGI-s). The PGI-s is a single item patient reported outcome that assesses change in a patient’s impression of their disease severity. The PGI-s item asks the respondent to best describe how his/her HS symptoms are now (*“check the one number that best describes how your HS symptoms are now”*) on a 4-point scale scored as: “normal” (1), “mild” (2), “moderate” (3), or “severe” (4)”.
- HSSD Symptom Scale Score (Other Than Pain in the Past 24 Hours). HSSD is a 7-item patient self-reported questionnaire that assesses 5 HS-related symptoms including pain, tenderness, hot skin feeling, odor, and itchiness. The participants are asked to rate the severity of each symptom on a 0 to 10 numerical rating scale, with 0 indicating no symptom experience and 10 indicating the worst possible

symptom experience. Change from baseline in each individual tenderness, hot skin feeling, odor and itchiness symptom score (rated on a scale of 0-10) will be determined.

- HSSD Total Symptom Score. HSSD is a 7-item patient self-reported questionnaire that assesses 5 HS-related symptoms including pain, tenderness, hot skin feeling, odor, and itchiness. The participants are asked to rate the severity of each symptom on a 0 to 10 numerical rating scale, with 0 indicating no symptom experience and 10 indicating the worst possible symptom experience. All 5 symptoms have a recall period of the past 7 days, except for 2 additional questions on pain which evaluate current pain and pain in the past 24 hours. Each individual symptom scale score, ranging from 0-10 will be summarized. A total symptom score, which will also range from 0-10, will be derived by averaging the 5 individual scale scores that utilize the past 7-day recall period with higher score indicates more severe disease.

Exploratory Assessments

- Hidradenitis Suppurativa Quality of Life Measure (HiSQOL). HiSQOL is an outcome measurement instrument specficially developed for HS. HiSQOL is a patient self-reported questionnaire that assesses various HS-related quality of life measures.
- International Hidradenitis Suppurativa Severity Score System (IHS4). IHS4 is a dynamic severity assessment of HS. IHS4 score is arrived at by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4-10 signifies moderate and 11 or higher signifies severe disease.
- Physician's Global Assessment of Inflammatory Skin Disease (PGA-ISD). The PGA-ISD is a tool developed by the International Dermatology Outcome Measures (IDEOM) organization to serve as a potential standardized outcome measure for assessment of inflammatory skin diseases.

9. ADVERSE EVENTS

9.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including laboratory findings), symptom, or disease temporally associated with the use of bermekimab, whether or not it is apparently related to bermekimab;
- A concurrent illness;
- An exacerbation, or an unexpected increase in frequency or intensity of a preexisting condition,

including intermittent or episodic conditions.

- A significant or unexpected worsening of the condition/indication under investigation.
- A suspected interaction between the investigational drug and concomitant medications
- Any clinically significant laboratory abnormality (including radiological interpretations, histopathological findings, etc.)

9.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Congenital anomaly/ birth defect;
- An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note that seriousness and severity should not be confused. A subject could experience a severe headache that would not qualify as an SAE, while another might experience a mild stroke that, while not severe, would be considered serious.

9.3 RECORDING OF ADVERSE EVENTS

All untoward events occurring between visit 1 (week 0) (post-injection) and the end of study (or if subject terminates from study prior to visit 34 (week 36), five weeks after the last administration of bermekimab) should be recorded on the eCRF, regardless of whether they are considered related to study drug.

All AEs should be recorded in a standard medical terminology as concisely as possible. The AE recorded should not be a procedure or a clinical/laboratory measurement but should reflect the event leading to the

procedure or the cause of the clinical/laboratory abnormality, if known. Whenever possible, AEs should be evaluated and recorded as a diagnosis, rather than individual signs and symptoms. However, if a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Any AE that worsens in intensity, or becomes serious, should be recorded as a new event.

9.4 EVALUATING ADVERSE EVENTS

All AEs will be graded according to the CTCAE version 5.

9.5 ASSESSMENT OF CAUSALITY

Investigators are required to assess the relationship, if any, of each AE or SAE to the investigational drug using clinical judgment to determine the degree of certainty with which an AE can be attributed to the investigational drug. Alternative causes, such as natural history of the underlying disease, other risk factors, and the temporal relationship of the event to the administration of the study medication must be considered.

Relationship to study drug is summarized as follows:

- **Not Related:** There is another obvious cause of the AE
- **Unlikely to be related:** There is another more likely cause of the AE
- **Possibly related:** The AE could have been due to the investigational drug
- **Probably related:** The AE is probably attributable to the investigational drug
- **Definitely related:** The AE is most likely attributable to the investigational drug

9.6 REPORTING REQUIREMENTS

Any grade 3 or greater adverse event and injection site reaction must be reported to the sponsor within 24 hours of learning of the event.

All serious adverse events (SAEs) should be reported to the Sponsor on the initial SAE report forms within 24 hours of knowledge of the event. These immediate reports should be followed promptly by detailed, written reports (follow-up SAE reports). The subject should be followed up with until stabilization of the reported SAE, either with full satisfactory resolution or resolution with sequelae, or until death of the subject. Before declaring the subject is lost to follow-up, three unsuccessful attempts at contact should be made and recorded on the SAE form. The immediate and follow-up reports should identify subjects by unique code numbers (generated by the safety database) assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The Investigator should also submit

SAEs to the IRB/EC according to their IRB/EC guidelines [ICH-GCP E6]. Drug-related Serious Adverse Events will be reported to the FDA by XBiotech's Medical Safety Officer according to 21 CFR 312.32.

9.7 REFERENCE SAFETY INFORMATION: POTENTIAL ADVERSE REACTIONS

More than 900 patients have been treated using bermekimab (either by infusions or subcutaneous injections) in patients with advanced solid tumors, advanced hematologic malignancies, metastatic colorectal cancer, peripheral vascular disease, type II diabetes, acne vulgaris, plaque psoriasis, pyoderma gangrenosum, atopic dermatitis and hidradenitis suppurativa. Repeat dose toxicity in relevant species, safety pharmacology, genotoxicity, carcinogenic potential, and toxicity to reproduction studies have not been performed. A repeat dose toxicity study in mice did not reveal any unspecific toxicity related to bermekimab. Over 5000 doses of bermekimab were administered intravenously (50 mg/mL) at 7.5 mg/kg and over 900 doses of bermekimab were administered subcutaneously with 100 mg/mL and 200 mg/ mL formulations.

Bermekimab is a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α). As such, it is an immunomodulator that has anti-inflammatory and anti-neoplastic properties. Other agents that could be considered in the same pharmacologic class include biologic agents that target IL-1 receptor antagonist and IL-1 beta. Potential risks for agents in this class include infusion or injection site reactions and risk of infection.

Bermekimab is True Human monoclonal antibody derived immune plasma B cells derived from a natural human immune response against IL-1α. Unlike previous generations of humanized or fully human antibodies, the entire bermekimab heavy and light chain sequences are identical to those found in naturally-occurring human IgG1κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual. No *in vitro* affinity maturation or modifications have been made to improve its natural binding affinity (211 +/- 31 pM). We believe that a true human antibody should be effectively non-immunogenic in humans and thus exhibit optimal activity and pharmacokinetics. To date, no treatment emergent anti-drug antibodies specific to bermekimab have been identified.

The mechanism behind infusion or injection site reactions is not well understood. In some cases, it may involve a reaction against the antibody products themselves, particularly where the primary sequence of the antibody has been modified in vitro or is derived from non-human system or, against some minor residual component from the manufacturing process (i.e. host cell proteins). Bermekimab is derived from and has undergone immunological selection in humans, thus anti-bermekimab responses are highly unlikely. To

date, there has been a very low incidence of injection site or infusion reactions observed (27 patients out of 911 total; 3.0%). In order to mitigate this class-specific risk, close monitoring is required during the bermekimab infusion/ injection and for at least 30 minutes after the end of the infusion/ injection for the first 3 doses. Availability of resuscitation equipment must be ensured although this has never been used for any patient in any of our studies. Pre-medication with antihistamines, NSAIDs or corticosteroids is not required but allowed at PI's discretion.

For the purposes of expedited safety reporting in clinical trials, the following should be considered expected events:

- Infusion Related Reactions
- Injection Site Reactions

9.8 TOXICITY MANAGEMENT

Subjects who develop a new infection while undergoing treatment with bermekimab should be monitored closely. Administration of study injections should be interrupted if a subject develops an infection requiring IV anti-infective treatment or if an infection meets the definition of "serious" (refer to Section 9.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE) for definition). Study medication may be restarted once the physician determines that the infection has been successfully treated. Otherwise prohibited concomitant medications may be given if medically necessitated. Specifically, if a patient develops an intercurrent infection, then topical and/or oral antibiotic usage is permitted. If a patient experiences an intercurrent illness associated with pain for which oral analgesia is required, then otherwise-prohibited oral analgesics are permitted. Topical and/or oral antibiotic usage are not permitted for worsening of HS (except as specified in Section 2.11.2 Antibiotic Rescue Therapy. Prior to use, every attempt should be made to contact the Sponsor's Medical Director for direction on re-introduction of bermekimab therapy after prohibited medication administration.

If the subject must undergo elective surgery, the study injections must be interrupted 2 weeks prior to the surgery. If the subject must undergo emergency surgery, the study injections must be interrupted at the time of the surgery. The injectable study medication can recommence at least 2 weeks after surgery once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

10. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol, and to make changes to adapt to unexpected issues in study execution and data that may affect planned analyses. Analysis variables are listed in Section 8.

10.1 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint is percent of patients who have a positive HiSCR score (achiever) at week 12. The positive HiSCR score is defined as a ≥ 50% reduction in inflammatory lesion AN count (sum of abscesses and inflammatory nodules), and no increase in abscesses or draining fistulas in HS compared with the lesions counted at baseline. The sample size is calculated for the bermekimab weekly injection group (Treatment Arm 1) versus placebo group (Treatment Arm 3) comparison (the primary comparison).

Assuming a positive HiSCR score is achieved in 60% of intent-to-treat (ITT) patients treated in the bermekimab weekly injection group (Treatment Arm 1) versus 30% in placebo treated patients (Treatment Arm 3), then, for a randomization ratio of 1:1:1, a sample size of 126 patients (42 in each treatment group) is required for approximately 80% power at a 0.05 significance level using a 2-sided Pearson chi-square test. In order to account for possible dropouts and to provide adequate safety data, approximately 150 patients will be randomized and treated.

10.2 RANDOMIZATION

A centralized block randomization schedule with a 1:1:1 allocation ratio will be utilized using an electronic randomization system. Patients will be randomly assigned to Arms 1, 2, or 3. The randomization schedule will be stratified by two factors: prior biologic use (yes/no) and Hurley Stage (II/III).

10.3 ANALYSIS SETS

- The safety analysis set (SAF) population will consist of all patients who receive at least one dose of study medication and will be analyzed as treated.
- The modified intent-to-treat (mITT) population will consist of all randomized and treated patients.

10.4 PATIENT DISPOSITION

A listing of all patients prematurely discontinued from the study, along with reasons for discontinuation will be provided. In addition, the total number of patients for each of the following categories will be summarized.

- The total number of screened patients: met the inclusion criteria regarding the target indication and signed the informed consent
- The total number of patients in each analysis set (SAF, and mITT populations)
- The total number of patients who complete the study and discontinued the study, and the reasons for discontinuation

10.5 STATISTICAL METHODS

Continuous data will be summarized for each treatment group using the number of observations available (N), means, standard deviation (SD), minimums, medians, and maximums. Categorical data will be summarized for each treatment group using counts and percentages. . All statistical tests will be two-sided unless otherwise noted.

10.5.1 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group.

10.5.2 Safety Analysis

The primary objective of this study is to evaluate the safety and efficacy of bermekimab. Safety endpoints will be evaluated by monitoring adverse events from clinical and laboratory reporting. The safety analysis will be based on the SAF population. A summary of safety results will be presented for each treatment group.

10.5.2.1 Analysis of Adverse Events

Adverse events reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary (version 22.0 or newer). Coding will be to lowest level terms. The verbatim text, the PT, and the primary SOC will be listed in patient listings.

Pre-treatment AEs are defined as those that develop or worsen in severity from the time the patient provides informed consent, prior to the first dose of study drug. Treatment emergent AEs (TEAEs) are defined as AEs that develop or worsen in severity following the first dose of study drug through the last study visit.

TEAEs will be grouped by MedDRA System Organ Class (SOC) and Preferred Term (PT) within SOC and will be presented for each treatment group. The number and percentage of patients experiencing AEs and TEAEs will be summarized by seriousness (SAEs), severity (grades 1-5), and relationship.

10.5.2.2 Other Safety

Vital Signs

Vital sign parameters (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) will be summarized descriptively by treatment group using actual values and change from baseline values.

Laboratory Tests

Clinical laboratory values will be converted to standard international units. Clinical laboratory (as described in the treatment plan) data will be listed for each subject. Laboratory data will be summarized descriptively by treatment group using actual values and change from baseline values. A listing will be provided for patients with grade 2 or greater laboratory AEs.

Electrocardiogram

12-lead ECG status (ie, normal, abnormal, clinically significant) will be summarized descriptively by treatment group.

10.5.3 Efficacy Analysis

In general, efficacy analyses will include all randomized and treated patients (mITT population) and will be analyzed based on the randomized treatment groups, regardless of the treatment they actually received.

In addition to the analyses that will be performed following the formal database lock at the end of the study at Week 36, an additional database lock may be performed at Week 16, and interim analyses utilizing unblinded efficacy data available as the study progresses, may also be conducted to help plan potential future development activities. An internal interim analysis committee (IAC) will be established to review the interim data and formulate recommended decisions/actions. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in study conduct or compound development), one of whom

will chair the committee, and may also include other members as required by the nature of the IAs. Details will be provided in a separate IAC charter, which will define the organization and roles and responsibilities of the committee, possible recommendations or requests, and the communication process following IA reviews. Results from the Week 16 DBL and/or interim analyses will not be disseminated to investigators or subjects participating in the study. In addition, results of the interim analyses will not be disseminated to individuals associated with the conduct of the study.

10.5.3.1 Primary Efficacy Analysis

For the primary efficacy endpoint, the two bermekimab treatment groups will be compared with placebo. To account for these two comparisons, testing will be done in a sequential manner, each at the 0.05 alpha level. The bermekimab weekly injection group (Treatment Arm 1) will be compared to the placebo group (Treatment Arm 3) first. If this test is significant at the 0.05 level, then the bermekimab every other week injection group (Treatment Arm 2) will be compared to the placebo group (Treatment Arm 3). Otherwise, the P-value for Treatment Arm 2 vs Treatment Arm 3 will be considered nominal. This method to control the type-1 error will only be implemented for the primary efficacy analysis variable.

The number and percentage of patients who have a positive HiSCR score (achiever) at week 12 will be presented by treatment group. Patients who terminate from the study early prior to week 12 will count as non-responders (non-achievers) in the primary efficacy analysis (Non-Responder Imputation). If a patient received rescue medication, the patient will be counted as a non-responder from the start of rescue medication. Additional treatment failure rules and sensitivity analyses will be discussed in the statistical analysis plan.

A Cochran-Mantel-Haenszel (CMH) general association test stratified by prior anti-tumor necrosis factor or IL-17 inhibitor therapy use (yes/no) and Hurley Stage (II/III) will be used to compare each bermekimab dose separately with placebo. The primary efficacy analysis population will be the mITT population.

10.5.3.2 Secondary Efficacy Analyses

Secondary efficacy endpoints (NRS pain & itch, HiSCR, mHSS, HS-PGA, PGA-ISD, HADS, DLQI, EQ-5D-3L, PGI-c, PGI-s, HiSQOL, IHS4 and HSSD) will be summarized using descriptive statistics on actual and change from baseline values over time by treatment group. The 95% CI of the mean change from baseline will be provided. The change from baseline in these endpoints at each week will be analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, week, stratification factors (prior anti-tumor necrosis factor, IL-17 inhibitor therapy

use (yes/no) and Hurley Stage (II/III)), baseline score, baseline score by week interaction, and the treatment-by-week interaction, if applicable. The impact of the stratification factors will also be assessed. Hurley Stage, PGI-c, and PGI-s categories will also be summarized descriptively.

Responder analyses will also be performed for select efficacy variables including NRS pain (categorized as ≥30% reduction on pain score among patients with baseline score of ≥3), NRS itch (3 point improvement in patients with ≥3 itch score at baseline as well as 4 point improvement in patient with ≥4 itch score at baseline) at each week. The number and percentage of patients who meet these criteria will be summarized by treatment group. Additional responder analyses may be performed for other efficacy variables. Full details will be provided in the statistical analysis plan.

10.5.4 Pharmacokinetics (PK) and Pharmacodynamics (PD) Analysis

Descriptive statistics of PK and PD concentrations and parameters will be presented.

10.5.5 Treatment Exposure

The number and percentage of patients exposed to study drug along with duration of exposure will be summarized descriptively by treatment group.

11. STUDY MANAGEMENT AND ADMINISTRATION

11.1 ETHICAL CONDUCT OF STUDY (GCP)

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (64th WMA General Assembly, Fortaleza, Brazil, October 2013), the guidelines of ICH GCP E6 (R2), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed. Approval will be obtained from the appropriate regulatory authorities before sites are initiated.

11.2 IRB AND ETHICS COMMITTEE APPROVAL

Prior to initiation of the study, the protocol, the informed consent form, the subject information sheet(s), details of the subject recruitment procedures and any other relevant study documentation will be submitted to the responsible IRB or Ethics Committee (EC). The Investigator will report promptly to the IRB/EC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the

Investigator will submit written summaries of the study status to the IRB/EC annually, or more frequently if requested by the IRB/EC. Upon completion of the study, the Investigator will provide the IRB/EC with a brief report of the outcome of the study, if required.

11.3 PROTOCOL MODIFICATIONS

Modifications of the signed protocol are only possible by approved protocol amendments and with the agreement of all responsible persons. The procedure for approval of a protocol amendment is identical to that for approval of the protocol. The IRB/EC must be informed of all protocol amendments and should be asked for its opinion as to whether a full re-evaluation of the ethical aspects of the study is necessary by the committee. This should be fully documented. The Investigator must not implement any deviation from or change to the protocol, without discussion with an agreement by the study Sponsor and prior review and documented approval/favorable opinion of the amendment from the relevant IRB/EC, except where it is necessary to eliminate an immediate hazard to study subjects, or where the change(s) involves only logistical or administrative aspects of the study (e.g., change in CRA(s), change of telephone number(s)). Protocol amendments will be submitted to the appropriate authority(ies) as required by the applicable regulatory requirement(s).

11.4 SUBJECT INFORMATION AND CONSENT

The Investigator is responsible for ensuring that no subject will receive any study-related examination or activity before that subject has given an IRB/EC approved informed consent. The subject must give written consent after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the subject. The Investigator will inform the subject of the aims, methods, anticipated benefits and potential hazards of the study, including any discomfort it may entail. The subject must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview, the subject may be given time to reflect if this is required, or if the subject requests more time. Subjects and/or legal guardian forms will be kept and archived by the Investigator in the Investigator's study file. It should be emphasized that the subject is at liberty to withdraw their consent to participate at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who refuse to give, or withdraw, written informed consent may not be included or continued in this study, but this will not impact their subsequent care. The Investigator will notify in writing each subject’s primary care physician (or equivalent) of the subject’s intent to participate in the study.

11.5 DATA PROTECTION AND CONFIDENTIALITY

By signing the final protocol, every participating Investigator agrees to keep all information and results concerning the study and the investigational product confidential. The confidentiality obligation applies to all personnel involved at the investigational site. The Investigator must ensure that each participant's anonymity will be maintained in accordance with applicable laws. On eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their name, but by subject ID number. The Investigator should keep a separate log of ID numbers, names and addresses. Documents that contain the names associated with these ID numbers (e.g., written consent/assent forms), are not for submission to the Sponsor and should be maintained by the Investigator in strict confidence except to the extent necessary to allow auditing by regulatory authorities, auditing or monitoring by the Institutional Review Board/EC, the Sponsor personnel or their affiliates and designees (such as CRAs).

Copies of radiological scans and autopsy reports (and other documents), if applicable, that may be requested by the Sponsor should be de-identified. The Investigator shall obtain all such permissions and authorizations as may be necessary or desirable to allow the collection and use of information protected under federal privacy laws and state privacy laws, including permission/authorization for monitoring and analysis (including re-analysis in combination with results of other studies), for regulatory submission purposes and for applicable reporting (if any) required to be made by Sponsor, its affiliates and their designee.

11.6 STUDY REPORT AND PUBLICATIONS

A final integrated clinical/statistical report will be prepared that is compliant with the ICH Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (E3). The results of this study will be published and/or presented at scientific meetings in a timely manner. The publication policy is described in the contract between the Sponsor and Investigator.

11.7 STUDY FILES AND RETENTION OF RECORDS

Copies of all study documents should be retained by the Investigator until at least two 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 two years have elapsed since the formal discontinuation of clinical development of the investigational product, in accordance with 21 CFR 312.62. These documents should be retained for a longer period however, if required by regulatory requirements or by agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when

these documents no longer need to be retained. The final database will be archived according to the regulatory requirements.

11.8 CASE REPORT FORMS

Data for this protocol will be captured electronically in an Electronic Data Capture (EDC) system. Designated study personnel will be provided unique usernames and passwords. Each study personnel will have specific access within the electronic data collection system based on their role. The EDC system contains an audit trail associated with each individual's unique password that will document date and time of data entry and revisions. All protocol-specified data is to be entered into the EDC system in a timely manner for review and audit by XBiotech. All data is to be entered such that it will allow accurate interpretation and tabulation. It is the Investigator's responsibility to ensure that all discontinued orders or changes in study or other medications entered into the database correspond to entries in the subject's medical records (i.e. source documents) and to acknowledge accurate completion of the eCRF.

11.9 DRUG ACCOUNTABILITY

A Drug Dispensing Log must be kept current and should contain the following information:

- Initial inventory upon receipt of supplies at the study site
- Identification number of each subject to whom test drug was administered
- Date(s), quantities, lot numbers and calculations for all test drugs administered
- Final inventory (upon completion of the study)

This inventory must be available for inspection by the Clinical Research Associate. The Investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study medication to the study site, the inventory at the site, the usage for each subject, and destruction. The inventory must be available for monitoring, auditing or inspection. A drug dispensing log must be kept current and should contain the following information:

- The subject identification number to whom the drug is dispensed
- The lot number of the drug dispensed
- The date(s) and the quantity of the drug dispensed to the subject

11.10 INSPECTIONS

Investigator sites, the study database and study documentation may be subject to quality assurance audits during the course of the study either by the Sponsor or their appointed representatives. In addition, regulatory bodies at their discretion may conduct inspections. The Investigator shall permit the authorized Sponsor, agents of the Sponsor, and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all records relating to an investigation, including subject records. The Sponsor will not, however, copy any source data from the patient's dossier. Completed eCRFs must be made available by the Investigator for review by the Sponsor, agents of the Sponsor, the CRA and the regulatory agencies. To ensure the accuracy of data submitted, it is mandatory that representatives of the Sponsor and of the regulatory agencies have direct access to source documents (e.g., subject medical records, charts, laboratory reports, etc.). Subject confidentiality will be protected at all times.

11.11 ACCESS TO INFORMATION FOR MONITORING

CRAs will establish and maintain regular contact between the Investigator and the Sponsor. CRAs will evaluate the competence the study center, informing the Sponsor about any problems relating to facilities, technical equipment or medical staff. During the study, CRAs will check that written informed consent has been obtained from all subjects correctly and that data are recorded correctly and completely. CRAs are also entitled to compare entries in eCRFs with corresponding source data and to inform the Investigator of any errors or omissions. CRAs will also monitor adherence to the protocol at the Investigator site. They will arrange for the supply of investigational product and ensure appropriate storage conditions are maintained. The CRA will make written reports to the Sponsor on each occasion when contact with the Investigator is made, regardless of whether it is by phone or in person. During monitoring visits, entries in the eCRFs will be compared with the original source documents. The Investigator must agree to meet with the CRA at regular intervals and to cooperate in resolving any queries or findings made during the monitoring process.

11.12 STUDY DISCONTINUATION

If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators/institutions and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/EC will also be promptly informed and provided with the reason(s) for the termination or suspension by the Sponsor or by the Investigator or/institution, as specified by the applicable regulatory requirement(s).

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Janssen Research & Development*

Clinical Protocol

COVID-19 Appendix

Protocol Title
A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

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Protocol 77474462HDS2002; Phase 2

JNJ-77474462 (bermekimab)

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Pharmaceutica NV; Janssen Sciences Ireland UC; Janssen Biopharma Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used throughout the protocol to represent these various legal entities; the sponsor is identified on the Contact Information page that accompanies the protocol.

United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

Status: Approved
Date: 27 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-37346 version 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL 77474462HDS2002

GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by patients and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related patient management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government guidelines or requirements or the clinical judgement of the investigator to protect the health and well-being of patients and site staff. If, at any time, a patient's safety is considered to be at unacceptable risk, drug product will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, patients will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Patients will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for patients on drug product, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation between the patient and investigator, and with the agreement of the sponsor (see below).

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a patient has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for drug product and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:

    - remote (eg, by phone / telemedicine) or in-person, off-site (eg, in-home) interactions between site staff (or designees) and patients for study procedures e.g. those related to safety monitoring / efficacy evaluation / drug product storage and administration (including training where pertinent)

    - procurement of drug product by patients (or designee) or shipment of drug product from the study site directly to patients for at home administration (including the potential for self-administration of drug product)

    - laboratory assessments using a suitably accredited local laboratory; for selected measures (eg, urine pregnancy), home testing may be employed

    - other procedures, eg, imaging, may be conducted at an appropriate facility

- Missed assessments/visits will be captured in the case report form (CRF) for protocol deviations. Discontinuations of drug products and withdrawal from the study should be documented with the prefix “COVID-19-related” in the CRF.

    - other relevant study data elements impacted by the pandemic should also be documented / labeled as “COVID-19-related” in CRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.

- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).

- Precaution: for those who may carry a higher risk for severe COVID-19 illness (eg, those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks during participation in the study.

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-77474462 (bermekimab) Clinical Protocol 77474462HDS2002

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the drug product, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

PPD

Signature: _____ Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 27 April 2020

Janssen Research & Development*

Clinical Protocol

COVID-19 Appendix

Protocol Title

A Phase II, Randomized, Double-Blind, Placebo-Controlled Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

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Protocol 77474462HDS2002; Phase 2

JNJ-77474462 (bermekimab)

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Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

PPD PPD
Reason: I agree to the terms defined by the placement of my signature on this document
Date: 2020.04.27 13:54:26 -04'00'

Signature: _____ Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

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Status: Approved, Date: 27 April 2020