

# Trial Protocol

A Phase II, Open Label Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

## SPONSOR

XBiotech USA Inc

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## Table of Contents

<b>BASIC INFORMATION</b> .....	<b>4</b>
<b>INVESTIGATOR/SPONSOR SIGNATURES</b> .....	<b>5</b>
<b>CLINICAL PROTOCOL SYNOPSIS</b> .....	<b>6</b>
<b>ABBREVIATIONS</b> .....	<b>10</b>
<b>1. BACKGROUND</b> .....	<b>11</b>
1.1 OVERVIEW .....	11
1.2 RATIONALE .....	12
<b>2. INVESTIGATIONAL PRODUCT</b> .....	<b>14</b>
2.1 ACTIVE INGREDIENT, PHARMACOLOGIC CLASS, STRUCTURE .....	14
2.2 DRUG PRODUCT (BERMEKIMAB 200 MG/ML) DESCRIPTION.....	16
2.3 STORAGE.....	17
2.4 STABILITY.....	17
2.5 METHOD OF ADMINISTRATION .....	17
2.6 AGENT ORDERING.....	19
2.7 POTENTIAL DRUG INTERACTIONS.....	19
2.8 PROHIBITED AND RESTRICTED THERAPIES .....	19
<b>3. STUDY DESIGN AND OBJECTIVES</b> .....	<b>19</b>
3.1 STUDY ENDPOINTS .....	20
<b>4. ELIGIBILITY CRITERIA</b> .....	<b>21</b>
4.1 INCLUSION CRITERIA .....	21
4.2 EXCLUSION CRITERIA .....	22
<b>5. TREATMENT PLAN</b> .....	<b>23</b>
5.1 STUDY PROCEDURES .....	23
5.2 STUDY CALENDAR.....	33
5.3 DISCONTINUATION OF THERAPY.....	34
5.4 TRIAL STOPPING RULES.....	34
5.5 PATIENT CROSSOVER RULES .....	34
<b>6. CORRELATIVE STUDIES</b> .....	<b>35</b>
<b>6.1 PHARMACOKINETICS (PK) SAMPLE COLLECTION</b> .....	<b>35</b>
<b>7. ASSESSMENT OF SAFETY</b> .....	<b>35</b>
<b>8. STUDY VARIABLES</b> .....	<b>35</b>
8.1 DEMOGRAPHIC AND DISEASE CHARACTERISTICS .....	35
8.2 STUDY ENDPOINTS .....	36
<b>9. ADVERSE EVENTS</b> .....	<b>37</b>
9.1 DEFINITION OF ADVERSE EVENT (AE) .....	37
9.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE) .....	38
9.3 RECORDING OF ADVERSE EVENTS .....	38
9.4 EVALUATING ADVERSE EVENTS .....	39
9.5 ASSESSMENT OF CAUSALITY .....	39
9.6 REPORTING REQUIREMENTS .....	39
9.7 REFERENCE SAFETY INFORMATION: POTENTIAL ADVERSE REACTIONS .....	40

<b>10. STATISTICAL PLAN.....</b>	<b>41</b>
10.1 STATISTICAL HYPOTHESIS.....	41
10.2 DETERMINATION OF SAMPLE SIZE.....	41
10.3 ANALYSIS SETS .....	42
10.3.1 SAFETY ANALYSIS SETS.....	42
10.4 PATIENT DISPOSITION .....	42
10.5 STATISTICAL METHODS .....	42
10.5.1 DEMOGRAPHY AND BASELINE CHARACTERISTICS .....	42
10.5.2 SAFETY ANALYSIS .....	43
10.5.3 ANALYSIS OF SECONDARY ENDPOINTS: .....	44
10.5.4 PHARMACODYNAMICS (PK) ANALYSIS: .....	44
10.5.5 TREATMENT EXPOSURE.....	45
<b>11. STUDY MANAGEMENT AND ADMINISTRATION.....</b>	<b>45</b>
11.1 ETHICAL CONDUCT OF STUDY (GCP).....	45
11.2 IRB AND ETHICS COMMITTEE APPROVAL.....	45
11.3 PROTOCOL MODIFICATIONS .....	46
11.4 SUBJECT INFORMATION AND CONSENT.....	46
11.5 DATA PROTECTION AND CONFIDENTIALITY .....	46
11.6 STUDY REPORT AND PUBLICATIONS.....	47
11.7 STUDY FILES AND RETENTION OF RECORDS .....	47
11.8 CASE REPORT FORMS.....	48
11.9 DRUG ACCOUNTABILITY .....	48
11.10 INSPECTIONS.....	48
11.11 ACCESS TO INFORMATION FOR MONITORING.....	49
11.12 STUDY DISCONTINUATION.....	49
<b>REFERENCES.....</b>	<b>50</b>

## Basic Information

**STUDY TITLE:** A Phase II, Open Label Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

**INVESTIGATIONAL PRODUCT:** Bermekimab

**IND NUMBER:** 112,459

**PROTOCOL NUMBER:** 2018-PT045

**PROTOCOL VERSION / DATE:** 3.1/ August 30<sup>th</sup>, 2018

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## Investigator/Sponsor Signatures

**STUDY TITLE:** A Phase II, Open Label Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

**STUDY PRINCIPAL 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, Open Label Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa

**Sponsor:**

XBiotech USA, Inc.

**Study Chair:**

Alice Gottlieb, M.D., Ph.D.

**Sample Size:**

20 Subjects

**Approximate Duration:** The duration of subject participation is approximately 16 weeks, including a 3 week screening period, and a 13 week treatment period.

**Study Objectives:**

**Primary Endpoint(s):**

- Safety and Tolerability

**Secondary Endpoints:**

- Hidradenitis Suppurativa Clinical Response (HiSCR) from baseline (visit 1) to visit 13.
- Assessment of Pharmacokinetics (PK)
- Change in patient reported outcomes from baseline (visit 1) to visit 13 (VAS for disease, VAS for pain, DLQI).
- Change in Physician's Global Assessment (PGA), Disease Activity Score, and modified Sartorius score from baseline (visit 1) to visit 13.
- Change in inflammatory lesion (abscesses and inflammatory nodules) count from baseline (visit 1) to visit 13.
- Change from baseline (visit 1) to visit 13 in Hospital Anxiety Depression Scale (HADS).

**Trial Design\*****A Phase II, Open Label Study of Bermekimab in Patients with Moderate to Severe Hidradenitis Suppurativa**

- Group A (n=10): patients that have failed anti-TNF therapy will receive a total of 13 X 400mg weekly subcutaneous injections of bermekimab.
- Group B (n=10): patients that have no prior treatment with biological agents that block TNF will receive a total of 13 X 400mg weekly subcutaneous injections of bermekimab.

\*Restricted medications may be administered once during the study to alleviate acute exacerbation for HS symptoms.

**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  $\geq 18$  years.
- For group A, patients must have received and failed anti-TNF therapy. For group B, subjects must not have received any prior treatment with any anti-TNF therapy.
- Patients who have received 200mg dose of Bermekimab in this study are eligible to begin receiving 400mg dose starting with the patient's next scheduled visit for the remainder of his/her treatment plan.
- 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 (AN) 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.

**Exclusion Criteria:**

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

- Age below 18 years.
- Receipt of oral antibiotic treatment for HS within 28 days prior to screening.
- Receipt of prescription topical therapies for the treatment of HS within 14 days prior to screening, and/or systemic therapies for HS (immunosuppressants, corticosteroids, retinoids, or hormonal therapies) within 28 days prior to screening.
- History of treatment with bermekimab for any reason EXCEPT patients previously treated with 200mg bermekimab dose in the previous version(s) of this study.
- History of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies.
- Has received a live (attenuated) vaccine over the 4 weeks prior to screening.
- New intake of opioid analgesics starting within 14 days prior to screening.
- 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  $\gamma$ -glutamyl transpeptidase ( $\gamma$ GT) or of total bilirubin  $> 3x$  upper normal limit.
- 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<sup>3</sup>.
- Pregnancy or lactation.

## Abbreviations

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
HIV	Human immunodeficiency virus
IFN- $\gamma$	Interferon Gamma
IGA	Investigator's Global Assessment
IgG	Immunoglobulin G
IL-1 $\alpha$	Interleukin-1 $\alpha$
IL-1 $\beta$	Interleukin-1 $\beta$
IL-1 RA	Interleukin-1 receptor antagonist
IRB	Institutional review board
PK	Pharmacokinetics
PGA	Physicians Global Assessment
pI	Isoelectric Point
SAE	Serious Adverse Event
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-1 $\alpha$  with high affinity and is an effective blocker of IL-1 $\alpha$  biological activity. IL-1 $\alpha$  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-1 $\alpha$  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-1 $\alpha$  (IL-1 $\alpha$ ). The entire bermekimab heavy and light chain sequences are identical to those found in naturally-occurring human IgG1 $\kappa$ , 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 several different dose levels and dosing schedules. Both intravenous and subcutaneous formulations have been explored for safety and evidence of efficacy.

Three phase 2 studies sponsored by XBiotech have been completed in dermatologic indications (acne, psoriasis and pyoderma gangrenosum), along with one investigator sponsored study in Hidradenitis Suppurativa<sup>1,2,3</sup>. 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). In both of these trials, there were few adverse events, which were all 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 study enrolled patients with moderate to severe HS that were refractory to or not eligible for treatment with TNF blocking agents. The study was double blind, randomized

and placebo controlled, and utilized the Hidradenitis Suppurativa Clinical Response (HiSCR) score as a primary endpoint. Ten patients were randomized to placebo and 10 patients to treatment with bermekimab. A positive HiSCR score after 12 weeks was found in one (10%) and six (60%) patients respectively (OR: 13.50; 95%CIs: 1.19-152.61; p: 0.035). After withdrawal of therapy at week 12, a positive HiSCR score was found in nil (0%) of the placebo group and four (40%) of the treated patients after 24 weeks (p: 0.043).

Endogenous anti-IL-1 $\alpha$  antibodies are present in 5% to 28% of the general population<sup>4,5,6,7</sup>. No negative correlations with disease have been noted for these individuals. To the contrary, the presence of natural anti-IL-1 $\alpha$  antibodies has been associated with favorable outcomes, both with respect to rheumatoid arthritis and ischemic heart disease. Animal studies also indicate that IL-1 $\alpha$  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-1 $\alpha$  represents a safe treatment approach.

## 1.2 Rationale

Hidradenitis suppurativa (HS) is a common disorder affecting areas of the skin rich in apocrine glands. HS typically starts at adolescence. The clinical course is characterized by exacerbations and remissions of flare-ups. During these flare-ups the affected gland becomes swollen and then ruptures, with the discharge of purulent material. 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. As the disease progresses, fistulas are formed under the dermis. These fistulas often suppurate continuously<sup>8</sup>. 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<sup>9</sup>.

HS is a common disorder. Its prevalence in Europe is 0.97%<sup>3</sup> whereas in Denmark this figure is reported to be 4%<sup>4</sup>. A recent review of electronic records in the United States revealed an incidence of 11.4 per 100,000 in the general population incidence<sup>10</sup>. The incidence was 2.5 times higher among African Americans than among white Americans<sup>11</sup>.

Based on findings showing high expression of tumor necrosis factor-alpha (TNF $\alpha$ ) in the lesions of patients<sup>12</sup>, 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<sup>13</sup>. 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<sup>14</sup>. 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 TNF $\alpha$  in their lesions, whereas others have lesions better characterized by the production of cytokines like interleukin (IL)-1 $\beta$  and IL-1 $\alpha$ <sup>15</sup>. 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-1 $\beta$  and IL-1 $\alpha$ ). A positive HiSCR score was achieved in 30% and 78% of patients, respectively (p: 0.039)<sup>16</sup>. 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.

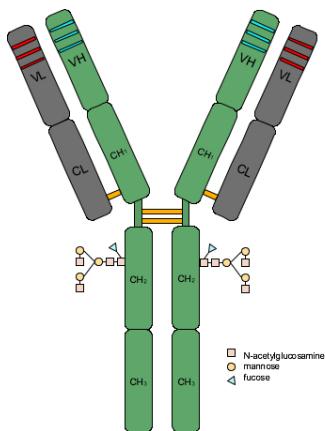
An investigator initiated phase II RCT trial among patients not eligible for adalimumab (EudraCT number 2015-002321-20; ClinicalTrials.gov NCT02643654) was recently completed and showed promising results for activity of bermekimab in HS. Twenty patients with severe HS and with either primary or secondary failure of previous antiTNF 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)<sup>17</sup>.

In previous dermatology studies bermekimab was well tolerated and showed impressive therapeutic activity. Dose ranging for the subcutaneous formulation of bermekimab is now being studied in a 12 week open label treatment regimen for HS in order to establish the basis for further randomized studies using subcutaneous administration.

## 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-1 $\alpha$  (IL-1 $\alpha$ ). The entire bermekimab heavy and light chain sequences are identical to those found in naturally-occurring human IgG1 $\kappa$ , 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 2.1: 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<sub>1</sub> 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<sub>2</sub> domains are glycosylated primarily with the oligosaccharide structure shown in Figure 2.1, 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<sup>18</sup>.

The entire bermekimab heavy and light chain sequences are identical to those found in naturally-occurring human IgG1 $\kappa$ , 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-1 $\alpha$  antibody has been reported in 5% to 28% of healthy serum or plasma samples<sup>19,20</sup>. It has been measured in cord blood, children and adults<sup>21</sup>. The anti-IL-1 $\alpha$  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<sup>22</sup>. Binding affinities reported for endogenous anti-IL-1 $\alpha$  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. The drug product is packaged in pre-filled syringes. The syringes used are OMPI EZ-Fill Nexa, 2.25mL 27G,  $\frac{1}{2}$  inch length needle, or a comparable alternative. The syringe is clear borosilicate type 1 glass containing 2mL of the formulation and is sealed using a West 1-3mL Novapure piston (plunger) with Flurotec coating. The needle is an AISI 304 stainless steel thin wall device. Drug product in syringes is stored at 5 $\pm$ 3°C and is recommended to be protected from light.

Up to 6 syringes will be packaged in each carton.

### Composition Drug Product 200mg/mL in 2 mL syringes

Ingredient	Ingredient Function	Grade	Manufacturer	Concentration	Amount per 2 mL syringe
Bermekimab Antibody	Active Substance	GMP	XBiotech USA Inc.	200 mg/mL	400 mg
Trehalose Dihydrate	Tonicity	GMP, USP/NF, EP, low endotoxin	Ferro-Pfanstiehl (USA)	60 mg/mL	120 mg
Sodium Phosphate Dibasic	pH Buffering Capacity	GMP, EP, USP	JT Baker (USA)	12 mg/mL	24 mg
Citric Acid Monohydrate	pH Buffering Capacity	GMP, EP, USP, BP, JP	Fisher (USA)	2 mg/mL	4 mg
Water for Injection	Solvent	GMP, EP, USP	Irvine Scientific (USA)	q.s.	q.s.

Phosphoric Acid	pH adjustment	GMP, EP, USP	JT Baker (USA)	pH adjustment	pH adjustment
Sodium Hydroxide,	pH adjustment	GMP, EP, USP	JT Baker (USA)	pH adjustment	pH adjustment

## 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 METHOD OF ADMINISTRATION

Patients in Groups A and B will receive 400 mg administered weekly by subcutaneous injection. Each injection should be located 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. 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

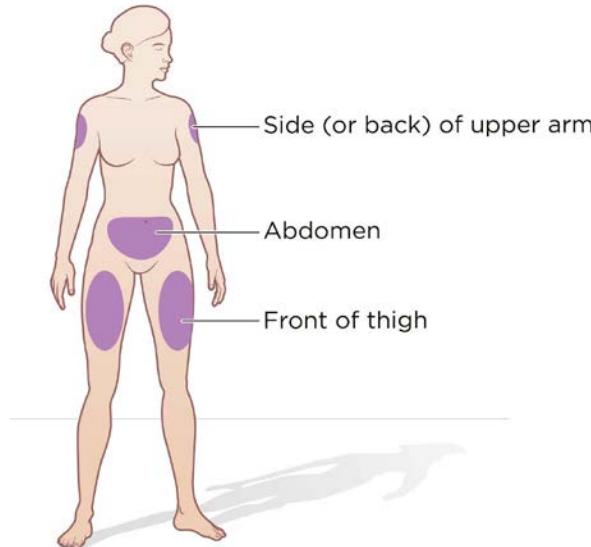
### Injection Site

Determine Injection site, *see illustration below:*

**Abdomen, at least 2 inches away from the belly button**, is the recommended injection site for patients with a body mass index (BMI) **below 30**. (This measurement is calculated at Screening.)

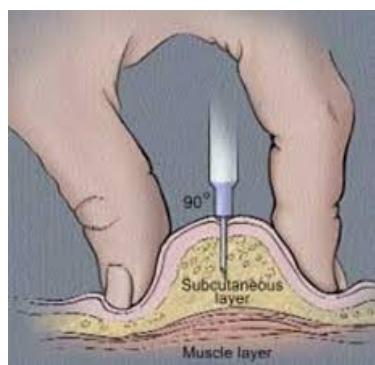
**Front Thigh or Upper Arm** is the recommended injection site for patients with a BMI of **30 or more**.

*(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 (see illustration below).



- Insert needle as illustrated above
- 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*).

## **2.6 AGENT ORDERING**

The Responsible Investigational Pharmacy will order study drug from XBiotech as needed.

## **2.7 POTENTIAL DRUG INTERACTIONS**

There are no known drug interactions with bermekimab. In controlled trials that combined the use of IL-1ra (anakinra) with TNF alpha inhibitors, a higher incidence of serious infection was noted. Bermekimab has not been administered concomitantly with these agents in clinical trials. However, due to potential risk, it is not recommended that bermekimab be used in combination with anti-TNF agents.

## **2.8 PROHIBITED AND RESTRICTED THERAPIES**

Treatment with certain restricted concomitant medications is allowed once during study to treat acute HS exacerbation, including:

- Systemic therapies with known effectiveness in HS, including corticosteroids, retinoids, or anti-androgen (hormonal) therapies.
- Intralesional/topical steroids
- Laser/light therapies

The use of rescue medications for worsening HS is to be reported in the electronic data capture system. A second flare up of disease and subsequent use of a second rescue therapy for any patient will result in the patient being treated as a non-responder for the purposes of data analysis.

The following concomitant therapies are *prohibited* for the entire duration of the trial:

- Biologics that target IL-1 or TNF-alpha
- Live virus vaccines
- Investigational agents other than bermekimab

## **3. STUDY DESIGN AND OBJECTIVES**

Phase 2, Open label, multicenter study of two dose cohorts of bermekimab in patients naïve to or having failed prior anti-TNF therapy with moderate to severe Hidradenitis Suppurativa. Bermekimab administered subcutaneously at a dose of 400 mg weekly (13 doses). Patients will be followed for 13 weeks to allow for assessment of safety and preliminary efficacy.

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](http://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:***

- Safety and Tolerability

#### ***Secondary Endpoints:***

- Hidradenitis Suppurativa Clinical Response (HiSCR) from baseline (visit 1) to visit 13.
- Assessment of Pharmacokinetics (PK)
- Change in patient reported outcomes from baseline (visit 1) to visit 13 (VAS for disease, VAS for pain, DLQI).
- Change in Physician's Global Assessment (PGA), Disease Activity Score, and modified Sartorius score from baseline (visit 1) to visit 13.
- Change in inflammatory lesion (abscesses and inflammatory nodules) count from baseline (visit 1) to visit 13.
- Change from baseline (visit 1) to visit 13 in Hospital Anxiety Depression Scale (HADS).

## 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  $\geq 18$  years.
- For group A, patients must have received and failed anti-TNF therapy. For group B, subjects must not have received any prior treatment with any anti-TNF therapy.
- Patients who have received 200mg dose of bermekimab in this study are eligible to begin receiving 400mg dose starting with the patient's next scheduled visit for the remainder of his/her treatment plan.
- 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 (AN) 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.

#### 4.2 EXCLUSION CRITERIA

Subjects will be excluded from the study if they meet any of the following criteria:

- Age below 18 years.
- Receipt of oral antibiotic treatment for HS within 28 days prior to screening.
- Receipt of prescription topical therapies for the treatment of HS within 14 days prior to screening, and systemic therapies for HS (immunosuppressants, corticosteroids, retinoids, or hormonal therapies) within 28 days prior to screening.
- History of treatment with bermekimab for any reason EXCEPT patients previously treated with 200mg bermekimab dose in the previous version(s) of this study.
- History of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies.
- Administration of any live (attenuated) vaccine over the last 4 weeks.
- New intake of opioid analgesics starting within 14 days prior to screening.
- Major surgery (requiring general anesthesia or respiratory assistance) within 28 days prior to visit 1, Day 0 of start of study drug.
- Hepatic dysfunction defined as any value of transaminases, of  $\gamma$ -glutamyl transpeptidase ( $\gamma$ GT) or of total bilirubin  $> 3 \times$  upper normal limit
- Stage C Child-Pugh liver cirrhosis.
- Chronic infection by the human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).
- Neutropenia defined as  $<1,000$  neutrophils/mm<sup>3</sup>.
- Pregnancy or lactation.

## 5. TREATMENT PLAN

### 5.1 STUDY PROCEDURES

**Screening (maximum 21 days):** The screening period begins once the informed consent is signed.

- Informed Consent
- Demographics
- Medical History
- Concomitant Medications
- Physical Exam
- Vital Signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Height
- Weight
- Body Mass Index (BMI) [BMI= weight (kg)/height (m<sup>2</sup>)]
- Blood Draw:
  - Chemistry panel: Albumin, Alkaline Phosphatase, ALT, AST, GGT, Bicarbonate (CO<sub>2</sub>), Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen
  - Hematology Panel: Complete Blood Count (CBC) with differential and platelets
  - Infectious disease screening: HIV antibody, Hepatitis C antibody, Hepatitis B panel (HBsAg, anti-HBc, anti-HBs), and interferon gamma release assay (IGRA)
  - Serum pregnancy test for WOCBP
  - Inflammation Markers: CRP (C-Reactive Protein), ESR (Erythrocyte Sedimentation Rate)

Visit 1 (day 0, must occur within 21 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
  - Physical Exam
  - DLQI

- Urine pregnancy
- HISCR
- PGA
- Disease Activity Score
- Modified Sartorius
- HADS
- VAS for disease
- VAS for pain
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Blood draw for PK and biomarker analysis
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

Visit 2 (day 7 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Urine pregnancy
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

## Visit 3 (day 14 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Physical Exam
  - DLQI
  - Urine pregnancy
  - HISCR
  - PGA
  - Disease Activity Score
  - Modified Sartorius
  - HADS
  - VAS for disease
  - VAS for pain
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
  - Blood draw for chemistry, hematology, CRP, ESR and blood draw for PK and biomarker analysis
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

## Visit 4 (day 21 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Urine pregnancy
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)

- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

Visit 5 (day 28 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Physical Exam
  - DLQI
  - Urine pregnancy
  - HISCR
  - PGA
  - Disease Activity Score
  - Modified Sartorius
  - HADS
  - VAS for disease
  - VAS for pain
  - Blood draw for chemistry, hematology, CRP, ESR and blood draw for PK and biomarker analysis
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

## Visit 6 (day 35 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Urine pregnancy
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

## Visit 7 (day 42 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Physical Exam
  - DLQI
  - Urine pregnancy
  - HISCR
  - PGA
  - Disease Activity Score
  - Modified Sartorius
  - HADS
  - VAS for disease
  - VAS for pain
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)

- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

Visit 8 (day 49 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Urine pregnancy
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

Visit 9 (day 56 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Physical Exam
  - DLQI
  - Urine pregnancy
  - HISCR
  - PGA
  - Disease Activity Score
  - Modified Sartorius

- HADS
- VAS for disease
- VAS for pain
- Blood draw for chemistry, hematology, CRP, ESR and blood draw for PK and biomarker analysis
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

Visit 10 (day 63 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Urine pregnancy
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

Visit 11 (day 70 +/-2):

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

- Physical Exam
- DLQI
- Urine pregnancy
- HISCR
- PGA
- Disease Activity Score
- Modified Sartorius
- HADS
- VAS for disease
- VAS for pain
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

Visit 12 (day 77 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
  - Urine pregnancy
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reaction
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

## Visit 13 (day 84 +/-2):

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre Injection
  - Physical Exam
  - DLQI
  - Urine pregnancy
  - HISCR
  - PGA
  - Disease Activity Score
  - Modified Sartorius
  - HADS
  - VAS for disease
  - VAS for pain
  - Blood draw for chemistry, hematology, CRP, ESR and blood draw for PK and biomarker analysis
  - Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Bermekimab subcutaneous injection, in accordance with injection site determined by BMI at Screening
- 1 hour monitoring for injection reactions
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- Adverse event monitoring
- Concomitant medications/treatments

## Visit 14 (day 91 +/-2):

- Physical Exam
- DLQI
- HISCR
- PGA
- Disease Activity Score
- Modified Sartorius

- HADS
- VAS for disease
- VAS for pain
- Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- Adverse event monitoring
- Concomitant medications/treatments

## 5.2 STUDY CALENDAR

Visit	Screen	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Study Day		0 ± 2	7 ± 2	14 ± 2	21 ± 2	28 ± 2	35 ± 2	42 ± 2	49 ± 2	56 ± 2	63 ± 2	70 ± 2	77 ± 2	84 ± 2	91 ± 2
Informed Consent	x														
Demographics	x														
Medical/ Surgical History	x														
Infectious Disease Panel+ (part of blood draw)	x														
Serum Pregnancy (part of blood draw)	x														
Height, Weight, Body Mass Index (BMI)	x														
Vital Signs <sup>△</sup>	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine Pregnancy		x	x	x	x	x	x	x	x	x	x	x	x	x	x
PK & Biomarker Blood Draw		x		x		x				x					x
Bermekimab Injection♦		x	x	x	x	x	x	x	x	x	x	x	x	x	x
DLQI		x		x		x		x		x		x		x	x
HADS		x		x		x		x		x		x		x	x
Physical Exam	x	x		x		x		x		x		x		x	x
Lab Blood Draw <sup>a,b,c</sup>	x		x		x					x				x	
HiSCR		x		x		x		x		x		x		x	x
PGA		x		x		x		x		x		x		x	x
Disease Activity Score		x		x		x		x		x		x		x	x
Modified Sartorius		x		x		x		x		x		x		x	x
VAS for disease		x		x		x		x		x		x		x	x
VAS for pain		x		x		x		x		x		x		x	x
Adverse Events		x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medications*	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

<sup>a</sup>Chemistry Panel including: Albumin, Alkaline Phosphatase, ALT, AST, GGT, Bicarbonate (CO<sub>2</sub>) Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen

<sup>b</sup>Hematology Panel including: Complete whole blood (WBC, HgB, Platelet, differential)

<sup>c</sup> CRP (C-Reactive Protein) and ESR (Erythrocyte Sedimentation Rate)

+ HIV antibody, Hepatitis C antibody, Hepatitis B panel (HBsAg, anti-HBc, anti-HBs), and interferon gamma release assay (IGRA)

△ Vital signs include blood pressure, pulse, oxygen saturation, respiratory rate and body temperature

♦ Each bermekimab injection will be followed by 1 hour monitoring for injection site reaction and vital signs 1 hour post injection (70+- 10 minutes)

\* 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.

**BMI:** Body Mass Index [BMI= weight (kg)/height (m<sup>2</sup>)]

**DQLI:** Dermatology Quality of Life Index

**HiSCR:** Hidradenitis Suppurativa Clinical Response Score

**PGA:** Physicians' Global Assessment

**VAS:** Visual Analogue Scale

**HADS:** Hospital Anxiety Depression Scale

### **5.3 DISCONTINUATION OF THERAPY**

If a patient is discontinued from study, the reason for discontinuation must be clearly documented in the source documentation and the EDC.

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.

### **5.4 TRIAL STOPPING RULES**

Enrollment of any further patients for the trial will be suspended for the following events:

- The death of a subject at any time during the trial that is deemed to be probably or definitely related to the administration of bermekimab.
- Any significant safety finding assessed as definitely related to bermekimab that in the opinion of an Investigator warrants stopping the trial for additional assessment of safety.
- The occurrence of 2 or more serious adverse events occurring in one patient that are probably or definitely related to the administration of bermekimab.

### **5.5 PATIENT CROSSOVER RULES**

Patients enrolled in the 200mg dose study are eligible to receive 400mg bermekimab injections upon consent to this protocol. Upon consent, patients will begin 400mg bermekimab dosing at next Study Day Visit, following patient calendar so that total number of bermekimab injections, 200mg + 400mg, is equal to 13 at end of study.

## 6. CORRELATIVE STUDIES

### 6.1 PHARMACOKINETICS (PK) SAMPLE COLLECTION

An enzyme-linked immunosorbent assay (ELISA) has been developed to specifically measure bermekimab levels in human plasma. Blood will be drawn into a single 6 ml collection tube at each PK collection time point (sample collection is pre-dose at visit 1, visit 3, visit 5, visit 9 and visit 13). These samples will be collected per the study lab manual and immediately shipped to the Sponsor for PK analysis. The PK samples will also be used to test for the presence of antibodies against bermekimab.

## 7. ASSESSMENT OF SAFETY

Safety will be assessed by monitoring adverse events, vital signs, physical examinations, and clinical laboratory measurements. All subjects will be included in the safety analysis. Adverse events will be monitored from visit 1 (post-injection) through visit 14. Any serious adverse events or grade 2 or greater probably or definitely related events will be followed up until resolution.

Study drug will be administered under close observation in a facility equipped to handle anaphylaxis. Subjects must be closely monitored until at least 1 hour following the administration of the antibody or 1 hour after their vital signs have stabilized.

Any AE (with the exception of worsening HS symptoms or injection site reactions) of grade 2 or higher must be reported to the sponsor within 24 hours of learning of the event. Any grade 3 or greater 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 Sartorius score, and physician's global assessment), baseline inflammatory lesion counts (abscesses and inflammatory nodules), and baseline patient reported

outcomes (VAS for pain, VAS for disease severity, and DLQI), will be collected. Baseline is defined as the visit 1, pre-injection assessment.

## 8.2 Study Endpoints

The primary endpoint of this study is the safety and tolerability of bermekimab at 400 mg weekly subcutaneous dose.

The secondary endpoints include:

- Hidradenitis Suppurativa Clinical Response (HiSCR) score (baseline to visit 13). For this score patients are defined as achievers or non-achievers. The positive HiSCR score is defined as a  $\geq 50\%$  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<sup>23</sup>. The HiSCR score, including inflammatory lesion count, will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.
- Pharmacokinetics (PK) (baseline to visit 13). An enzyme-linked immunosorbent assay (ELISA) has been developed to specifically measure bermekimab levels in human plasma. Blood will be drawn into a single 6 ml collection tube at each PK collection time point (sample collection is pre-dose at visit 1, visit 3, visit 5, visit 9 and visit 13). These samples will be collected per the study lab manual and immediately shipped to the Sponsor for PK analysis. The PK samples will also be used to test for the presence of antibodies against bermekimab.
- Physician's Global Assessment (PGA) (baseline to visit 13). 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<sup>24</sup>. The PGA will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.

- Disease Activity Score (baseline to visit 13). This is defined as the sum of scores of all affected areas of each patient. Each area will be evaluated by the following formula: (multiplication of the two largest diameters in each affected area in mm) x (the degree of inflammation of each lesion). This score has been proposed by our study group<sup>25</sup>. The Disease Activity Score will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.
- The modified Sartorius score (baseline to visit 13). 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. The modified Sartorius score will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.
- Change in AN count (baseline to visit 13). The sum of abscesses and inflammatory nodules for each patient will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.
- Change in VAS for Disease Severity and Pain (baseline to visit 13). Patient reported visual analogue scales for pain and disease severity will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.
- Change in Dermatology Life Quality Index (DLQI) (baseline to visit 13). This will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.
- Change in Hospital Anxiety Depression Scale (HADS) (baseline to visit 13). This will be measured on visits 1, 3, 5, 7, 9, 11, 13 and 14.

Changes in secondary endpoints will be presented by individual cohort, as well as combined across both cohorts.

## 9. ADVERSE EVENTS

### 9.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event is defined as any untoward medical occurrence in a subject participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical or biological agent under study. 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)**

A serious adverse event is defined as any untoward medical occurrence that meets any of the following criteria:

- Results in death;
- Life-threatening;
- Requires or prolongs inpatient hospitalization;
- Results in a persistent or significant disability;
- An important medical event that, while it may not result in death or be immediately life-threatening or require/prolong hospitalization, may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

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 and visit 14 (or if subject terminates from study prior to visit 14, seven days after the last administration of bermekimab) 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 4.03.

#### **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 AE (with the exception of worsening HS symptoms or injection site reactions) of grade 2 or higher must be entered into the eCRF within 24 hours of learning of the event. Any grade 3 or greater 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 within 24 hours of knowledge of the event. These immediate reports should be followed promptly by detailed, written reports. The subject should be followed up 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 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**

831 patients have been treated using bermekimab in patients with advanced solid tumors, advanced hematologic malignancies, metastatic colorectal cancer, peripheral vascular disease, type II diabetes, acne vulgaris, plaque psoriasis, and pyoderma gangrenosum. Over 1200 doses of bermekimab were administered at 7.5 mg/kg to refractory, metastatic CRC patients with cancer associated symptoms at baseline (ECOG performance status 1 and 2). In this trial (PT026), which is the largest controlled trial completed with bermekimab to date (N=309), patients were dosed at 7.5 mg/kg for metastatic colorectal cancer. The most common AEs reported (>10%) were abdominal pain, peripheral edema, fatigue, anemia, constipation, decrease in weight, asthenia, decreased appetite, and nausea. The majority of these events were grade 1 or 2 and appeared to be related to the underlying CRC. The prevalence of these events was similar in the bermekimab and placebo groups. Two infusion reactions were reported in this trial, and they were not serious or severe (grade I or II).

Bermekimab is a recombinant human IgG1 monoclonal antibody specific for human interleukin-1 $\alpha$  (IL-1 $\alpha$ ). 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 considered to be a True Human monoclonal antibody. 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 IgG1 $\kappa$ , 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 reactions is not clear in all cases. It may involve a reaction against the antibody products themselves, or, against some minor residual component from the manufacturing process (i.e. host cell proteins). To date, there has been a very low incidence of injection site or infusion reactions observed (20 patients out of 831 total; 2.4%). All except two of these patients had grade 1 or 2 reactions that did not result in discontinuation. In order to mitigate this class-specific risk, close monitoring is required during the bermekimab infusion and for at least 1 hour after the end of the infusion. Availability of resuscitation equipment must be ensured. Pre-medication with antihistamines or corticosteroids is not required.

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

- Infusion Related Reactions
- Injection Site Reactions

## **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 Statistical Hypothesis**

No formal hypothesis tests will be performed for the primary endpoints.

### **10.2 Determination of Sample Size**

The sample size chosen was one of convenience, and no formal sample size calculations were performed.

## 10.3 Analysis Sets

### 10.3.1 Safety Analysis Sets

The safety analysis set (SAF) consists of all patients that receive at least one dose of study medication and will be analyzed as treated.

The secondary endpoints will be analyzed based upon the SAF, as well as the per protocol population (PP). The per protocol population will consist of those patients that complete both the baseline (visit 1) and visit 13 assessments of their hidradenitis (HISCR, PGA, Modified Sartorius, VAS, and DLQI).

## 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 enrolled patients: met all inclusion/exclusion criteria and receive at least one dose of therapy
- The analysis sets (SAF, PP)
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients prematurely discontinued from treatment, along with 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. Missing data will not be categorized in the summaries.

### 10.5.1 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. Continuous variables will be summarized with mean, median, SD, minimum, and maximum. Categorical variables will be summarized with frequency and percentage.

## 10.5.2 Safety Analysis

The primary objective of this study is to evaluate the safety and tolerability of 400mg dose 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 defined as all subject who received at least one dose of study medication. 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 21.0 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 percent of subjects reporting at least one adverse event by PT will be summarized across groups A & B. The number and percentage of patients experiencing AEs and TEAEs will be summarized by seriousness (SAEs), severity (grades 1-5), SOC, and PT.

### 10.5.2.2 Other Safety

#### Vital Signs

Summaries of vital sign parameters by treatment dose cohort will include:

- Each vital sign parameter (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) and change from baseline
- The number (n) and percentage (%) of patients with grade 2 or greater vital sign AEs
- Listings will be provided with flags indicating the AE grade

#### Laboratory Tests

Clinical laboratory values will be converted to standard international units. Clinical laboratory (hematology and chemistry) data will be listed for each subject. Laboratory data will be summarized by treatment group. Values outside the normal reference range will be flagged as high or low on the listings. Summaries of

laboratory variables by treatment group will include:

- Each laboratory result and change from baseline
- The number (n) and percentage (%) of patients with grade 2 or greater laboratory AEs

#### **10.5.3 Analysis of Secondary Endpoints:**

Proportion of patients achieving a positive Hidradenitis Suppurativa Clinical Response (HiSCR) score after 13 weeks will be summarized by treatment group (and pooled overall population). The corresponding 95% confidence interval (CI) for the point estimate will be provided. Subjects previously enrolled in the 200mg/weekly dosing cohort who have received *two or fewer* bermekimab injections (2 x 200mg doses) before beginning the 400mg weekly doses will be included for data analysis together with those receiving all doses at 400mg/weekly. Patients who have received more than 2 bermekimab injections of 200mg may enter the 400mg/week arm; however, only patients who have received *two or fewer* bermekimab injections will be included in the data analysis.

Change in outcomes from baseline to week 13 (VAS for disease, VAS for pain, DLQI, inflammatory lesion count, PGA, Disease Activity Score, and modified Sartorius score) will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum value). The 95% CI of the mean change from baseline will be provided.

A rank-ordered analysis will be performed for the total abscess and inflammatory nodule count (ranked at 0, 1 or 2) and reduction in pain score (categorized as  $\geq 30\%$  reduction on pain score among patients with baseline score of  $\geq 3$ ). The change in modified Sartorius score will be dichotomized at 4 ( $\leq 4$  least severe disease, higher indicates severe disease). Number and percent under each treatment group (and pooled overall) will be summarized.

#### **10.5.4 Pharmacodynamics (PK) analysis:**

Descriptive statistics of PK parameters will be presented in a table format. The summary will include average bermekimab concentration at visit cycles along with the standard deviation and coefficient of variation (CV).

### **10.5.5 Treatment Exposure**

The duration of exposure during the study will be presented by treatment and calculated as:

$$(\text{Date of last study drug injection} - \text{date of first study drug injection}) + 7$$

The number (%) of patients exposed to study drug will be presented by specific time periods for each treatment group. The time periods of interest will be specified in the SAP.

In addition, duration of exposure during the study will be summarized for each treatment group using number of patients, means, SD, minimums, medians, and maximums.

A summary of the number of doses, and dose volume by treatment arm will be provided.

## **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 (48th General Assembly, Somerset West, Republic of South Africa, October 1996), the guidelines of ICH GCP (CPMP/ICH/135/95), 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 (CPMP/ICH/137/95). 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 user names 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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