Trial Protocol

A Phase II, Open Label, Dose Escalation Study of Bermekimab (MABp1) in Patients with Moderate to Severe Atopic Dermatitis

SPONSOR

XBiotech USA Inc

22 August 2018

Basic Information

STUDY TITLE: A Phase II, Open Label, Dose Escalation Study of Bermekimab (MABp1) in Patients with Moderate to Severe Atopic Dermatitis

INVESTIGATIONAL PRODUCT: Bermekimab (MABp1)

IND NUMBER: **112,459**

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Investigator/Sponsor Signatures

STUDY TITLE: A Phase II, Open Label, Dose Escalation Study of Bermekimab (MABp1) in Patients with Moderate to Severe Atopic Dermatitis

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.

Mark Williams M.D., MBA, Medical Director

_____
Signature

_____
Date

Clinical Protocol Synopsis

Study Title: A Phase II, Open Label, Dose Escalation Study of Bermekimab (MABp1) in Patients with Moderate to Severe Atopic Dermatitis

Sponsor:

XBiotech USA, Inc.

Study Chair:

Francisco Armando Kerdel M.D

Sample Size:

29 Subjects

Approximate Duration: The study duration of subject participation is approximately 10 weeks, including a 2 week screening period, a 7 week treatment period, and 1 week follow up period.

Study Objectives:

Primary Endpoint(s):

- Safety and Tolerability

Secondary Endpoints:

- Change in Eczema Area and Severity Index Score (EASI) from baseline to visit 8
- Assessment of Pharmacokinetics (PK)
- Patients (%) achieving Investigator's Global Assessment (IGA) Response (0 or 1) at visit 8
- Patients (%) achieving ≥2 IGA Score Reduction at visit 8
- Change (%) for peak weekly averaged pruritus and pain numerical rating scores (NRS) from baseline to visit 8
- Change in weekly averaged peak NRS from baseline to visit 8
- Change in SCORing Atopic Dermatitis (SCORAD) score from baseline to visit 8
- Patients (%) achieving 50% or greater reduction in EASI Score from baseline at visit 8
- Patients (%) achieving 50% or greater reduction in SCORAD Score at visit 8
- Change (%) in Patient Oriented Eczema Measure (POEM) Scores from baseline to visit 8
- Changes in Global Individual Signs Score (GISS) from baseline to visit 8
- Change from baseline to visit 8 in Dermatology Life Quality Index (DLQI)
- Change from baseline to visit 8 in Hospital Anxiety Depression Scale (HADS)

- Change (%) from pre- and post- injection of Visit 1 Questionnaire for pruritus, pain and erythema

Trial Design:
Phase 2, Open label, Dose Escalation Study of Bermekimab (MABp1) in Patients with Moderate to Severe Atopic Dermatitis.

Group A (n=9): patients will receive a total of 4 X 200mg subcutaneous injections of bermekimab. Dosing will occur weekly from visit 1 to visit 4.

Group B (n=20): patients will receive a total of 8 X 400mg subcutaneous injections of bermekimab. Dosing will occur weekly from visit 1 to visit 8.

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
- Age ≥18 years
- Chronic Atopic Dermatitis present for at least 3 years
- Disease is not responsive to topical medications, or for whom topical treatments are not indicated or desired
- Willing and able to comply with all clinic visits and study-related procedure
- EASI score ≥16 at screening and baseline visits
- IGA score ≥3 at screening and baseline visits
- ≥10% body surface area (BSA) of AD involvement at screening and baseline visits
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable or undesired

Exclusion Criteria:

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

- Treatment with an investigational drug within 8 weeks of baseline visit
- Having received the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment:
  a. Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
  b. Phototherapy for AD
- Treatment with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) within 1 week before the baseline visit
- Initiation of treatment during the screening period with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit)
- Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit
- History of severe allergic or anaphylactic reactions to monoclonal antibodies
- Administration of any live (attenuated) vaccine within 4 weeks prior to the baseline
- Any history of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: patients may be rescreened after infection resolves
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per investigator judgment
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
- Positive with hepatitis B surface antigen (HBsAg) or hepatitis C antibody at the screening visit
- Presence of skin comorbidities that may interfere with study assessments

- Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to, patients with short life expectancy, patients with uncontrolled diabetes (HbA1c ≥ 9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepatobiliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc.)
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
- Where relevant, women unwilling to use adequate birth control

Abbreviations

AD	Atopic Dermatitis
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 counts
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
EASI	Eczema Area and Severity Index Score
EC	Ethics Committee
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
GISS	Global Individual Signs Score
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
HIV	Human immunodeficiency virus
IFN-γ	Interferon Gamma
IGA	Investigator's Global Assessment
IGRA	Interferon Gamma Release Assay
IgG	Immunoglobulin G
IL-1 α	Interleukin-1 α
IL-1β	Interleukin-1 β
IL-1 RA	Interleukin-1 receptor antagonist
IRB	Institutional review board
NRS	Pruritus numerical rating score
POEM	Patient Oriented Eczema Measure
pI	Isoelectric Point
PK	Pharmacokinetics
SAE	Serious Adverse Event
SCORAD	Severity Scoring of Atopic Dermatitis
TB	Tuberculosis
TCI	Topical calcineurin inhibitor
TCS	Topical corticosteroid
ULN	Upper limit of normal
UV	Ultraviolet
VAS	Visual Analogue 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 is bermekimab, 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.

Three phase 2 studies sponsored by XBiotech have been completed in dermatologic indications (acne, psoriasis, pyoderma gangrenosum), as well as 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). 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 adalimumab. 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 bermekiamb. 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%) and four (40%) patients after 24 weeks (p: 0.043).

Endogenous anti-IL-1α antibodies are present in 5% to 28% of the general population[4,5,6,7]. 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 other strategies to block IL-1 activity suggest that bermekimab's targeting of IL-1α represents a safe treatment approach.

1.2 RATIONALE

Atopic dermatitis (AD) is an inflammatory skin disease affecting as much as 20% of the population in western industrial societies. Chronic eczema in AD and associated pruritus can be a significant cause of morbidity and impact life quality. Disease pathogenesis is complex but ultimately converges on a pathological inflammatory process that disrupts the protective barrier function of the skin.

The prototypical inflammatory cytokine interleukin-1 alpha (IL-1α) plays a key role in the pathophysiology of a wide range of inflammatory skin disorders[8]. Bermekimab is a natural human antibody that exhibits immunoregulatory activity through blocking IL-1α activity. Keratinocytes are a major reservoir of IL-1α and may be a key source of inflammatory stimulus in AD. IL-1α is present on leukocytes, where its role in leukocyte trafficking and infiltration may represent a key step in the chronic inflammation of AD. IL-1α is a key inducer of matrix metalloproteinases activity which could be directly involved in the epithelial barrier breakdown in AD[9]. Loss of regulation of IL-1 results in systemic inflammation with extensive skin involvement[10].

In previous dermatology studies bermekimab was well tolerated and showed impressive therapeutic activity. Dose ranging of the subcutaneous formulation of bermekimab is now being studied in a 6 week open label treatment regimen for AD in order to establish the basis for further randomized studies.

2. INVESTIGATIONAL PRODUCT

2.1 ACTIVE INGREDIENT, PHARMACOLOGIC CLASS, STRUCTURE

The active ingredient in the drug product is bermekimab, 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 2.1: Bermekimab Antibody
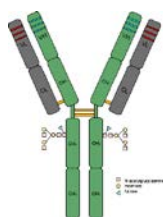
The bermekimab primary glycoform has a molecular weight of 148.1 kilodaltons. Like all IgG1 molecules, the heavy chains are joined at their hinge regions through two disulfide linkages, and each heavy chain is joined to one light chain through one disulfide linkage between their CH_1 and CL domains respectively.

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 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[11].

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[12,13]. It has been measured in cord blood, children and adults[14]. 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[15]. Binding affinities reported for endogenous anti-IL-1α antibodies, ranging from 4 to 16 pM, are comparable to that for bermekimab, the specification for which is 22 to 260 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 100 MG/ML) DESCRIPTION

XBiotech's dosage form is a sterile liquid formulation of 100 mg/mL bermekimab in a stabilizing isotonic subcutaneous formulation buffer at pH 6.2-6.5.   Each 2-mL Type I borosilicate glass serum vial contains 2 mL of the formulation and is sealed with a 13-mm Daikyo Flurotec butyl rubber stopper and flip-off aluminum seal. The exact composition of the Drug Product is shown in the table below.

Composition of Drug Product [100 mg/mL]

Ingredient	Ingredient Function	Grade	Manufacturer	Concentration	Amount per 2mL vial
Bermekimab Antibody	Active Substance	GMP	XBiotech USA Inc.	100 mg/mL	200 mg
Trehalose Dihydrate	Tonacity	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 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 pre-filled syringes used are OMPI EZ-Fill Nexa, 2.25mL 27G ½ needle, or a comparable alternative. The barrel of the syringe is clear glass borosilicate type 1 with AISI 304 stainless steel thin wall needle containing 2mL of the formulation and is sealed with West 1-3mL Novapure piston (plunger) with Flurotec coating.

Composition Drug Product [200mg/mL]

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

2.4 STORAGE

The recommended storage condition is 2-8°C. **Product should be warmed to room temperature approximately 45-60 minutes prior to injection.

2.5 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 and aggregation, as well as 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 100 mg/ml and 200 mg/ml drug product is labeled with a 12-month retest date. Every lot of both the 100/200mg/ml dosage forms is also subjected to ongoing stability analysis per ICH guidelines.

2.6 METHOD OF ADMINISTRATION

The dose of bermekimab for Group A is 200 mg (2ml of the 100 mg/ml formulation) and for Group B is 400 mg (2ml of the 200 mg/ml formulation) administered weekly by subcutaneous injection.

* 45-60 minutes prior to injection, remove the pre-filled syringe from refrigeration and allow it to 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).
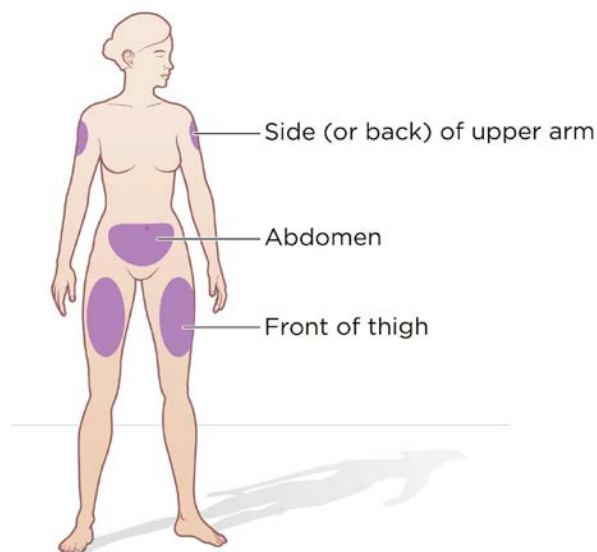
Injection

- Put on gloves

- Wipe injection site clean with alcohol pads

- Raise a fold of skin between the thumb and forefinger (see illustration below).
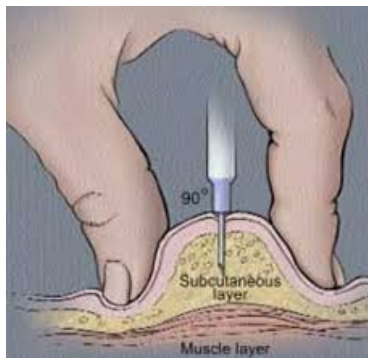
- Insert needle as illustrated above

- 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*).

2.7 ORDERING OF STUDY DRUG

Drug may be ordered from the sponsor as needed.

2.8 POTENTIAL DRUG INTERACTIONS

There are no known drug interactions with the IL-1 antagonist bermekimab. In controlled trials that combined the use of IL-1ra (anakinra), an IL-1 antagonist, together 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 or other IL-1 antagonists.

2.9 CONCOMITANT MEDICATIONS AND PROCEDURES

Any treatment (including nutritional supplements) or procedure administered from the time of consent to the end-of-study visit (visit 9) is considered concomitant and will be recorded in the case report form (CRF). This includes permitted medications ongoing at the time of consent and throughout the study. Concomitant procedures are allowed with the exception of those listed in section 2.9.1.

2.9.1 Prohibited and Restricted Therapies

Treatment with the following concomitant medications is prohibited through visit 9:

- Treatment with a live (attenuated) vaccine.
- Treatment with an investigational drug (other than bermekimab).
- Treatment with TCS or TCI
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

Study drug will be discontinued if any of the following are used through visit 9:

- Treatment with a live (attenuated) vaccine
- Treatment with an investigational drug (other than dupilumab)
- Treatment with systemic corticosteroids or non-steroidal systemic immunosuppressive drugs (eg, cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

NOTE: If a patient receives treatment with systemic corticosteroids or other systemic immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate mofetil, azathioprine, etc.), study treatment will be immediately discontinued.

The following concomitant procedures are prohibited during study participation:

- Major elective surgical procedures
- Phototherapy
- Tanning in a bed/booth

2.9.2 Permitted Medications and Procedures

Other than the prohibited medications listed in section 5.9.1, treatment with concomitant medications is permitted during the study. This includes basic skin care (cleansing and bathing, including bleach baths), emollients (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications for any duration. Medications used to treat chronic disease such as diabetes, hypertension, and asthma are also permitted; if there is any question regarding whether a concomitant medication may be used during the study, the study site should contact the medical monitor.

3. STUDY DESIGN AND OBJECTIVES

Phase 2, open label, dose escalation study of two dose cohorts of bermekimab in patients with moderate to severe atopic dermatitis. The study is multicenter, and will consist of two dose levels: Bermekimab administered subcutaneously at a dose of 200 mg weekly (4 doses) and bermekimab administered subcutaneously at a dose of 400 mg weekly (8 doses). Patients taking the 200mg dose will be followed for 5 weeks (6 visits, day 35 +/-2), and patients taking the 400mg dose will be followed for 8 weeks (9 visits, day 56 +/-2) to allow for assessment of safety and preliminary efficacy.

Dose escalation details can be found in Section 5.3.

The protocol of the study 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:
- Safety and Tolerability

Secondary Endpoints:
- Change in Eczema Area and Severity Index Score (EASI) from baseline to visit 8

    EASI score will assess severity and extent of AD with respect to erythema, excoriation, infiltration and lichenification at 4 anatomic sites of the body: lower and upper extremities, trunk and head. The total EASI score shall be in a range (from 0 to 72 points (from no disease to maximum disease severity, respectively).

- Patients (%) achieving Investigator's Global Assessment (IGA) Response (0 or 1) at Visit 8

    IGA assesses disease severity and clinical response using a 5-point scale: 0 = clear; 1 = almost clear; 2 = mild; 3 = moderate; 4 = severe. The score is determined by ranking the extent of erythema and papulation/infiltration. A clinical response to therapy will be an IGA score of 0 (clear) or 1 (almost clear). Patients receiving more than one treatment with additional medication to treat AD exacerbation during the study or missing IGA scores at Visit 8 will be treated as non-responders.

- Patients (%) achieving ≥2 IGA Score Reduction at Visit 8
- Pharmacokinetics (PK) Assessment

    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 Na-Heparin collection tube at each PK collection time point (sample collection is pre-dose at visit 1, visit 3, visit 5, and visit 8). 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.

- Change (%) for peak weekly averaged pruritus numerical rating scores (NRS) from baseline to visit 8

1. The NRS rating system captures the intensity of patient's itch and pain over a 24-hour period. The following question will be presented to patients: "how would a participant rate his or her itch at the worst moment and on average during the previous 24 hours (scale 0 - 10 [0 = no itch; 10 = worst possible itch])?" and "how would you rate your pain on average during the previous 24 hours [0 = no pain; 10 = severe pain])?

- Change in weekly averaged peak NRS from baseline to visit 8
- Change in SCORing Atopic Dermatitis (SCORAD) score from baseline to visit 8

  SCORAD was developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index) as a measure of disease severity in AD. It includes assessment of the eczema in addition to patient reported symptoms. Total score ranges from 0 to 103 (no disease to most severe disease, respectively).

- Patients (%) achieving 50% or greater reduction in EASI Score from baseline to Visit 8
- Patients (%) achieving 50% or greater reduction in SCORAD Score to Visit 8
- Change (%) in Patient Oriented Eczema Measure (POEM) Scores from baseline to Visit 8

  POEM is a 7-item is a patient reported quality of life outcome measure based on a questionnaire to determine disease symptoms, including bleeding, cracking, dryness, flaking, itching, sleep loss and weeping. The scoring range is from 0 to 28 (no disease to most severe disease, respectively).

- Changes in Global Individual Signs Score (GISS) from baseline to visit 8

  GISS assesses AD lesions for erythema, excoriations, lichenification and edema/papulation. Each component will be rated on a global basis (over the entire body surface rather than by region) using a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe) according to the EASI grading severity. Total score will range from 0 to 12 (no disease to most severe disease, respectively).

- Change from baseline to visit 8 in Dermatology Life Quality Index (DLQI)
- Change from baseline to visit 8 in Hospital Anxiety Depression Scale (HADS)
- Change (%) from pre- and post- injection of Visit 1 Questionnaire for pruritus, pain and erythema

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
- Age ≥18 years
- Chronic Atopic Dermatitis present for at least 3 years
- Disease is not responsive to topical medications, or for whom topical treatments are not indicated or desired
- Willing and able to comply with all clinic visits and study-related procedure
- EASI score ≥16 at screening and baseline visits
- IGA score ≥3 at screening and baseline visits
- ≥10% body surface area (BSA) of AD involvement at screening and baseline visits
- Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications or for whom topical treatments are otherwise medically inadvisable or undesired

4.2 EXCLUSION CRITERIA

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

- Treatment with an investigational drug within 8 weeks of baseline visit
- Having received the following treatments within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment:
    a. Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-γ, Janus kinase inhibitors, azathioprine, methotrexate, etc.)
    b. Phototherapy for AD
- Treatment with topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) within 1 week before the baseline visit
- Initiation of treatment during the screening period with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit)
- Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit
- History of severe allergic or anaphylactic reactions to monoclonal antibodies
- Administration of any live (attenuated) vaccine within 4 weeks prior to the baseline
- Any history of dysplasia or history of malignancy (including lymphoma and leukemia) other than a successfully treated non-metastatic cutaneous squamous cell carcinoma, basal cell carcinoma or localized carcinoma in situ of the cervix
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit. NOTE: patients may be rescreened after infection resolves
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution: or unusually frequent, recurrent, or prolonged infections, per investigator judgment
- History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
- Positive with hepatitis B surface antigen (HBsAg) or hepatitis C antibody at the screening visit
- Presence of skin comorbidities that may interfere with study assessments

- Severe concomitant illness(es) that, in the investigator's judgment, would adversely affect the patient's participation in the study. Examples include, but are not limited to, patients with short life expectancy, patients with uncontrolled diabetes (HbA1c $\geq$ 9%), patients with cardiovascular conditions (eg, stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepato-biliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc.), other severe endocrinological, gastrointestinal, metabolic, pulmonary or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc.)
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
- Where relevant, women unwilling to use adequate birth control

5. TREATMENT PLAN

5.1 STUDY PROCEDURES

Screening

The screening period begins once the informed consent is signed (Max 14 days).

- ➢ Informed Consent
- • Demographics
- • Medical History
- • Concomitant Medications/Treatments
- • Physical Examination
- • Vital Signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
- • Height
- • Weight
- • Body Mass Index (BMI) [BMI= weight (kg)/height (m^2)]
- • EASI
- • IGA
- • SCORAD
- • Blood Draw, 21mL:
  - o Chemistry panel: Albumin, Alkaline Phosphatase, ALT, AST, GGT, Bicarbonate (CO2) Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen, 8.5 mL blood
  - o Hematology Panel: Complete Blood Count (CBC) with differential and platelets, 4.0 mL blood
  - o Infectious disease screening: HIV antibody, Hepatitis C antibody, Hepatitis B panel (HBsAg, anti-HBc, anti-HBs), and interferon gamma release assay (IGRA), 8.5 mL blood
  - o Serum pregnancy test for WOCBP, 8.5 mL blood
- • Pruritus/Pain NRS: the baseline level of itching and pain will be recorded. Patients will be given a study diary that has the NRS (0-10 scale) for days 0 to 35. The patient will be instructed to complete the scale daily (three questions, each on a 0-10 scale). The patient should bring this diary to all subsequent visits for review by the site staff.

<u>Visit 1 (Day 0)</u>

- ➢ *At least 45 minutes before injection*: When using pre-filled syringes, remove syringe from

  refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
  - o Concomitant medications/treatments
  - o Urinalysis
  - o Electrocardiogram (ECG) (patient should be supine for at least 5 minutes prior to performating ECG)
  - o DLQI
  - o Urine pregnancy
  - o EASI
  - o IGA

- o HADS
- o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
- o SCORAD
- o POEM
- o GISS
- o Blood draw:
    - ▪ PK and Biomarker Analysis, 6mL
- o Visit 1 Questionnaire, Part 1: Pruritus, Pain and Erythema
- o 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

Post bermekimab subcutaneous injection
- ➢ 1 hour monitoring post-injection
    - o Injection reaction
    - o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
    - o Visit 1 Questionnaire, Part 2: Pruritus, Pain and Erythema—data from this form must be recorded one hour post-injection (70 +/- 10 minutes)
- ➢ Adverse event monitoring

Visit 2 (Day 7 +/-2)
- ➢ ***At least 45 minutes before injection***: When using pre-filled syringes, remove syringe from

    refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
- o Concomitant medications/treatments
- o DLQI
- o Urine pregnancy
- o EASI
- o IGA
- o HADS
- o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
- o SCORAD
- o POEM
- o GISS
- o 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

Post bermekimab subcutaneous injection
- ➢ 1 hour monitoring post-injection
    - o Injection reaction
    - o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- ▪ Adverse event monitoring

Visit 3 (Day 14 +/-2)

➢ *At least 45 minutes before injection*: When using pre-filled syringes, remove syringe from

refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
- o Concomitant medications/treatments
- o DLQI
- o Urine pregnancy
- o EASI
- o IGA
- o HADS
- o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
- o SCORAD
- o POEM
- o GISS
- o Blood draw:
  - ▪ chemistry and hematology, 12.5mL
  - ▪ PK and Biomarker Analysis, 6mL
- o 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

Post bermekimab subcutaneous injection
- ➢ 1 hour monitoring post-injection
  - o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- ▪ Adverse event monitoring

Visit 4 (Day 21 +/-2)

➢ *At least 45 minutes before injection*: When using pre-filled syringes, remove syringe from

refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
- o Concomitant medications/treatments
- o Urinalysis
- o DLQI
- o Urine pregnancy
- o EASI
- o IGA
- o HADS
- o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
- o SCORAD
- o POEM
- o GISS
- o 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

Post bermekimab subcutaneous injection
- ➢ 1 hour monitoring post-injection
  - o Injection reaction
  - o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- ➢ Adverse event monitoring

Visit 5 (day 28 +/-2)

- ➢ ***At least 45 minutes before injection***: When using pre-filled syringes, remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
- o Concomitant medications/treatments
- o Physical Examination
- o DLQI
- o Urine pregnancy
- o EASI
- o IGA
- o HADS
- o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
- o SCORAD
- o POEM
- o GISS
- o Blood draw:
  - ▪ chemistry and hematology, 12.5mL
  - ▪ PK and Biomarker Analysis, 6mL
- o 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

Post bermekimab subcutaneous injection
- ➢ 1 hour monitoring post-injection
  - o Injection reaction
  - o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
- ▪ Adverse event monitoring

Visit 6 (day 35 +/-2)

- ➢ ***At least 45 minutes before injection***: When using pre-filled syringes, remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
- o Concomitant medications/treatments

o DLQI
o Urine pregnancy
o EASI
o IGA
o HADS
o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
o SCORAD
o POEM
o GISS
o 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

Post bermekimab subcutaneous injection
➢ 1 hour monitoring post-injection
    o Injection reaction
    o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
➢ Adverse event monitoring

Visit 7 (day 42 +/-2)

➢ ***At least 45 minutes before injection***: When using pre-filled syringes, remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
    o Concomitant medications/treatments
    o DLQI
    o Urine pregnancy
    o EASI
    o IGA
    o HADS
    o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
    o SCORAD
    o POEM
    o GISS
    o 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

Post bermekimab subcutaneous injection
➢ 1 hour monitoring post-injection
    o Injection reaction
    o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
➢ Adverse event monitoring

Visit 8 (day 49 +/- 2)

➢ *At least 45 minutes before injection*: When using pre-filled syringes, remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat

Pre-injection
- o Concomitant medications/treatments
- o Urinalysis
- o Electrocardiogram (ECG) (patient should be supine for at least 5 minutes prior to performating ECG)
- o Physical Examination
- o DLQI
- o Urine pregnancy
- o EASI
- o IGA
- o HADS
- o Pruritus/Pain NRS: data from patient diary to be recorded at this time if available
- o SCORAD
- o POEM
- o GISS
- o Blood draw:
    - ▪ chemistry and hematology, 12.5mL
    - ▪ PK and Biomarker Analysis, 6mL
- o 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

Post bermekimab subcutaneous injection
➢ 1 hour monitoring post-injection
- o Injection reaction
- o Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature) one hour post injection (70 +/- 10 minutes)
▪ Adverse event monitoring

Visit 9 (56 +/- 2)

➢ Concomitant medications/treatments
➢ DLQI
➢ Physical Examination
➢ EASI
➢ IGA
➢ HADS
➢ Pruritus/Pain NRS: patient diary to be retained and data to be recorded
➢ SCORAD
➢ POEM
➢ GISS
➢ Vital signs (blood pressure, pulse, oxygen saturation, respiratory rate and body temperature)
➢ Adverse Event Monitoring

5.2 STUDY CALENDAR

Visit	Screen	1	2	3	4	5	6	7	8	9
Study Day		0	7 ±2	14 ± 2	21± 2	28 ± 2	35 ± 2	42 ± 2	49 ± 2	56 ± 2
Informed Consent	x									
Demography, Height, Weight[f]	x									
Medical History	x									
Infectious Disease Panel✢	x									
IGRA[e]	x									
Serum Pregnancy	x									
Physical Examination	x					x			x	x
Urinalysis▲		x			x				x	
Electrocardiogram (ECG)£		x							x	
Visit 1 Questionnaire✦		x								
Vital Signs[+]	x	x	x	x	x	x	x	x	x	x
Urine Pregnancy		x	x	x	x	x	x	x	x	
Blood Draw	x^{ab}	x^{c}		x^{abc}		x^{abc}			x^{abc}	
Bermekimab Injection❖		x	x	x	x	x	x	x	x	
EASI	x	x	x	x	x	x	x	x	x	x
IGA	x	x	x	x	x	x	x	x	x	x
SCORAD	x	x	x	x	x	x	x	x	x	x
DLQI		x	x	x	x	x	x	x	x	x
Pruritus/pain NRS[d]		x	x	x	x	x	x	x	x	x
POEM		x	x	x	x	x	x	x	x	x
GISS		x	x	x	x	x	x	x	x	x
HADS		x	x	x	x	x	x	x	x	x
Adverse Events		x	x	x	x	x	x	x	x	x
Concomitant Meds/Treatments✶	x	x	x	x	x	x	x	x	x	x

[a] Chemistry Panel including: Albumin, Alkaline Phosphatase, ALT, AST, GGT, Bicarbonate (CO2) Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen

[b] Hematology Panel including: Complete whole blood (WBC, HgB, Platelet, differential)

[c] Blood draw for PK and Biomarker analysis

[d] Data from patient diary for the previous 7 days to be recorded at this time.

[e] Interferon gamma release assay

[f] BMI will be calculated at this visit using height and weight

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

▲ Urinalysis will assess pH, protein, glucose, and blood cells

£ A standard 12-lead ECG will be performed. The ECG strips and/ or reports will be retained with the source documentation.

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

[+] Vital signs include blood pressure, pulse, oxygen saturation, respiratory rate and body temperature

✦ Assessment of patients Pruritus, Pain and Erythema will be recorded twice [once pre-injection, once post-injection of bermekimab] during visit 1.

✶ 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^2)]
IGRA: Interferon Gamma Release Assay
DLQI: Dermatology Life Quality Index
EASI: Eczema Area and Severity Index Score
IGA: Investigator's Global Assessment
NRS: Numerical Rating Scores
SCORAD: Severity Scoring of Atopic Dermatitis
POEM: Patient Oriented Eczema Measure
GISS: Global Individual Signs Score
HADS: Hospital Anxiety Depression Scale

5.3 DOSE ESCALATION RULES

The sponsor will review safety data for all patients after the last patient in Group A has completed the week 4 visit or discontinued for any reason other than DLT. The sponsor will initiate escalation to the Group B dosing cohort after confirmation that no safety signals are identified and no study stopping rules have been met.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 will be used to grade the severity of adverse events.

- Any AE (with the exception of worsening AD symptoms or injection site reactions) of grade 2 or higher that is probably or definitely related to study drug 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.

- If three or more probably or definitely related grade 2 or greater AEs, and/or three or more grade 3 or greater injection site reactions occur in either group, dosing will be stopped for safety assessment.

5.4 RESCUE TREATMENT(S)

If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. For the purpose of efficacy analysis, patients who receive rescue treatment during the study treatment period will be considered treatment failures, but they will continue study treatment if rescue consisted of topical medications. Topical calcineurin inhibitors may be used for rescue, but should be reserved for problem areas only, eg, face, neck, intertriginous and genital areas, etc. If possible, investigators should attempt to limit the first step of rescue therapy to topical medications, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. If a patient receives rescue treatment with systemic corticosteroids or non-steroidal systemic

immunosuppressive drugs (cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.) study treatment will be immediately discontinued. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment.

5.5 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 for a given patient 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 treatment of either a psychiatric or physical (e.g., infectious disease) illness
▪ Any Grade 2 or greater adverse event (with the exception of worsening AD symptoms or injection site reactions) that is determined to be probably or definitely related to study drug administration.
▪ Any Grade 3 or greater injection site reaction
▪ Certain rescue treatments as specified in section 5.4

5.6 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 MABp1

• The occurrence of 2 or more serious adverse events occurring cumulatively and irrespective of dose cohort, that are probably or definitely related to the administration of MABp1

- Any significant safety finding assessed as probably or definitely related to MABp1 that in the opinion of the investigator warrants stopping the trial for additional assessment of safety.

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 (pre-dose sample collection at visit 1, visit 3, visit 5, and visit 8). 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 and biomarker analysis.

7. ASSESSMENT OF SAFETY

Safety will be assessed by monitoring adverse events, vital signs, physical examinations, ECG and clinical laboratory measurements. All subjects who have received at least one dose of bermekimab will be included in the safety analysis. Adverse events will be monitored from Visit 1 (post-infusion) to Visit 9. Any serious adverse events or grade 2 or greater probably or definitely related events will be followed 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 AD 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, weight, and BMI), medical history, medication history, and prior biologic use for each patient. Characteristics of the patient's atopic dermatitis, including duration of disease, baseline EASI score (including individual signs score), baseline Investigator's Global Assessment, baseline body surface area involvement, baseline pruritus numerical rating score, baseline SCORAD score, baseline patient oriented eczema measure, baseline DLQI, and baseline HADS score, will be collected. ***Baseline is defined as the visit 1 pre-injection assessment.***

8.2 STUDY ENDPOINT DEFINITIONS

Eczema Area and Severity Index
The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, arms, and legs and converted to a score of 0 to 6.

Pharmacokinetic Assessment
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 Na-Heparin collection tube at each PK collection time point (sample collection is pre-dose at visit 1, visit 3, visit 5, and visit 8). 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.

Investigator's Global Assessment
The IGA is an assessment scale used in clinical studies to determine severity of AD and clinical response to treatment based on a 5-point scale ranging from 0 (clear) to 4 (severe).

Global Individual Signs Score
Individual components of the AD lesions (erythema, edema/papulation, excoriations, and lichenification) will be rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria.

SCORing Atopic Dermatitis

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD. There are 3 components to the assessment: A = extent or affected body surface area, B = intensity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area and reported as the sum of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The intensity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/ lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C where the maximum is 103.

Patient Assessment of Pruritus and Pain

The NRS is a simple assessment tool that patients will use to report the intensity of their pruritus (itch) and pain during a daily recall period using a study diary. Patients will be asked to complete the following questions:

- For average itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch **on average** during the previous 24 hours?"

- For maximum itch intensity: "On a scale of 0 to 10, with 0 being 'no itch' and 10 being the 'worst itch imaginable', how would you rate your itch at the **worst moment** during the previous 24 hours?"

- For pain intensity: "On a scale of 0 to 10, with 0 being 'no pain' and 10 being the 'most severe pain', how would you rate your pain **on average** during the previous 24 hours?"

Patients will be instructed to record their NRS score daily from day 0 to day 56 (+/-2). Sites will be expected to review the diary at each visit and enter the data from the previous 7 days.

Visit 1 Questionnaire for Pruritus, Pain and Erythema

The following questions assess the intensity of pruritus (itch) and pain experienced by the patient before and after the injection of bermekimab during visit 1. The patient will answer the following questions:

1. On a scale of 0 to 10, what is the current intensity of itch, with 0 being 'no itch' and 10 being the 'worst itch imaginable'.

2. On a scale of 0 to 10, what is the current intensity of pain, with 0 being 'no pain' and 10 being 'severe pain'.

The Investigator will assess the patient's Erythema and complete the following on the Visit 1 Questionnaire:

3. What is the current status of the patient's erythema overall?

   a. None☐   Mild ☐ Moderate ☐ Severe ☐

   b. Please describe area(s) and degree(s) of the patient's erythema in detail and if applicable any post-injection changes observed.

The Visit 1 Questionnaire will be performed twice:

1. Visit 1, pre-injection of bermekimab;

2. Visit 1, sixty minutes post-injection of bermekimab.

Patient Oriented Eczema Measure

The POEM is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease symptoms in children and adults. The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on frequency during the past week (ie, 0 = no days, 1 = 1 to 2 days, 2 = 3 to 4 days, 3 = 5 to 6 days, and 4 = every day) with a scoring system of 0 to 28; the total score reflects disease-related morbidity.

Hospital Anxiety and Depression Scale

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.

Dermatology Life Quality Index

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.

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. However, anticipated day-to-day fluctuations or expected progression of the preexisting condition (based upon the Investigator's clinical judgment) are not to be considered AEs

- A significant or unexpected worsening of the condition/indication under investigation. However, anticipated day-to-day fluctuations or expected progression of the disease under investigation (based upon the Investigator's clinical judgment) are not to be considered AEs

- 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

- Congenital anomaly/birth defect

- 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; 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 AEs and SAEs must be recorded on the case report form (CRF)/eCRF and in the patient's source documents occurring between visit 1 (post-injection) and visit 9 (or if subject terminates from study prior to visit 9, seven days after the last administration of bermekimab).

All AEs should be recorded in 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 AD 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 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 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-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, particularly with respect to IL-1ra, although in this case is likely related to the unanticipated agonist effects of the receptor antagonist when it is present in high local concentration at the site of injection and thus this effect is not relevant to bermekimab.

Bermekimab is human monoclonal antibody derived immune plasma B cells derived from a natural human immune response against IL-1a. 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 reactions is not clear in all cases. It may involve a reaction against the antibody, against excipients in the preparation such as polysorbate, 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 mild 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 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 and visit 8 assessments of their atopic disease (as specified for the secondary endpoints).

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

All analyses will be summarized using descriptive statistics and data will be presented in tabular format for each treatment group and pooling all bermekimab dose groups together. 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 Handling Missing Data

If baseline assessment is not available, the baseline value will remain missing. The subject will not be included in baseline summaries.

10.5.2 Adjustment for Multiple Comparisons

No adjustment for multiple comparisons will be made.

10.5.3 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.

10.5.4 Efficacy Analysis

All primary and secondary efficacy analyses will be performed for SAF and PP populations. Summary statistics will be provided to evaluate the overall treatment effect and effect within the treatment group. No statistical comparison of differences will be performed across bermekimab dose groups.

Change from baseline to visit 8 will be summarized using descriptive statistics. Corresponding 95% confidence interval of the point estimate of mean change will be provided by treatment group and for overall pooled population. The number and percent of subjects achieving the response (as specified for the secondary endpoints) will be summarized by treatment groups and overall population along with 95% confidence interval for the point estimate. Number and percent of patients achieving response in EASI, and SCORAD core from baseline at visit 8, will be reported separately, along with 95% confidence interval for 50% or greater reduction.

10.6 SAFETY ANALYSIS

The safety analysis will be based on the SAF. This includes reported AEs and other safety information (ie, clinical laboratory evaluations and vital signs). A summary of safety results will be presented for each treatment group.

10.6.1 Analysis of Adverse Events

Adverse events reported in this study will be coded using the currently available version of MedDRA. 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.

The number and percentage of patients experiencing AEs and TEAEs will be summarized by seriousness (SAEs), severity (grades 1-5), SOC, and PT.

10.6.2 Other Safety

Vital Signs

Summaries of vital sign parameters by treatment group will include:

- Each vital sign parameter 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. 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
- Listings will be provided with flags indicating the out-of-laboratory-range values as well

as the AE grade.

Electrocardiogram

12- Lead ECG analyses

Summaries of 12-lead ECG parameters by treatment group will include:

- ECG status (ie, normal, abnormal, clinically significant)

10.7 PK ANALYSIS

Pharmacokinetic analysis of plasma concentrations of bermekimab will be performed for the PK population using non-compartmental model. Standard PK parameters such as maximum concentration (C_{max}) and its occurrence (Tmax), average concentration at steady state (Cavg), area under concentration version time curve from time 0 to selected time point (AUC0-t), elimination rate constant (Kel) and half-life (T1/2), will be presented. Other non-compartmental PK parameter values, as considered appropriate, will be calculated.

10.7.1 Treatment Exposure

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

(Date of last study drug injection – date of first study drug injection) + 7

The number (%) of patients and 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) 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/institution, as specified by the applicable regulatory requirement(s).

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