Trial Protocol

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

SPONSOR

XBiotech USA Inc

22 January 2020

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Basic Information

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

INVESTIGATIONAL PRODUCT:	Bermekimab
IND Number:	**112,459**
PROTOCOL NUMBER:	**2019-PT046**
PROTOCOL VERSION / DATE:	**2.0/ 22 January 2020**
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Investigator/Sponsor Signatures

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

PROTOCOL VERSION / DATE: 2.0 / 22 January 2020

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, Randomized, Double-Blind, Placebo-Controlled Study of Bermekimab in Patients with Moderate to Severe Atopic Dermatitis

Sponsor:

XBiotech USA, Inc.

Study Chair:

Seth Forman, M.D.

Sample Size:

Approximately 90 patients will be enrolled in the US

Approximate Duration:

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

Study Endpoints:

Primary Endpoint(s):

- Percentage of patients achieving Eczema Area and Severity Index-75 (EASI-75) (≥75% improvement from baseline) at week 16.

Secondary Endpoints:

- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average peak daily Pruritus Numeric Rating Scale (NRS) score from baseline to weeks 4, 8, 12, 16, and 32 in patients with baseline score ≥4.*
- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average overall Pruritus Numeric Rating (NRS) from baseline to weeks 4, 8, 12 16, and 32 in patients with baseline score ≥4.*
- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average peak daily Pain Numeric Rating Scale (NRS) score from baseline to weeks 4, 8, 12, 16, and 32 in patients with baseline score ≥4.*

- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average overall Pain Numeric Rating (NRS) from baseline to weeks 4, 8, 12, 16, and 32 in patients with baseline score ≥4.*
- Percentage of patients achieving EASI-75 (≥75% improvement in Eczema Area and Severity Index Score [EASI] from baseline) at weeks 4, 8, 12, and 32.*
- Percentage of patients achieving an Investigators Global Assessment (IGA) score of 0 or 1 (on a 5-point scale) and a reduction in this measure from baseline of at least 2 points at week 16.
- Percentage of patients achieving EASI-90 (≥90% improvement in Eczema Area and Severity Index Score [EASI] from baseline) at weeks 12, 16, and 32.*
- Change in Dermatology Life Quality Index (DLQI) from baseline to weeks 8, 12, 16, and 32.*
- Change in Hospital Anxiety Depression Scale (HADS) (Anxiety) from baseline to weeks 8, 12, 16, and 32.*
- Change in Hospital Anxiety Depression Scale (HADS) (Depression) from baseline to weeks 8, 12, 16, and 32.*
- Change in Patient Oriented Eczema Measure (POEM) Scores from baseline to weeks 8, 12, 16, and 32.*
- Change in SCORing Atopic Dermatitis (SCORAD) score from baseline to weeks 8, 12, 16, and 32.*
- Change in Global Individual Signs Score (GISS) from baseline to weeks 8, 12, 16, and 32.*

Exploratory Endpoints:

- Percentage of patients achieving an IGA score 0 or 1 (on a 5-point scale) and a reduction in this measure from baseline of at least 2 points at week 12.
- Change in Eczema Area and Severity Index Score (EASI) from baseline to weeks 8, 12, 16, and 32.
- Change from baseline to week 4 in Dermatology Life Quality Index (DLQI).
- Patients (%) achieving 50% reduction in SCORAD Score at Weeks 4, 8, 12, 16, and 32.*
- Patients (%) achieving 75% reduction in SCORAD Score at Weeks 4, 8, 12, 16, and 32.*
- Patients (%) achieving 90% reduction in SCORAD Score at Weeks 4, 8, 12, 16, and 32.*
- Change from baseline to week 8, 12, 16, and 32 in percent Body Surface Area (BSA).*

Safety Endpoints:

- Incidence of skin infection treatment-emergent adverse events (TEAEs) requiring systemic treatment from baseline through week 16 and 32.
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16 and 32.
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16 and 32.

*Each listed time point (in weeks) will be measured separately and treated as an individual endpoint.

Trial Design:

This is a phase II, randomized, double-blind, placebo-controlled study to further establish the efficacy and safety and explore dose effects for bermekimab monotherapy in adults with moderate to severe Atopic Dermatitis (AD). Patients will be assessed for study eligibility at the initial screening visit after providing informed consent. Thirty days are allowed in the screening window to complete all screening procedures and randomize the subject. During the screening period, certain treatments will be washed out, as applicable, according to eligibility requirements. Patients who fail initially may be re-screened once based on the investigator discretion but only if inclusion criteria are met at time of re-screening.

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

The primary efficacy endpoint is the percentage of patients achieving ≥75% improvement from baseline in EASI score at week 16. The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. Secondary measures will include Pruritus NRS, Pain NRS, SCORAD, POEM, GISS, DLQI, HADS, BSA and IGA.

Patients who meet the eligibility criteria at screening will be randomized in a 1:1:1 ratio to one of two treatment arms or placebo:

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

In order to maintain blinding, all patients will receive two injections at week 0 and 16, followed by weekly injections from week 1 to 31. Additionally, at least one qualified individual will be designated at each study site to perform all preparation and injection of the investigational product. The designated

injector(s) should have no other contact with the participant during the study, should not discuss the participant's treatment with the participant, participant's caregiver, or other site personnel at any time, and will not be permitted to review the participant's medical records, questionnaires, or the electronic CRF prior to each injection. The designated injector(s) should be documented in the source documents at each visit.

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

During the 32-week treatment period, patients will attend weekly clinical study visits. Clinical assessments, collection of samples for bermekimab concentrations, and safety testing will be performed at specified clinic visits. After completion of the 36-week study period, data will be locked and analyzed for safety and efficacy endpoints for all arms. In addition to the analyses that will be performed following the formal database lock at the end of the study at Week 36, an additional database lock may be performed at Week 16, and interim analyses utilizing unblinded efficacy data available as the study progresses, may also be conducted to help plan potential future development activities. An internal interim analysis committee (IAC) will be established to review the interim data and formulate recommended decisions/actions. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in study conduct or compound development), one of whom will chair the committee, and may also include other members as required by the nature of the IAs. Details will be provided in a separate IAC charter, which will define the organization and roles and responsibilities of the committee, possible recommendations or requests, and the communication process following IA reviews. Results from the Week 16 database lock and/or interim analyses will not be disseminated to investigators or subjects participating in the study. In addition, results of the interim analyses will not be disseminated to individuals associated with the conduct of the study.

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

Procedures and Assessments:

Multiple parameters will be collected during the study to evaluate the efficacy of bermekimab, including measures of AD severity, and patient-reported measures of AD symptoms and quality of life.

The safety of bermekimab in this population will be assessed by evaluating treatment emergent adverse events (TEAEs), vital signs, thorough physical examination, detailed medical history, electrocardiograms (ECGs), and clinical laboratory testing. Concomitant medications and procedures will be collected from time of informed consent to the end of study. Safety data will be reviewed on an ongoing basis by the sponsor.

Blood samples will be collected for laboratory testing including chemistry, hematology, inflammation markers, bermekimab concentration (PK), PD marker(s), anti-drug antibody (ADA) and research analysis etc. at pre-determined time points.

Figure 1. Study Flow Diagram

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

Inclusion Criteria:

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

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

- Written informed consent provided by the patient.
- Male or female, at least 18 years.
- Willing and able to attend all clinic visits and comply with study-related procedures.
- Is able to understand and complete study-related questionnaires.
- Chronic atopic dermatitis present for at least 3 years.
- EASI score ≥16 at screening and baseline visits.
- IGA score ≥3 at screening and baseline visits.

- Baseline pruritis numerical rating scale average score for maximum intensity of at least 3, based on the average of daily pruritis numerical rating scale scores for maximum itch intensity reported during the 7 days prior to randomization.
- Has applied a stable dose of topical moisturizer twice daily for at least 7 consecutive days immediately prior to the baseline visit and is willing to continue this regimen on a daily basis for the duration of the study.
- ≥10% body surface area (BSA) of AD involvement at screening and baseline visits.
- Documented recent history (within 6 months prior to screening) of inadequate response to treatment with topical medications, or patients for whom topical treatments are medically inadvisable (because of important side effects or safety risks).
    a) Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0-2), despite treatment with a daily regimen of topical corticosteroids of medium to higher potency (with or without topical calcineurin inhibitors as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever is shorter.
    b) Patients with documented systemic treatment for atopic dermatitis in the preceding 6 months are also considered to be inadequate responders to topical treatments and are potentially eligible for treatment with bermekimab, after appropriate washout.
    c) Important side effects or risks are those that outweigh the potential treatment benefits, and include: intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and adverse systemic effects.
    d) Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician.

Exclusion Criteria:

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

- Age below 18 years as the current study is evaluating bermekimab in adult patients only.
- Subject has been treated for AD with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to baseline.
- Treatment with bermekimab at any time in the past.
- Treatment with immunosuppressive/immunomodulatory drugs or phototherapy for atopic

dermatitis within 4 weeks of baseline, 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.

- Treatment with topical corticosteroids or topical calcineurin inhibitors for the treatment of AD within 14 days prior to baseline].
- Treatment with biologics as follows:

  a) Any cell-depleting agents including, but not limited to, rituximab, within 5 half-lives (if known) or 30 days prior to baseline visit, or until lymphocyte count returns to normal, whichever is longer.

  b) Other biologics: within 5 half-lives (if known) or 30 days prior to baseline visit, whichever is longer
- Initiation of treatment of atopic dermatitis with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue to use 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.
- Planned or anticipated use of any prohibited medications and procedures during study treatment.
- Treatment with a live (attenuated) vaccine within 30 days prior to the screening visit.
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to the baseline visit, or superficial skin infections within 1 week prior to the baseline visit. NOTE: patients may be rescreened after infection resolves.
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, 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 for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody at the screening visit.
- At baseline, presence of any conditions listed as criteria for study drug discontinuation.
- Presence of skin comorbidities that may interfere with study assessments.
- History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, and completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.

- 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.).
- Planned or anticipated major surgical procedure during the patient's participation in this study.
- Patient or immediate family member is part of the current clinical investigational team.
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study.
- Women unwilling to use adequate birth control, if of reproductive potential and sexually active. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception throughout the duration of the study and for 120 days after the last dose of study drug. These methods include oral contraceptives (stable use for more than 3 months before Screening), intrauterine device (IUD), hormonal contraceptives such as Depo-Provera (stable use for more than 3 months before Screening), Implanon implants (stable use for more than 3 months before Screening), double barrier contraception such as condom or diaphragm used with contraceptive sponge, foam, or jelly. For men participating in the study, unwillingness of sexual partner to use any of the above contraception methods.
- History of severe allergic or anaphylactic reactions to monoclonal antibodies.
- Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in the study, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms, etc.)

Abbreviations

ADA	Anti-Drug Antibody
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/EKG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
GISS	Global Individual Signs Score
GCP	Good clinical practice
HADS	Hospital Anxiety Depression Scale
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
IFN-□	Interferon Gamma
IGA	Investigator's Global Assessment
IGRA	Interferon Gamma Release Assay
IgG	Immunoglobulin G
IL-6	Interleukin-6
IL-1 α	Interleukin-1 α
IL-1β	Interleukin-1 β
IL-1 RA	Interleukin-1 receptor antagonist
IRB	Institutional review board
NRS	Numerical Rating Scale
NSAID	Non-Steroidal Anti-Inflammatory Drug
PD	PharmacodynamicspI Isoelectric Point
PK	Pharmacokinetics
POEM	Patient Oriented Eczema Measure
SAE	Serious Adverse Event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis software
SCORAD	Severity Scoring of Atopic Dermatitis
TB	Tuberculosis
UV	Ultraviolet
VAS	Visual Analogue Scale
WOCBP	Women of childbearing potential

1. BACKGROUND

1.1 OVERVIEW

XBiotech USA, Inc. has developed a True Human recombinant IgG1 monoclonal antibody, bermekimab, that binds the cytokine interleukin-1alpha (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 means of undermining the inflammatory process that drives a wide array of diseases, including dermatologic conditions.

The active ingredient in the drug product bermekimab is MABp1, a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α). The entire MABp1 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 13 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. Five Phase II studies sponsored by XBiotech have been completed in dermatologic indications (psoriasis [NCT01384630], acne vulgaris [NCT01474798], pyoderma gangrenosum [NCT01965613], atopic dermatitis [NCT03496974], and hidradenitis suppurativa [NCT03512275]), as well as one investigator sponsored study in Hidradenitis Suppurativa[i,ii,iii].

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). Similarly, when MABp1 was used in patients with pyoderma gangrenosum, there was a marked improvement in lesions over a short period of time. In the two most recent studies for hidradenitis suppurativa and atopic dermatitis, statistically significant improvement was seen for nearly every efficacy endpoint by the end of the study.

Results from atopic dermatitis study showed that bermekimab appeared to be safe, well tolerated, and active at reducing the severity of atopic dermatitis, including reducing itch and pain. This study was a phase II, open label, dose escalation study of bermekimab in subjects with moderate to severe atopic dermatitis. Thirty-eight patients across 9 clinical sites in two treatment groups received one of two subcutaneous (SC) doses: a low (200 mg, n=10) or high (400 mg, n=28) dose of bermekimab once weekly for either a 4 or 8-week treatment regimen, respectively. Safety was assessed by pre- and post-treatment measurements of vital signs, clinical laboratory assessments (blood chemistry, urinalysis, hematology), allergic reaction monitoring, and adverse event monitoring. Efficacy was assessed by change in EASI, IGA, NRS, SCORAD, POEM, DLQI, and GISS from baseline to visit 9. The primary measure of efficacy was the EASI. In the study, 39% of high dose patients achieved 75% improvement in EASI score (EASI-75) after 4 weeks of therapy and 75% of patients achieved EASI-75 at week 8. Of note, participants were not allowed to use concomitant topical corticosteroids during the study and thus these improvements were most likely due to the study drug alone.

While clinically and statistically significant improvement was seen for all clinical endpoints in the high dose group, also notable was the speed, magnitude, and trajectory of responses seen. In the high dose group, for example, after only four weeks of treatment, 61% of patients achieved a 4-point improvement in the Pruritus Numerical Rating Scale (NRS) for overall itch; and 75% of patients achieved a 4-point improvement by week 8. For the Pruritus Numerical Rating Scale (NRS) – worst moment itch after only four weeks of treatment, 63% of patients achieved a 4-point improvement and 78% of patients achieved a 4-point improvement by week 8. Furthermore, 80% of patients achieved a 4-point improvement in the Numerical Rating Scale (NRS) for pain by week 8.

Overall, bermekimab appeared safe, well tolerated, and showed significant therapeutic activity in most subjects. In all of these trials, there were few adverse events, most of which were grade 1 (mild).

1.2 RATIONALE

Atopic dermatitis (AD), is an inflammatory skin disease affecting 1-20% of the adult population. Chronic eczema in AD and associated pruritus can be a significant cause of morbidity and can impact quality of life. Disease pathogenesis is complex but ultimately converges on a pathological inflammatory process that disrupts the protective barrier function of the skin.

IL-1α plays a key role in the pathophysiology of a wide range of inflammatory skin disorders[v]. 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 an essential 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[vi]. Further, in a study by Archer et al, IL-1α, rather than IL-1β, was not only a fundamental component for inducing chronic skin inflamation, but the primary driving force[vii]. The study included mice with epidermal birth defects and showed that keratinocytes, which constitute approximately 90% of skin cells, secrete aberrant stores of intracellular IL-1α in response to skin injury (e.g. scratching), leading to chronic skin inflammation. Atopic Dermatitis is strongly associated with epidermal barrier defects, most commonly caused by mutated copies of the filaggrin gene[viii]. Filaggrin deficiencies are associated with changes in the composition of bacteria living on the skin, whereby bacteria can colonize and infect the skin with greater success thereby exacerbating aberrant IL-1α secretion[ix]. Neutralizing IL-1α activity resolved chronic skin inflammation in this study and strongly supported IL-1α as a key target for treating atopic dermatitis, along with other inflammatory skin diseases.

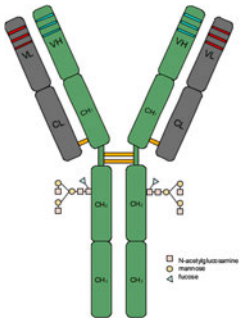
Endogenous anti-IL-1α antibodies are present in 5% to 28% of the general population[x,xi,xii,xiii]. No negative correlations with disease have been noted for these individuals. To the contrary, the presence of natural anti-IL-1α antibodies has been associated with favorable outcomes, both with respect to rheumatoid arthritis and ischemic heart disease. Animal studies also indicate that IL-1α loss or antagonism does not result in harm. Moreover, the well-tolerated use of other approved biological agents that employ alternative strategies to block IL-1 activity suggest that MABp1's targeting of IL-1α represents a safe treatment approach.

In previous dermatology studies bermekimab was well tolerated and showed impressive therapeutic activity. The safety data from XBiotech's open label studies: PT044 atopic dermatitis and PT045 hidradenitis suppurativa established good levels of safety and tolerability for 400mg bermekimab (2mL of 200mg/mL) subcutaneous injections and in both studies no safety signals were identified and no study stopping rules were met.

2. INVESTIGATIONAL PRODUCT

2.1 ACTIVE INGREDIENT, PHARMACOLOGIC CLASS, STRUCTURE

Figure 2: 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, 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[xiv].

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[x,xi] and cord blood[xv]. The anti-IL-1α antibodies measured in human plasma are IgG, in particular IgG1, IgG2, and IgG4 sublasses. Relatively equal prevalence for these antibody are seen in male and female plasma[xvi]. 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 MABp1. Also important is the fact that, unlike most other therapeutic IgG products, for which the Fc regions are derived from a rare human allele, XBiotech's product includes a heavy chain in which the constant (CH) region represents an allele found in approximately 70% of the human population. These two features should make for a drug product with reduced potential for immunogenicity.

2.2 DRUG PRODUCT (BERMEKIMAB 200 MG/ML) DESCRIPTION

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

2.3 STORAGE

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

2.4 STABILITY

The drug product is formulated in a buffer in which most of the tonicity comes from trehalose rather than salt. Trehalose is an effective stabilizer against oxidation, aggregation, and thermal or 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 been shown to have no negative effect on the product. However, the study treatment products are not to be frozen at any time. The drug product is labeled with a 12-month retest date. Every lot is also subjected to ongoing stability analysis per ICH guidelines.

2.5 DESIGNATED INDIVIDUAL FOR DRUG ADMINISTRATION

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

electronic CRF prior to each injection. The designated injector should be documented in the source documents at each visit.

2.6 METHOD OF ADMINISTRATION

Each injection should be administered at least one inch from previous injection sites.

Instructions For Subcutaneous Injection

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

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

Materials

Bermekimab pre-filled syringe for injection, warmed to room temperature

Sterile alcohol wipes

Band-aids, along with 2x2 gauze bandages and paper tape

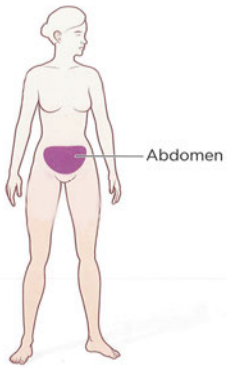
Latex-free gloves

Injection Site

Abdomen, at least 2 inches away from the belly button (Figure 3)

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

Figure 3

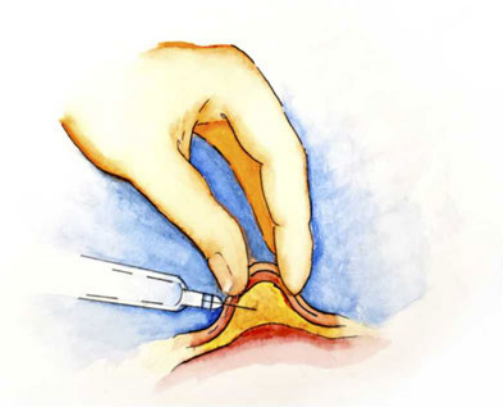


Injection

- Put on gloves
- Wipe injection site clean with alcohol pads

- Raise a fold of skin between the thumb and forefinger and insert needle as illustrated (Figure 4).
- Inject drug as rapidly as is comfortable for the patients.
- Withdraw needle. Place band-aid over injection site if desired (*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*).

Figure 4



2.7 AGENT ORDERING

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

2.8 POTENTIAL DRUG INTERACTIONS

There are no known drug interactions reported with bermekimab.

2.9 CONCOMITANT THERAPY

2.9.1 Antihistamine/NSAID Use

Concomitant medications such as antihistamines and/or NSAIDs (ibuprofen is recommended) are allowed based on the Investigator's judgement, in order to prevent or treat injection site reaction or discomfort. This information must be captured in eCRF.

2.9.2 Required Treatment

All patients are required to apply moisturizers at least twice daily for at least 7 days before visit 1 (day 0) and to continue the treatment throughout the study (up to 36 weeks where applicable). All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study. Patients may continue

using stable doses (for at least 7 days prior to screening visit) of such moisturizers if initiated before the screening visit. All moisturizer use must be captured in eCRF.

2.9.3 Permitted Medications and Procedures

Use of concomitant medications is permitted if not listed in section 2.9 Prohibited Medications and Procedures. Permitted concomitant medications includes basic skin care (cleansing and bathing, including bleach baths), moisturizers (required as background treatment), topical anesthetics, antihistamines, and topical and systemic anti-infective medications for any duration. In addition, medications used to treat chronic disease such as diabetes, hypertension, and asthma are permitted.

Any questions regarding treatment with concomitant medication during the study, should be directed to the medical monitor.

2.10 PROHIBITED MEDICATIONS AND PROCEDURES

Treatment with the following concomitant medications is *prohibited* during the entire duration of the study:

- Topical tacrolimus and pimecrolimus
- Treatment with a live (attenuated) vaccine
- Treatment with other investigational drugs (besides Bermekimab)
- Treatment with topical corticosteroids or topical calcineurin inhibitors; such agents may be administered during the study only if required for atopic dermatitis rescue. If topical corticosteroids and/or topical calcineurin inhibitors are used during the study, study treatment may continue as planned.
- Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.), except if required for atopic dermatitis rescue, or if critically medically needed to treat concurrent medical conditions (e.g., asthma).
    - The use of systemic corticosteroids for indications other than AD should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤2 weeks. Longer-term use of corticosteroids should be discussed with the medical monitor or designee and may require discontinuation of study drug. Inhaled, otic, ocular, nasal or other routes of mucosal delivery of corticosteroids are allowed throughout the study.
- Leukotriene inhibitors

- Allergen immunotherapy
- Systemic treatment for AD with an immunosuppressive/immunomodulating substance (including, but not limited to, cyclosporine, mycophenolate-mofetil, IFN-γ, azathioprine, methotrexate, or biologics)

Study drug will be discontinued if any of the following are used through week 16:

- Treatment with a live (attenuated) vaccine
- Treatment with investigational drugs other than bermekimab.
- Treatment with systemic corticosteroids or nonsteroidal systemic immunosuppressive drugs (e.g., cyclosporine, methotrexate, mycophenolate-mofetil, azathioprine, etc.)

The following concomitant procedures are prohibited during study participation:

- Surgical procedures
- Concomitant ultraviolet (UV) procedures (phototherapy [NBUVB, UVB, UVA1, or PUVA])
- Tanning in a bed/booth
- Patients are not allowed more than 2 bleach baths per week during study participation

2.11 RESCUE TREATMENT

Rescue treatment for AD may be provided to patients if medically necessary (ie, to control intolerable AD symptoms) at the discretion of the investigator. Topical calcineurin inhibitors may be used for rescue treatment, but should only be used for problem areas (e.g. face, neck, intertrinous and genital areas, etc). If possible, investigators should attempt to limit the first line of rescue treatment to topical medications. However, if the patient does not respond adequately to topical medications after at least 7 days, systemic medications may be used.

3. STUDY DESIGN AND OBJECTIVES

This is a phase II, randomized, double-blind, placebo-controlled study to further establish the efficacy and safety and explore dose effects for bermekimab monotherapy in adults with moderate to severe Atopic Dermatitis (AD). Patients will be assessed for study eligibility at the initial screening visit after providing informed consent. Thirty days are allowed in the screening window to complete all screening procedures and randomize the subject. During the screening period, certain treatments will be washed out, as

applicable, according to eligibility requirements. Patients who fail initially may be re-screened once based on the investigator discretion but only if inclusion criteria are met at time of re-screening.

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

Patients who meet the eligibility criteria at screening will be randomized in a 1:1:1 ratio to one of two treatment arms or placebo:

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

In order to maintain blinding, all patients will receive two injections at week 0 and 16, followed by weekly injections from week 1 to 31. Additionally, at least one qualified individual will be designated at each study site to perform all preparation and injection of the investigational product. The designated injector(s) should have no other contact with the participant during the study, should not discuss the participant's treatment with the participant, participant's caregiver, or other site personnel at any time, and will not be permitted to review the participant's medical records, questionnaires, or the electronic CRF prior to each injection. The designated injector(s) should be documented in the source documents at each visit.

During the 32-week treatment period, patients will attend weekly clinical study visits. Clinical assessments, collection of samples for bermekimab concentrations, and safety testing will be performed at specified clinic visits. After completion of the 36-week study period, data will be locked and analyzed for safety and efficacy endpoints for all arms. In addition to the analyses that will be performed following the formal database lock at the end of the study at Week 36, an additional database lock may be performed

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

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

The 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 into the study. The trial will be conducted in compliance with the protocol, GCP, and all applicable regulatory requirements.

3.1 Study Endpoints:

Primary Endpoint(s):

- Percentage of Patients achieving Eczema Area and Severity Index-75 (EASI-75) (≥75% improvement from baseline) at week 16.

Secondary Endpoints:

- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average peak daily Pruritus Numeric Rating Scale (NRS) score from baseline to weeks 4, 8, 12, 16, and 32 in patients with baseline score ≥4.*
- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average overall Pruritus Numeric Rating (NRS) from baseline to weeks 4, 8, 12 16, and 32 in patients with baseline score ≥4.*

- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average peak daily Pain Numeric Rating Scale (NRS) score from baseline to weeks 4, 8, 12, 16, and 32 in patients with baseline score ≥4.*
- Percentage of patients achieving ≥4-point improvement (reduction) in the weekly average overall Pain Numeric Rating (NRS) from baseline to weeks 4, 8, 12, 16, and 32 in patients with baseline score ≥4.*
- Percentage of patients achieving EASI-75 (≥75% improvement in Eczema Area and Severity Index Score [EASI] from baseline) at weeks 4, 8, 12, and 32.*
- Percentage of patients achieving an Investigators Global Assessment (IGA) score of 0 or 1 (on a 5-point scale) and a reduction in this measure from baseline of at least 2 points at week 16.
- Percentage of patients achieving EASI-90 (≥90% improvement in Eczema Area and Severity Index Score [EASI] from baseline) at weeks 12, 16, and 32.*
- Change in Dermatology Life Quality Index (DLQI) from baseline to weeks 8, 12, 16, and 32.*
- Change in Hospital Anxiety Depression Scale (HADS) (Anxiety) from baseline to weeks 8, 12, 16, and 32.*
- Change in Hospital Anxiety Depression Scale (HADS) (Depression) from baseline to weeks 8, 12, 16, and 32.*
- Change in Patient Oriented Eczema Measure (POEM) Scores from baseline to weeks 8, 12, 16, and 32.*
- Change in SCORing Atopic Dermatitis (SCORAD) score from baseline to weeks 8, 12, 16, and 32.*
- Change in Global Individual Signs Score (GISS) from baseline to weeks 8, 12, 16, and 32.*

Exploratory Endpoints:

- Percentage of patients achieving an IGA score 0 or 1 (on a 5-point scale) and a reduction in this measure from baseline of at least 2 points at week 12.
- Change in Eczema Area and Severity Index Score (EASI) from baseline to weeks 8, 12, 16, and 32.
- Change from baseline to week 4 in Dermatology Life Quality Index (DLQI).
- Patients (%) achieving 50% reduction in SCORAD Score at Weeks 4, 8, 12, 16, and 32.*
- Patients (%) achieving 75% reduction in SCORAD Score at Weeks 4, 8, 12, 16, and 32.*
- Patients (%) achieving 90% reduction in SCORAD Score at Weeks 4, 8, 12, 16, and 32.*
- Change from baseline to week 8, 12, 16, and 32 in percent Body Surface Area (BSA).*

Safety Endpoints:

- Incidence of skin infection treatment-emergent adverse events (TEAEs) requiring systemic treatment from baseline through week 16 and 32.
- Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through week 16 and 32.
- Incidence of TEAEs leading to treatment discontinuation from baseline through week 16 and 32.

*Each listed time point (in weeks) will be measured separately and treated as an individual endpoint.

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, at least 18 years.
- Willing and able to attend all clinic visits and comply with study-related procedures
- Is able to understand and complete study-related questionnaires
- Chronic atopic dermatitis present for at least 3 years.
- EASI score ≥16 at screening and baseline visits.
- IGA score ≥3 at screening and baseline visits.
- Baseline pruritis numerical rating scale average score for maximum intensity of at least 3, based on the average of daily pruritis numerical rating scale scores for maximum itch intensity reported during the 7 days prior to randomization.
- Has applied a stable dose of topical moisturizer twice daily for at least 7 consecutive days immediately prior to the baseline visit and is willing to continue this regimen on a daily basis for the duration of the study.
- ≥10% body surface area (BSA) of AD involvement at screening and baseline visits.
- Documented recent history (within 6 months prior to screening) of inadequate response to treatment with topical medications, or patients for whom topical treatments are medically inadvisable (because of important side effects or safety risks).
    a) Inadequate response is defined as failure to achieve and maintain remission or a low disease activity state (comparable to an IGA score of 0-2), despite treatment with a daily regimen of topical corticosteroids of medium to higher potency (with or without topical calcineurin inhibitors as appropriate), applied for at least 28 days or for the maximum duration recommended by the product prescribing information, whichever is shorter.
    b) Patients with documented systemic treatment for atopic dermatitis in the preceding 6 months are also considered to be inadequate responders to topical treatments and are potentially eligible for treatment with bermekimab, after appropriate washout.
    c) Important side effects or risks are those that outweigh the potential treatment benefits, and include: intolerance to treatment, hypersensitivity reactions, significant skin atrophy, and adverse systemic effects.

d) Acceptable documentation includes contemporaneous chart notes that record topical medication prescription and treatment outcome, or investigator documentation based on communication with the patient's treating physician.

4.2 EXCLUSION CRITERIA

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

- Age below 18 years as the current study is evaluating bermekimab in adult patients only
- Subject has been treated for AD with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) of the drug prior to baseline
- Treatment with bermekimab at any time in the past.
- Treatment with immunosuppressive/immunomodulatory drugs or phototherapy for atopic dermatitis within 4 weeks of baseline, 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
- Treatment with topical corticosteroids or topical calcineurin inhibitors for the treatment of AD within 14 days prior to baseline]
- Treatment with biologics as follows:
    a) Any cell-depleting agents including, but not limited to, rituximab, within 5 half-lives (if known) or 30 days prior to baseline visit, or until lymphocyte count returns to normal, whichever is longer.
    b) Other biologics: within 5 half-lives (if known) or 30 days prior to baseline visit, whichever is longer
- Initiation of treatment of atopic dermatitis with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue to use 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
- Planned or anticipated use of any prohibited medications and procedures during study treatment
- Treatment with a live (attenuated) vaccine within 30 days prior to the screening visit
- Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks prior to the baseline visit, or superficial skin infections within 1 week prior to the baseline visit. NOTE: patients may be rescreened after infection resolves

- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (e.g., tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, pneumocystis, 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 for hepatitis B surface antigen, hepatitis B core antibody, or hepatitis C antibody at the screening visit
- At baseline, presence of any conditions listed as criteria for study drug discontinuation
- Presence of skin comorbidities that may interfere with study assessments
- History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, and completely treated and resolved non-metastatic squamous or basal cell carcinoma of the skin.
- 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.)
- Planned or anticipated major surgical procedure during the patient's participation in this study
- Patient or immediate family member is part of the current clinical investigational team
- Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
- Women unwilling to use adequate birth control, if of reproductive potential and sexually active. Adequate birth control is defined as consistent practice of an effective and accepted method of contraception throughout the duration of the study and for 120 days after the last dose of study drug. These methods include oral contraceptives (stable use for more than 3 months before Screening), intrauterine device (IUD), hormonal contraceptives such as Depo-Provera (stable use for more than 3 months before Screening), Implanon implants (stable use for more than 3 months before Screening), double barrier contraception such as condom or diaphragm used with

contraceptive sponge, foam, or jelly. For men participating in the study, unwillingness of sexual partner to use any of the above contraception methods.

- History of severe allergic or anaphylactic reactions to monoclonal antibodies.
- Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in the study, may make patient's participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms, etc.)

5. TREATMENT PLAN

5.2 STUDY PROCEDURES

PLACEBO-CONTROLLED PERIOD

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

- Informed Consent
- Inclusion/ Exclusion
- Demographics
- Medical History
- Concomitant Medications/Treatments
- Physical Exam
- Electrocariogram
- Vital Signs (blood pressure, pulse, oxyen saturation, respiratory rate and body temperature)
- Height
- Weight
- Body Mass Index (BMI) [BMI= weight (kg)/height (m^2)]
- Patient Diary
- Patient Oriented Eczema Measure (POEM)
- Hospital Anxiety and Depression Scale (HADS)
- Dermatology Life Quality Index (DLQI)
- Investigator's Global Assessment (IGA)
- Eczema Area and Severity Index (EASI)
- Global Individual Signs Score (GISS)
- SCORing Atopic Dermatitis (SCORAD)
- Body Surface Area (BSA) involvement with atopic dermatitis (must be greater than 10%)
- Urinalysis: pH, protein, glucose and blood cells (RBCs and WBCs)
- Blood Draw:

- Chemistry panel: Albumin, Alkaline Phosphatase, ALT, AST, GGT, Bicarbonate (CO2), Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen
- 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)
- Randomization to study arm (once confirmed patient has passed screening requirements).

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

Visit 1 (Baseline/Week 0/Day 0) (must occur within 30 days of signing informed consent)

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Syringe may be held in hand to warm. Do not heat.
- Pre-injection
  - Verify patient still meets all Inclusion/ Exclusion criteria
  - Height, Weight, BMI
  - Patient Diary
  - POEM, HADS, DLQI
  - EASI, GISS, SCORAD, BSA, IGA
  - Vital signs, Urine Pregnancy
  - Urinalysis
  - Blood draw for chemistry, hematology, inflammation markers, PK/ADA, PD (including IL-6), biomarker and research analysis
- Bermekimab/placebo subcutaneous injection (To deliver a loading dose to subjects in the bermekimab groups while maintaining blinding, all subjects will receive two injections)
- Post-injection
  - Adverse event monitoring
  - Concomitant medications/treatments

Visit 2 (Week 1/Day 7 ± 3 days); Visit 3 (Week2/Day 14 ± 3 days)

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Syringe may be held in hand to warm. Do not heat.
- Pre-injection
  - Patient Diary
  - POEM, HADS, DLQI
  - IGA, EASI, GISS, SCORAD, BSA
  - Vital signs, Urine Pregnancy
  - Blood draw for PK/ADA, PD (including IL-6), biomarker and research analysis

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

Visit 4 (Week 3/Day 21 ± 3 days); Visit 6 (Week 5/Day 35 ± 3 days)

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

Visit 5 (Week 4/Day 28 ± 3 days); Visit 13 (Week 12/Day 85 ± 3 days)

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Syringe may be held in hand to warm. Do not heat.
- Pre-injection
    - Patient Diary
    - POEM, HADS, DLQI
    - EASI, GISS, SCORAD, BSA, IGA
    - Vital signs, Urine Pregnancy
    - Blood draw for chemistry, hematology, inflammation markers, PK/ADA, PD (including IL-6), biomarker and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

Visit 7 (Week 6/Day 42 ± 3 days)

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Syringe may be held in hand to warm. Do not heat.
- Pre-injection
    - Patient Diary
    - POEM, HADS, DLQI
    - EASI, GISS, SCORAD, BSA, IGA
    - Vital signs, Urine Pregnancy
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring

- Concomitant medications/treatments

Visit 8 (Week 7/Day 49 ± 3 days); Visit 10 (Week 9/Day 63 ± 3 days); Visit 11 (Week 10/Day 70 ± 3 days); Visit 12 (Week 11/Day 77 ± 3 days); Visit 14 (Week 13/Day 91 ± 3 days); Visit 15 (Week 14/Day 98 ± 3 days); Visit 16 (Week 15/Day 105 ± 3 days)

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

Visit 9 (Week 8/Day 56 ± 3 days)

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Syringe may be held in hand to warm. Do not heat.
- Pre-injection
  - Patient Diary
  - POEM, HADS, DLQI
  - EASI, GISS, SCORAD, BSA, IGA
  - Vital signs, Urine Pregnancy
  - Urinalysis
  - Blood draw for chemistry, hematology, inflammation markers, PK/ADA, PD (including IL-6), biomarker and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
  - Adverse event monitoring
  - Concomitant medications/treatments

BLINDED ACTIVE DOSING PERIOD

Visit 17 (Week 16/Day 112 ± 3 days)

- ***At least 45 minutes before injection:*** Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Syringe may be held in hand to warm. Do not heat
- Pre-injection
  - Patient Diary
  - POEM, HADS, DLQI
  - EASI, GISS, SCORAD, BSA, IGA
- Physical Examination, Vital signs, Urine Pregnancy
- Urinalysis

- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, PD (including IL-6), biomarker and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

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

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

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

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
    - Patient Diary
    - POEM, HADS, DLQI
    - EASI, GISS, SCORAD, BSA, IGA
- Vital Signs, Urine Pregnancy
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

Visit 25 (Week 24/Day 168 ± 3 days)

- ***At least 45 minutes before injection***: Remove syringe from refrigeration and lay flat; allow to warm to room temperature. Do not heat
- Pre-injection
    - Patient Diary
    - POEM, HADS, DLQI
    - EASI, GISS, SCORAD, BSA, IGA

- Vital Signs, Urine Pregnancy
- Urinalysis
- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, biomarkers and research analysis
- Bermekimab/placebo subcutaneous injection
- Post-injection
    - Adverse event monitoring
    - Concomitant medications/treatments

Visit 33 (Week 32/Day 224 +/-3)

- Patient Diary
- POEM, HADS, DLQI
- IGA, EASI, GISS, SCORAD, BSA
- Physical Exam, Vital Signs, Urine Pregnancy
- Urinalysis
- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, biomarkers and research analysis
- Adverse event monitoring
- Concomitant medications/treatments

FOLLOW-UP PERIOD

- POEM, HADS, DLQI
- IGA, EASI, GISS, SCORAD, BSA
- Physical Exam, Vital Signs, Urine Pregnancy
- Urinalysis
- Blood draw for chemistry, hematology, inflammation markers, PK/ADA, biomarkers and research analysis
- Adverse Events
- Concomitant medications/treatments

UNSCHEDULED VISIT (if applicable)

- Patient Diary
- POEM, HADS, DLQI
- IGA, EASI, GISS, SCORAD, BSA
- Physical Exam, Vital Signs, Electrocardiogram, Urine/ Serum Pregnancy
- Urinalysis
- Blood draw for chemistry, hematology, inflammation markers, infectious disease panel, PK/ADA, biomarkers and research analysis
- Adverse Events
- Concomitant medications/treatments

EARLY TERMINATION VISIT (if applicable)

- Patient Diary
- POEM, HADS, DLQI
- IGA, EASI, GISS, SCORAD, BSA
- Physical Exam, Vital Signs
- Urinalysis
- Blood draw for chemistry, hematology, inflammation markers, infectious disease panel, PK/ADA, biomarkers and research analysis, Serum Pregnancy
- Adverse Events
- Concomitant medications/treatments

5.2 STUDY CALENDARS

5.2.1 Placebo-controlled Period

Study Procedure	Screening	Baseline	Placebo-controlled Period															
Visit (V)		**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17**
Week (W)		**W0**	**W1**	**W2**	**W3**	**W4**	**W5**	**W6**	**W7**	**W8**	**W9**	**W10**	**W11**	**W12**	**W13**	**W14**	**W15**	**W16**
Day (D)	**-30 to -1**	**D0**	**D7**	**D14**	**D21**	**D28**	**D35**	**D42**	**D49**	**D56**	**D63**	**D70**	**D77**	**D84**	**D91**	**D98**	**D105**	**D112**
Visit Window (d)		±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d	±3d
Screening/Baseline:[1,3]																		
Informed Consent	X																	
Inclusion/Exclusion	X	X																
Medical History/ Demographics	X																	
Height, Weight, BMI	X	X																
Randomization	X																	
Treatment:[2,3,5]																		
Administer Study Drug/ Placebo		X[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[7]
Conmed Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy: [4]																		
Patient Daily Diary (Pain NRS, Pruritus NRS)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
POEM, DLQI, HADS	X	X	X	X		X		X		X				X				X
IGA, EASI, GISS, SCORAD, BSA	X	X	X	X		X		X		X				X				X
Safety:[4]																		
Physical Examination	X																	X
Electrocardiogram	X																	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Testing:[4]																		
Infectious disease panel (HIV ab, HBsAg, Hep C Ab, TB)	X																	
Hematology, Chemistry, Inflammation Markers	X	X				X				X				X				X
Urinalysis	X	X								X								X
Pregnancy Test (WOCBP only) *X designates a urine test	Serum	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK/PD/ADA:[4]																		
PK/ADA,PD (including IL-6), biomarker analysis, Research Samples (serum/plasma)		X	X	X	X	X	X			X				X				X

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

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

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

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

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

[6] Loading Doses: Treatment arm 1: 800 mg loading dose of bermekimab + placebo (one 2mL SC injection containing 400 mg of bermekimab and one 2mL SC injection of placebo) at week 0; Treatment arm 2: 800 mg loading dose of bermekimab (2 x 2mL SC injections each containing 400 mg of bermekimab) at week 0; Arm 3: 4 mL loading dose of placebo (2 x 2mL SC injections of placebo) at week 0.

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

5.2.2 Blinded Active Dosing Period

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

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

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

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

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

5.2.3 Follow-up Period

Study Procedure	**Follow-up Period**	**Unscheduled Visit**[2] (if applicable)	**Early Termination** (if applicable)
Visit (V)	**V34**		
Week (W)	**W36**		
Day (D)	**D252**		
Visit Window (d)	±3d		
Treatment:[3]			
Con Meds/Treatments	X	X	X
Efficacy:[1]			
IGA, EASI, GISS, SCORAD, BSA	X	X	X
POEM, DLQI, HADS	X	X	X
Patient Diary (daily)		X	X
Safety:[1]			
Vital Signs	X	X	X
Physical Examination	X	X	X
Electrocardiogram		X	
Adverse Events	X	X	X
Laboratory Testing:[1]			
Hematology, Chemistry, Inflammation Markers	X	X	X
Infectious Disease Panel		X	
Urinalysis	X	X	X
Pregnancy Test (WOCBP only)	Urine	Urine/Serum	Serum
PK/PD/ADA:[1]			
PK/ADA, IL-6, PD, biomarker & research samples (serum/plasma)	X	X	X

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

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

5.3 DISCONTINUATION OF THERAPY

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

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

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

5.4 TRIAL STOPPING RULES

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

5.5 EMERGENCY UNBLINDING

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

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

6. CORRELATIVE STUDIES

6.1 PHARMACOKINETICS (PK) SAMPLE COLLECTION

The process for the collection, storage, future use and disposal of biological samples will follow company policies and SOPs. Patient blood will be drawn into blood collection tubes at each collection time point per the study protocol for PK/ADA/PD/research analysis. These samples will be processed by the collection lab per the study laboratory manual and the obtained plasma/serum will be sent to a central laboratory before being shipped to XBiotech in monthly batches for analysis.

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

7. ASSESSMENT OF SAFETY

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

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

Any grade 3 or greater 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 week 0 (visit 1), pre-injection assessment.

8.2 STUDY ASSESSMENTS

- **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.

- **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, infiltration/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 = severity, 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 severity 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.

Body surface area affected by AD will be assessed for each section of the body (the possible highest score for each region is: head and neck [9%], anterior trunk [18%], back [18%], upper limbs [18%], lower limbs [36%], and genitals [1%]) and will be reported as a percentage of all major body sections combined. Body Surface Area (BSA) will be extracted using SCORAD.

- **Numerical Rating Scale (NRS) for Pruritus & Pain**

Patients will be given a diary to complete each night before bed. Patients will be asked to report "average pain", and "worst moment pain" as well as "average itch" and "worst moment itch" on a 0-10 numeric rating scale. Patient diaries will be collected weekly.

- **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 = all days) with a scoring system of 0 to 28; the total score reflects disease-related morbidity. The POEM is provided in the study reference manual.

- **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. The HADS is provided in the study reference manual.

- **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. The DLQI is provided in the study reference manual.

- **Pharmacokinetics (PK) and Interleukin-6 (IL-6)**

An enzyme-linked immunosorbent assay (ELISA) has been developed to specifically measure bermekimab levels in human plasma. Blood will be drawn into three 6 ml collection tubes at each research draw collection time point as outlined in section 5. These samples will be collected per the study lab manual and shipped to the Sponsor for PK and IL-6 analyses. The samples will also be used for various pharmacodynamic (PD), biomarker, and general research analyses. The PK samples will also be used to test for the presence of antibodies against bermekimab. The IL-6 samples will be used to test for change in serum IL-6 levels in patients, which has shown to correlate with disease severity in HS and potentially a more reliable predictor of treatment response in HS patients than CRP[xvii, xviii].

9. ADVERSE EVENTS

9.1 DEFINITION OF ADVERSE EVENT (AE)

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

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

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

- Death;

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

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

9.3 RECORDING OF ADVERSE EVENTS

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

All AEs should be recorded in standard medical terminology as concisely as possible. The AE recorded should not be a procedure or a clinical/laboratory measurement but should reflect the event leading to the procedure or the cause of the clinical/laboratory abnormality, if known. Whenever possible, AEs should be evaluated and recorded as a diagnosis, rather than individual signs and symptoms. However, if a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Any AE that worsens in intensity, or becomes serious, should be recorded as a new event.

9.4 EVALUATING ADVERSE EVENTS

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

9.5 ASSESSMENT OF CAUSALITY

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

Relationship to study drug is summarized as follows:

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

9.6 REPORTING REQUIREMENTS

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

All serious adverse events (SAEs) should be reported to the Sponsor on the initial SAE report forms within 24 hours of knowledge of the event. These immediate reports should be followed promptly by detailed, written reports (follow-up SAE reports). The subject should be followed up with until stabilization of the reported SAE, either with full satisfactory resolution or resolution with sequelae, or until death of the subject. Before declaring the subject is lost to follow-up, three unsuccessful attempts at contact should be made and recorded on the SAE form. The immediate and follow-up reports should identify subjects by unique code numbers (generated by the safety database) assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The Investigator should also submit SAEs to the IRB/EC according to their IRB/EC guidelines [ICH-GCP E6]. Drug-related Serious Adverse Events will be reported to the FDA by XBiotech's Medical Safety Officer according to 21 CFR 312.32.

9.7 REFERENCE SAFETY INFORMATION: POTENTIAL ADVERSE REACTIONS

911 patients have been treated using bermekimab (either by infusions or subcutaneous injections) in patients with advanced solid tumors, advanced hematologic malignancies, metastatic colorectal cancer, peripheral vascular disease, type II diabetes, acne vulgaris, plaque psoriasis, pyoderma gangrenosum, atopic dermatitis and hidradenitis suppurativa. Over 5000 doses of bermekimab were administered intravenously at 7.5

mg/kg and over 900 doses of bermekimab were administered subcutaneously with 50 mg/mL, 100 mg/mL and 200 mg/ mL formulations.

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

Bermekimab is 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 IgG1κ, with the light and heavy chain variable regions being identical to those originally expressed by a peripheral blood B lymphocyte that was obtained from a healthy individual. No *in vitro* affinity maturation or modifications have been made to improve its natural binding affinity (211 +/- 31 pM). We believe that a true human antibody should be effectively non-immunogenic in humans and thus exhibit optimal activity and pharmacokinetics. To date, no treatment emergent anti-drug antibodies specific to bermekimab have been identified.

The mechanism behind infusion or injection site reactions is not well understood. In some cases, it may involve a reaction against the antibody products themselves, particularly where the primary sequence of the antibody has been modified in vitro or is derived from non-human system or, against some minor residual component from the manufacturing process (i.e. host cell proteins). Bermekimab is derived from and has undergone immunological selection in humans, thus anti-bermekimab responses are highly unlikely. To date, there has been a very low incidence of injection site or infusion reactions observed (27 patients out of 911 total; 3.0%). In order to mitigate this class-specific risk, close monitoring is required during the bermekimab infusion/ injection and for at least 30 minutes after the end of the infusion/ injection for the first 3 doses. Availability of resuscitation equipment must be ensured although this has never been used for any patient in any of our studies. Pre-medication with antihistamines, NSAIDs or corticosteroids is not required but allowed at PI's discretion.

An expanded discussion of potential risks and monitoring with bermekimab therapy is located in Section 4.6 of the Investigator's Brochure.

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

A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the statistical analysis plan (SAP).

10.1 DETERMINATION OF SAMPLE SIZE

The primary efficacy endpoint is percentage of patients with Eczema Area and Seveirty Index-75 (EASI-75) (≥75% improvement from baseline) at week 16 . The sample size is calculated for the bermekimab weekly injection group (arm 1) versus placebo group (arm 3) comparison (the primary comparison).

Assuming EASI-75 is achieved in 60% of intent-to treat (ITT) patients treated in the bermekimab weekly injection group (arm 1) versus 20% in placebo treated patients (arm 3), then, for a randomization ratio of 1:1:1, a sample size of 69 patients (23 in each treatment group) is required for approximately 80% power at a 0.05 significance level using a 2-sided Pearson chi-square test. In order to account for possible dropouts and to provide adequate safety data, approximately 90 patients will be randomized and treated.

10.2 RANDOMIZATION

A centralized block randomization schedule with a 1:1:1 allocation ratio will be utilized using an electronic randomization system. Patients will be randomly assigned to either the bermekimab weekly injection group (arm 1), the bermekimab every other week injection group (arm 2), or the placebo group (arm 3). The randomization schedule will be stratified by baseline EASI severity (less severe (EASI ≥16 and <28) or more severe (EASI ≥28)).

10.3 ANALYSIS SETS

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

10.4 PATIENT DISPOSITION

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

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

10.5 STATISTICAL METHODS

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

10.5.1 Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by treatment group. 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 the study is to analyze the safety and efficacy of different dose regimens of bermekimab compared to placebo treatment in adult patients with moderate-to-severe AD

Safety endpoints will be evaluated by monitoring adverse events from clinical and laboratory reporting. The safety analysis will be based on the SAF population. A summary of safety results will be presented for each treatment group.

10.5.2.1 Analysis of Adverse Events

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

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

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

10.5.2.2 Other Safety

Vital Signs

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

- Each vital sign parameter and change from baseline

Laboratory Tests

Clinical laboratory values will be converted to standard international units. Clinical laboratory (as described in the treatment plan) data will be listed for each subject. Laboratory data will be summarized by treatment group. Summaries of laboratory variables by treatment group will include:

- Each laboratory result and change from baseline
- Listing will be provided for patients with grade 2 or greater laboratory AEs

Electrocardiogram

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

10.5.3 Efficacy Analysis

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

10.5.3.1 Primary Efficacy Analysis

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

3 will be considered nominal. This method to control the type-1 error will only be implemented for the primary efficacy analysis variable.

The number and percentage of patients with Eczema Area and Seveirty Index-75 (EASI-75) (≥75% improvement from baseline) at week 16 will be presented by treatment group. Patients who terminate from the study early prior to week 16 will count as non-responders (non-achievers) in the primary efficacy analysis (Non-Responder Imputation). If a patient received rescue medication, the patient will be counted as a non-responder from the start of rescue medication. Additional treatment failure rules and sensitivity analyses will be discussed in the statistical analysis plan.

A Cochran-Mantel-Haenszel (CMH) general association test stratified by baseline EASI severity will be used to compare each bermekimab dose separately with placebo. The primary efficacy analysis population will be the mITT population.

10.5.3.2 Secondary Efficacy Analyses

Secondary and exploratory efficacy endpoints will be summarized using descriptive statistics for continuous variables (n, mean, standard deviation, median, minimum and maximum value) and number and percentage for categorical variables.. The 95% CI of the mean change from baseline will be provided. The change from baseline in these endpoints at each week will be analyzed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for treatment, week, stratification factor (baseline EASI severity), baseline score, baseline score by week interaction, and the treatment-by-week interaction, if applicable. The impact of the stratification factor will also be assessed. Categorical variables will be analyzed using CMH tests as used for the primary efficacy analysis. Full details will be provided in the SAP.

10.5.4 Treatment Exposure

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

10.5.5 Pharmacokinetic (PK) and Pharmacodynamics (PD) Analysis:

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

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 and agreement by the study Sponsor. There also must first be 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(s) 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, to 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. Subject 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, and 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.

Access to the study data will be strictly controlled. These data will be processed and archived in accordance with the applicable policies and SOPs. The Sponsor's Electronic Database has security features which include but are not limited to the following: all application ports are secured behind a firewall; all data and network traffic is encrypted; the database is role-based and roles are customized to allow restricted access to specific features; a password policy is enforced including a secure password length and complexity; all database changes and user logins are logged to an audit trail; fields containing Protected Health Information are obfuscated from study users (sponsor, data managers, etc.); and EU data are contained on a dedicated data server in the EU, so the data is not stored offshore.

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 collected on to the source documents and later will be captured electronically in an Electronic Data Capture (EDC) system by the site coordinators. Source documents are original

records of clinical findings, observations, or other activities in a clinical trial necessary for the evaluation of the trial. Examples of source documents (electronic or hardcopy documents) include but are not limited to subject diaries, physician and/or patient completed questionnaires or scales, laboratory results, ECGs and reports. Designated study personnel will be provided unique usernames and passwords with 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

The sites will follow their internal SOPs for discarding the used (empty) syringes after the injection. The designated personnel at the sites will review drug accountability logs to account for administered syringes. Unused inventory by investigative sites at study completion should be returned to drug distributor for destruction per guidance provided in the study’s pharmacy manual.

11.10 AUDITS AND 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

The study will be conducted in compliance with Good Clinical Practice (GCP). Sponsor will arrange the clinical research associates (CRAs) to monitor the conduct of the clinical trial at the investigative sites. XBiotech ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the investigator and the staff at a study initiation visit (SIV). Prior to enrolling subjects into the study, a XBiotech representative will review the protocol, eCRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator and his/her staff. Monitoring will include on-site visits at regular intervals with the investigator and his/her staff as well as any appropriate communications by mail, email, facsimile, or telephone. During monitoring visits, the facilities, IP storage area and conditions, eCRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the XBiotech representative. Accuracy and protocol compliance will be checked by performing source data verification that is a direct comparison of the entries made onto the eCRFs against the appropriate source documentation. Any resulting discrepancies or deviations from the protocol will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the eCRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to study protocol and documentation of AEs and SAEs and their proper recording be verified. 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.

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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Janssen Research & Development*

Clinical Protocol

COVID-19 Appendix

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

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Protocol JNJ-77474462ADM2002; Phase 2

JNJ-77474462 (bermekimab)

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

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

Status: Approved
Date: 27 April 2020
Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-37782 version 1.0

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL JNJ-77474462

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

COVID-19 APPENDIX

GUIDANCE ON STUDY CONDUCT DURING THE COVID-19 PANDEMIC

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

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

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

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

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

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

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

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

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

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

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

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

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

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

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

INVESTIGATOR AGREEMENT

COVID-19 Appendix
JNJ-77474462 (bermekimab) Clinical Protocol JNJ-77474462ADM2002

INVESTIGATOR AGREEMENT

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

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

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD _____

Institution: Janssen Research & Development _____

PPD Digitally signed by PPD
DN: c=US, o=JNJ, c
Reason: I agree to the terms defined by the placement of my signature on this document
Date: 2020.04.27 09:32:15 -04'00'

Signature: _____ Date: _____
(Day Month Year)

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

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Status: Approved, Date: 27 April 2020