1. BACKGROUND

1.1 OVERVIEW

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

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

Three phase 2 studies sponsored by XBiotech have been completed in dermatologic indications (acne, psoriasis, pyoderma gangrenosum), as well as one investigator sponsored study in Hidradenitis Suppurativa[1,2,3]. Subjects with moderate to severe psoriasis experienced a rapid reduction in their psoriasis area and severity index (PASI), and subjects with acne vulgaris experienced reductions of inflammatory lesion counts, as well as reduced hospital anxiety and depression scores (HADS). In both of these trials, there were few adverse events, which were all grade 1 (mild) and the only events that appeared to be related to therapy were mild injection site reactions in two patients.

The investigator initiated study enrolled patients with moderate to severe HS that were refractory to adalimumab. The study was double blind, randomized and placebo controlled, and utilized the

3.1 STUDY ENDPOINTS

Primary Endpoint:

- Safety and Tolerability

Secondary Endpoints:

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

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

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

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

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

  An enzyme-linked immunosorbent assay (ELISA) has been developed to specifically measure bermekimab levels in human plasma. Blood will be drawn into a single 6 ml Na-Heparin collection tube at each PK collection time point (sample collection is pre-dose at visit 1, visit 3, visit 5, and visit 8). These samples will be collected per the study lab manual and immediately shipped to the Sponsor for PK analysis. The PK samples will also be used to test for the presence of antibodies against bermekimab.

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

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

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

  SCORAD was developed by the European Task Force on Atopic Dermatitis (Severity scoring of atopic dermatitis: the SCORAD index) as a measure of disease severity in AD. It includes assessment of the eczema in addition to patient reported symptoms. Total score ranges from 0 to 103 (no disease to most severe disease, respectively).
- Patients (%) achieving 50% or greater reduction in EASI Score from baseline to Visit 8
- Patients (%) achieving 50% or greater reduction in SCORAD Score to Visit 8
- Change (%) in Patient Oriented Eczema Measure (POEM) Scores from baseline to Visit 8

  POEM is a 7-item is a patient reported quality of life outcome measure based on a questionnaire to determine disease symptoms, including bleeding, cracking, dryness, flaking, itching, sleep loss and weeping. The scoring range is from 0 to 28 (no disease to most severe disease, respectively).
- Changes in Global Individual Signs Score (GISS) from baseline to visit 8

  GISS assesses AD lesions for erythema, excoriations, lichenification and edema/papulation. Each component will be rated on a global basis (over the entire body surface rather than by region) using a 4-point scale (0=none, 1=mild, 2=moderate and 3=severe) according to the EASI grading severity. Total score will range from 0 to 12 (no disease to most severe disease, respectively).
- Change from baseline to visit 8 in Dermatology Life Quality Index (DLQI)
- Change from baseline to visit 8 in Hospital Anxiety Depression Scale (HADS)
- Change (%) from pre- and post- injection of Visit 1 Questionnaire for pruritus, pain and erythema

SCORing Atopic Dermatitis

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

Patient Assessment of Pruritus and Pain

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

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

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

Visit 1 Questionnaire for Pruritus, Pain and Erythema

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

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

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

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

a. None☐ Mild ☐ Moderate ☐ Severe ☐

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

The Visit 1 Questionnaire will be performed twice:

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

Patient Oriented Eczema Measure

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

Hospital Anxiety and Depression Scale

The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state. The HADS consists of 14 items, 7 each for anxiety and depression symptoms; possible scores range from 0 to 21 for each subscale. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression.

Dermatology Life Quality Index

The DLQI is a 10-item, validated questionnaire used in clinical practice and clinical trials to assess the impact of AD disease symptoms and treatment on QOL. The format is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10 questions, which assess QOL over the past week, with an overall scoring system of 0 to 30; a high score is indicative of a poor QOL.

9. ADVERSE EVENTS

9.1 DEFINITION OF ADVERSE EVENT (AE)

An adverse event is defined as any untoward medical occurrence in a subject participating in a clinical study that does not necessarily have a causal relationship with the pharmaceutical or biological agent under study. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including laboratory findings), symptom, or disease temporally associated with the use of bermekimab, whether or not it is apparently related to bermekimab
- A concurrent illness
- An exacerbation, or an unexpected increase in frequency or intensity of a preexisting condition, including intermittent or episodic conditions. However, anticipated day-to-day fluctuations or expected progression of the preexisting condition (based upon the Investigator's clinical judgment) are not to be considered AEs
- A significant or unexpected worsening of the condition/indication under investigation. However, anticipated day-to-day fluctuations or expected progression of the disease under investigation (based upon the Investigator's clinical judgment) are not to be considered AEs
- A suspected interaction between the investigational drug and concomitant medications
- Any clinically significant laboratory abnormality (including radiological interpretations, histopathological findings, etc.)

9.2 DEFINITION OF SERIOUS ADVERSE EVENT (SAE)

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

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

bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

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

9.3 RECORDING OF ADVERSE EVENTS

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

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

9.4 EVALUATING ADVERSE EVENTS

All AEs will be graded according to the CTCAE version 4.03.

9.5 ASSESSMENT OF CAUSALITY

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

Relationship to study drug is summarized as follows:

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

- **Definitely related:** The AE is most likely attributable to the investigational drug

9.6 REPORTING REQUIREMENTS

Any AE (with the exception of worsening AD symptoms or injection site reactions) of grade 2 or higher must be entered into the eCRF within 24 hours of learning of the event. Any grade 3 or greater injection site reaction must be reported to the sponsor within 24 hours of learning of the event.

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

9.7 REFERENCE SAFETY INFORMATION: POTENTIAL ADVERSE REACTIONS

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

as the AE grade.

Electrocardiogram

12- Lead ECG analyses

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

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

10.7 PK ANALYSIS

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

10.7.1 Treatment Exposure

The duration of exposure during the study will be presented by treatment and calculated as:
(Date of last study drug injection – date of first study drug injection) + 7

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

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

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

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

Endogenous anti-IL-1α antibodies are present in 5% to 28% of the general population[4,5,6,7]. No negative correlations with disease have been noted for these individuals. To the contrary, the presence of natural anti-IL-1α antibodies has been associated with favorable outcomes, both with respect to rheumatoid arthritis and ischemic heart disease. Animal studies also indicate that IL-1α loss or antagonism does not result in harm. Moreover, the well-tolerated use of other approved biological agents that employ other strategies to block IL-1 activity suggest that bermekimab's targeting of IL-1α represents a safe treatment approach.

1.2 RATIONALE

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

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

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

4. ELIGIBILITY CRITERIA

4.1 INCLUSION CRITERIA

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

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

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

Bermekimab is a recombinant human IgG1 monoclonal antibody specific for human interleukin-1α (IL-1α). As such, it is an immunomodulator that has anti-inflammatory and anti-neoplastic properties. Other agents that could be considered in the same pharmacologic class include biologic agents that target IL-1 receptor antagonist and IL-1 beta. Potential risks for agents in this class include infusion or injection site reactions, particularly with respect to IL-1ra, although in this case is likely related to the unanticipated agonist effects of the receptor antagonist when it is present in high local concentration at the site of injection and thus this effect is not relevant to bermekimab.

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

The mechanism behind infusion reactions is not clear in all cases. It may involve a reaction against the antibody, against excipients in the preparation such as polysorbate, or against some minor residual component from the manufacturing process (i.e. host cell proteins). To date, there has been a very low incidence of mild injection site or infusion reactions observed (20 patients out of 831 total; 2.4%). All except two of these patients had grade 1 or 2 reactions that did not result in discontinuation. In order to mitigate this class-specific risk, close monitoring is required during the bermekimab infusion and for at least 1 hour after infusion. Availability of resuscitation equipment must be ensured. ***Pre-medication with antihistamines or corticosteroids is not required.***

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

- Infusion Related Reactions
- Injection Site Reactions

11. STUDY MANAGEMENT AND ADMINISTRATION

11.1 ETHICAL CONDUCT OF STUDY (GCP)

The guidelines of the World Medical Association Declaration of Helsinki in its revised edition (48th General Assembly, Somerset West, Republic of South Africa, October 1996), the guidelines of ICH GCP (CPMP/ICH/135/95), as well as the demands of national drug and data protection laws and other applicable regulatory requirements, will be strictly followed. Approval will be obtained from the appropriate regulatory authorities before sites are initiated.

11.2 IRB AND ETHICS COMMITTEE APPROVAL

Prior to initiation of the study, the protocol, the informed consent form, the subject information sheet(s), details of the subject recruitment procedures and any other relevant study documentation will be submitted to the responsible IRB or Ethics Committee (EC). The Investigator will report promptly to the IRB/EC any new information that may adversely affect the safety of subjects or the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB/EC annually, or more frequently if requested by the IRB/EC. Upon completion of the study, the Investigator will provide the IRB/EC with a brief report of the outcome of the study, if required.

11.3 PROTOCOL MODIFICATIONS

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