SYNOPSIS

Study Title: A Phase 2a, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Interventional Study to Assess the Efficacy, Safety, Pharmacokinetics, and Immunogenicity of Multiple IV doses of Bermekimab for the Treatment of Adult Participants with Moderate-to-Severe Atopic Dermatitis

Study Number: 77474462ADM2003

Study Phase: 2a

Name of Study Intervention: JNJ-77474462 (bermekimab)

Name of Sponsor/Company: Janssen Research and Development, LLC

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Status: Approved

Date: 7 September 2022

Prepared by: Janssen Research & Development, LLC

Study Name: LUNA

Regulatory Agency Identifier Number:

IND	112459
NCT	NCT04990440

Number of Study Center(s) and Countries:

This study was conducted at 4 centers that enrolled participants in the United States (US) and Argentina.

Publications (if any):

None

Study Period:

21 August 2021 to 22 February 2022

Rationale:

Bermekimab (also known as JNJ 77474462 and monoclonal antibody (mAb) protein 1) is a recombinant human immunoglobulin G1 kappa mAb specific for human interleukin 1 alpha (IL-1α). Interleukin 1 alpha is a key mediator of cutaneous inflammation and is constitutively and inducibly expressed by several cell types, including keratinocytes where high levels of IL-1α are present in healthy individuals, these data suggest that IL-1α has the potential to mediate inflammation in the skin.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of 16 weeks of multiple intravenous (IV) doses of bermekimab, compared with placebo, in participants with moderate-to-severe atopic dermatitis (AD).	Proportion of participants with Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 16.
Secondary	
To evaluate the pharmacokinetics (PK) and immunogenicity of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in adult participants with moderate-to-severe AD.	Analyses of the following at all applicable visits from Week 0 through Week 16: • Serum concentrations of bermekimab over time, including steady-state trough serum concentrations. • The incidence and titers of antibodies to bermekimab.
To assess the safety and tolerability of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in participants with moderate-to-severe AD.	• Proportion of participants with treatment-emergent adverse events (TEAEs). • Proportion of participants with treatment-emergent serious adverse events (SAEs). • Proportion of participants with AEs leading to discontinuation of study intervention. • Proportion of participants with AEs reasonably related to study intervention. • Proportion of participants with AEs of infusion-related reactions. • Proportion of participants with AEs of infections, including serious infections and infections requiring oral or parenteral antimicrobial treatment. • Proportion of participants with clinically significant abnormalities in vital signs and laboratory tests.

To characterize additional assessments of efficacy of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in participants with moderate-to-severe AD.	Analyses of the following at applicable visits through Week 16 by visit, respectively: • Proportion of participants with both Validated Investigator Global Assessment scale (vIGA)-AD of 0 or 1 and a reduction from baseline of ≥2 points. • Proportion of participants with improvement (reduction) of eczema-related itch numerical rating scale (NRS) ≥4 from baseline among participants with a baseline itch value ≥4. • Proportion of participants with EASI-90.

HYPOTHESIS

The hypothesis for this study is that intravenous (IV) bermekimab treatment is superior to placebo as assessed by the proportion of participants achieving an Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at Week 16.

Methodology:

This was a Phase 2, double blind, randomized, placebo controlled, multicenter, interventional study designed conducted in the US and Argentina to assess the efficacy, safety, PK, biomarkers, and immunogenicity of multiple doses of bermekimab administered via IV infusion for the treatment of moderate to severe AD in adult participants.

The study had 3 periods planned: a screening period of up to 4 weeks, a double blinded placebo-controlled period of 16 weeks, and a Safety Follow Up period of 4 weeks, which included an End of Study visit. The study was to have 3 parts (A, B, and C) within the double blinded placebo-controlled period that was to run in parallel and/or staggered.

All participants were to be randomized in a 4:1 ratio to receive a weekly IV infusion of either bermekimab or placebo. Part A was planned to consist of approximately 10 participants receiving bermekimab 800 mg IV weekly or placebo. Part B was planned to consist of approximately 30 participants receiving bermekimab 1200 mg IV weekly or placebo. An analysis of the data from all 10 participants of Part A and the first 10 participants of Part B was to support optimization and selection of the bermekimab dose for Part C. Selection of the Part C bermekimab dose was to be based on PK, pharmacodynamics (PD), efficacy, and safety analyses. Part C was planned to consist of approximately 20 participants receiving bermekimab or placebo at a higher or lower dose (not <800 mg) than Part B, but with a maximum dose of 2400 mg IV weekly.

The study plan also included 4 mandatory skin biopsies (2 at baseline and 2 after dosing). All participants of Part A and the first 10 participants of Part B were required to have skin biopsies done at Week 0 (1 lesional and 1 non lesional), and at Week 6 (2 lesional). The rest of the participants were to be biopsied at Week 0 (1 lesional and 1 non lesional), and at Week 16 (2 lesional).

An internal and independent DRC was commissioned for this study. One database lock was planned for the end of the study.

Based on the data reviewed by the unblinded Interim Analysis Committee from a Phase 2b bermekimab study (GENESIS [77474462ADM2001]), it was determined that the GENESIS study had met its prespecified futility criteria (related to the primary endpoint) for both bermekimab dosing arms (bermekimab 350 mg or 700 mg weekly). The decision was made to terminate further clinical development

in AD, which included immediate termination of the LUNA (77474462ADM2003) study. Data from the GENESIS study also showed that the safety of bermekimab was consistent with its known safety profile and there were no new safety concerns for bermekimab in treated AD participants.

This abbreviated clinical study results summarizes only limited efficacy and safety data from participants who were enrolled and dosed with study intervention prior to early termination at the Sponsor's discretion.

Number of Participants (planned and analyzed):

A target of approximately 60 participants was to be randomly assigned in this study.

A total of 9 participants were screened of which 6 participants with moderate to severe AD from the US and Argentina were randomized.

Diagnosis and Main Criteria for Inclusion and Exclusion:

The participant population was comprised of men and women ≥18 years of age, with moderate to severe AD, that had been present for at least 1 year prior to the first administration of study intervention, as determined by the investigator through participant interview and/or review of the medical history. Participants were also required to have a history of inadequate response to treatment for AD with topical medications or for whom topical treatments were otherwise medically inadvisable, an EASI score ≥16, an IGA score ≥3, and an involved percent body surface area ≥10% at both screening and at baseline. Participants had to agree to apply moisturizers at least once daily for at least 7 days before randomization and continue the treatment throughout the study.

Study Interventions, Dose, Mode of Administration, and Batch Numbers:

The study intervention presentation used in this study was a sterile liquid formulation of 350 mg (175 mg/mL) of bermekimab in a prefilled syringe with an injectable volume of 2.0 mL.

Bermekimab was manufactured and provided under the responsibility of the sponsor. The manufacturing lot numbers for the study intervention(s) available to be dispensed in this study are provided below:

Lot Numbers	Kit	DP Lot	Expiry
T317190	Active	042120M1	21-Apr-2022
T320372	Active	062620M1B	26-Jun-2022
T323521	Active	072420M1B	24-Jan-2023
T316983	Placebo	DT1474	1-Apr-22
T323522	Placebo	EK9712	1-Nov-22

Duration of Study Intervention:

Approximately, 10 participants were planned to receive weekly 800 mg of IV bermekimab or placebo in Part A. Approximately, 30 participants were planned to receive a weekly dose of 1200 mg of IV bermekimab or placebo in Part B. After the initial 10 participants (8A [active]:2P [placebo]) had completed 6 weeks of dosing in Part B, safety, PK, PD, and efficacy were to be analyzed to determine an appropriate dose to be used in Part C. Approximately, 20 participants were planned to receive the determined dose of bermekimab or placebo in Part C. The maximum dose to be considered for Part C was to be 2400 mg IV weekly.

Statistical Methods:

This study was designed to enroll approximately 60 participants in order to have sufficient power to detect a difference between the participants receiving bermekimab and the participants receiving placebo for the primary endpoint of the proportion of participants achieving EASI-75 at Week 16.

The efficacy analyses were based on the full analysis set that included all participants (n=6) who were randomized at Week 0 and received at least 1 dose of study intervention. Efficacy data, including EASI, NRS, and vIGA-AD score were to be listed.

All safety analyses were made on the Safety Population, which included all participants who received at least 1 dose of study intervention. Safety data, including but not limited to, AEs, SAEs, infections, changes in laboratory assessments, and abnormal vital signs were listed. Treatment-emergent AEs were listed by treatment group and Medical Dictionary for Regulatory Activities system organ class and preferred terms.

SUMMARY OF RESULTS AND CONCLUSIONS:

Demographic and Baseline Characteristics:

A total of 9 participants were screened of which 6 participants with moderate to severe AD from the US and Argentina were randomized: 5 participants were randomized in Part A (4 participants to the bermekimab 800 mg treatment arm and 1 participant to the placebo arm) and 1 participant to the bermekimab 1200 mg treatment arm in Part B by interactive web response system (IWRS) error. Five participants discontinued treatment due to sponsor's decision but completed the safety follow-up while 1 participant from the bermekimab 1200 mg treatment arm was terminated early from the study at Week 1 at the sponsor's discretion as the IWRS had dispensed the incorrect investigational product kit.

The age of the participants ranged from 19 to 51 years and their body mass index ranged from 17.3 to 37.9 kg/m^2. There were 3 male and 3 female participants, of which 4 participants were White, 1 participant was American Indian or Alaskan Native, and 1 participant was Black or African American.

Two major protocol deviations were reported for 1 participant in the bermekimab 1200 mg treatment arm during the study. On 2 occasions (Days 1 and 7), the participant received incorrect dose due to an IWRS error. This participant was subsequently terminated from the study at the sponsor's discretion.

The study was subsequently terminated at the sponsor's discretion (02 February 2022) with the last participant's last visit on 09 March 2022.

Efficacy Results:

Due to the small sample size and short duration of treatment, the efficacy assessment was limited. Some participants showed improvements in EASI-75 assessments at certain timepoints; however, no meaningful conclusions can be drawn from these results.

Safety Results:

Summaries of AEs and other safety data are based on 6 participants who were randomized, received at least 1 dose of double-blind study intervention. Participants were analyzed according to the actual treatment received.

Five participants reported a total of 7 AEs during the study. The AEs were assessed as mild or moderate in intensity. A total of 3 cases of worsening AD were reported (2 participants in the bermekimab 800 mg treatment arm and 1 participant in the placebo arm). Of the 7 AEs, all but 2 had resolved; 1 AE of moderate vulvovaginal candidiasis had not resolved, and 1 AE of mild otitis externa was resolving at the time of this report. One AE of accidental overdose was reported in a participant who was mistakenly assigned to a higher dose cohort (bermekimab 1200 mg) due to an IWRS error. No safety related concerns were reported for this participant.

No deaths were reported during the study.

One participant from the bermekimab 800 mg treatment arm experienced a Grade 2 decrease in serum potassium level (3.0 mmol/L; normal range: 3.5 to 5.2 mmol/L) on Day 15. The serum potassium level had subsequently normalized during the study (Day 23: 4.2 mmol/L). No other clinical chemistry findings were reported during this study.

Except for 1 participant in the placebo arm who had a markedly abnormal respiratory rate, there were no clinically meaningful findings in the vital signs related to safety in this study.

Conclusions:

Due to the premature termination of the LUNA study, a small number of participants were treated over a short period of time (maximum of 6 weeks). This led to significant limitations in assessing the efficacy and safety of higher doses of bermekimab in participants with AD.

The lack of supportive positive data on efficacy, particularly from the higher dose (700 mg) cohort in the GENESIS (77474472ADM2001) study, suggests that there may not have been substantial additional benefit for AD patients from a higher dose of bermekimab. However, no safety concerns were observed with the study participants.

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