Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2b, Multicenter, Randomized, Placebo- and Active-comparator-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Bermekimab (JNJ-77474462) for the Treatment of Participants with Moderate to Severe Atopic Dermatitis

GENESIS

A Study of Bermekimab (JNJ-77474462) in the Treatment of Participants with Moderate to Severe Atopic Dermatitis

Protocol 77474462ADM2001; Phase 2b
Amendment 1
JNJ-77474462 (bermekimab)

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

Regulatory Agency Identifier Numbers:

IND: **112459**
EudraCT NUMBER: **2020-002587-31**

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Prepared by: Janssen Research & Development, LLC
EDMS number: EDMS-RIM-54593, 2.0

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

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Amendment 1	02 June 2021
Original Protocol	12 November 2020

Amendment 1 (02 June 2021)

Overall Rationale for the Amendment: Clarifications to the protocol have been implemented to provide guidance regarding the use of rescue therapy, correct the calculation error in Total Volume of Blood sample to be collected, and include additional safety measures related to 12-lead ECG (triplicate). Additional changes are also listed in the amendment table below.

Section Number and Name	Description of Change	Brief Rationale
1.3, Schedule of Activities; 8.2.3, Electrocardiograms	In Table 1, added Physical examination assessment at screening and removed assessment at Week 0. In Table 1, added Vital sign assessment at screening and added 12-lead ECG (triplicate) assessment at Week 16. In Section 8.2.3 (Electrocardiograms), added Week 16 timepoint to align with the Schedule of Activities (SoA) (Table 1).	Added Physical examination assessment at screening to evaluate eligibility. Added Vital sign and 12-lead ECG (triplicate) at Week 16 to monitor changes while on study intervention.
2.3.2, Dupilumab	Added details regarding hypersensitivity and eosinophilic conditions.	To provide details regarding hypersensitivity and eosinophilic conditions.
5.1, Inclusion Criteria; 5.3, Lifestyle Considerations	Criterion #10 was modified and the following text was removed: and/or ultraviolet [UV] therapy. Criterion #11 was modified to note that the participant agrees not to receive a live virus or live bacterial vaccination during the study, and for 90 days after the last administration. In Section 5.3, Criterion #7 was revised to participants must not receive a live virus or bacterial vaccination during the study and for 90 days after the last administration.	Ultraviolet therapy text was removed because the washout period of phototherapy is specified in exclusion criterion #21. The study protocol criterion was amended to note that the participant agrees not to receive a live virus or bacterial vaccination for 90 days to align with the Bermekimab Investigator's Brochure guidance on the use of live virus or live bacterial vaccination.
5.3, Lifestyle Considerations; 6.8.6, Vaccinations (including COVID-19)	Added COVID-19 vaccinations to lifestyle considerations and concomitant therapy.	To provide guidance regarding locally approved vaccinations (including emergency use-authorized COVID-19 vaccine).
6.8.1, Rescue Medication	Provided guidance that an IGA assessment will be required prior to starting rescue therapy. Removed language that hydrocortisone 2.5% ointment may be given to the participants for rescue treatment. Clarified that any topical corticosteroids and topical calcineurin inhibitors are allowed as rescue medication.	To provide guidance on the use of topical corticosteroids and topical calcineurin inhibitors as rescue medications during the study.

Section Number and Name	Description of Change	Brief Rationale
	Removed the following sentence from the last paragraph: No more than 2 rounds of rescue therapy may be used by a participant and these rounds must be separated by at least 1 week.	
6.8.4, Prohibited Therapy	Added the following clarifying text to topical calcineurin inhibitors: "except for rescue therapy". Added text to clarify both systemic and topical JAK inhibitors are prohibited in the study.	To allow topical calcineurin inhibitors as rescue medications. Topical JAK therapies are available in some countries.
7.1, Discontinuation of Study Intervention	From the 4th bullet point, removed restrictive clinical details regarding hypersensitivity assessment. From the 5th bullet point, removed "occurring 1 to 14 days" after study intervention because this was considered a restrictive time frame.	The revised sentences allow the investigator to perform clinical assessment without restrictive details/time frame.
8, Study Assessments and Procedures	In Table 3, the TB testing sample with a Volume per Sample (mL) was updated to 4 mL and the Approximate Total Volume of Blood (mL) was updated to 4 mL. In Table 3, the Serum Biomarker with a Volume per Sample (mL) was updated to 8.5 mL and No. of Samples per Participant was updated to 9. The Approximate Total Volume of Blood (mL) was updated to 76.5 mL. In Table 3, updated the Approximate Total Volume to 344 mL. Updated total blood volume in the paragraph above Table 3.	The tube size for TB collection changed. Corrected calculation error in Total Volume of Blood (mL) in the previous version of the protocol.
8.2.7, Injection-site Reactions	Added guidance regarding monitoring for injection-site reactions after study intervention administration.	Added for clarification.
8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information	A definition was provided to clarify what constitutes a possible Hy's Law case.	Added for clarification.
10.3, Appendix 3: Contraceptive Guidance	Minor updates to the appendix.	Minor edits were made to align with the sponsor's most current template.
10.4, Appendix 4: Hepatitis B Virus (HBV) Screening with HBV DNA Testing	Added Japan specific guidance regarding surface antigen (HBsAg), core antibody (anti-HBc), and/or surface antibody (anti-HBs) monitoring.	To provide guidance and evaluations to be obtained in the setting of specific patterns of hepatitis B virus test abnormalities.
10.5.1, Appendix 5: Regulatory, Ethical, and Study Oversight Considerations	Added text regarding the use of a "Protocol Clarification Communication".	The sponsor's template was updated to include potential use of a "Protocol Clarification Communication".
10.20, Appendix 20: Clinical Laboratory Tests	Added a Clinical Chemistry footnote description about liver abnormalities that cross-references	A Clinical Chemistry footnote was added to align with the sponsor's most current template.

Section Number and Name	Description of Change	Brief Rationale
	Appendix 21. Potential Hy's Law case description was added (cross-reference to Section 8.3.1).	
10.21, Appendix 21: Liver Safety: Suggested Actions and Follow-up Assessments	The following new subsections were added: 10.21.1, Stopping Algorithm; 10.21.2, Follow-up Assessments; and 10.21.2.1, Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments.	The sponsor's template was updated to provide guidance and evaluations to be obtained in the setting of specific patterns of liver enzymes abnormalities.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol number: 77474462ADM2001

A Phase 2b, Multicenter, Randomized, Placebo- and Active-comparator-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Bermekimab (JNJ-77474462) for the Treatment of Participants with Moderate to Severe Atopic Dermatitis

JNJ-77474462 (bermekimab) is a recombinant human immunoglobulin G1 kappa monoclonal antibody (mAb) that binds with high affinity and selectivity for human interleukin-1 alpha (IL-1α) and is an effective blocker of IL-1α biological activity. IL-1α is a key mediator of sterile inflammatory responses. Skin is a significant reservoir of preformed IL-1α, and it has been postulated that IL-1α may play a role in the pathophysiology of multiple inflammatory skin disorders, including atopic dermatitis (AD).

Bermekimab has been investigated in dermatologic clinical studies and in other indications. Two Phase 2 studies (1 in AD and 1 in hidradenitis suppurativa) are currently ongoing.

Bermekimab was initially developed by XBiotech, Inc and is currently being developed by Janssen Research and Development, LLC (sponsor).

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of bermekimab in participants with moderate to severe AD	• Proportion of participants with Eczema Area and Severity Index-75 (EASI-75, ≥75% improvement from baseline) at Week 16
Secondary	
• To characterize additional assessments of efficacy for bermekimab in participants with moderate to severe AD	• Proportion of participants with both validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) of 0 or 1 and a reduction from baseline of ≥2 points at Week 16 • Proportion of participants with improvement (reduction) of eczema-related itch numeric rating scale (NRS) ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 • Proportion of participants with EASI-90 at Week 16
• To evaluate the efficacy of bermekimab relative to dupilumab in participants with moderate to severe AD	• Proportion of participants with EASI-75 at Week 16 • Proportion of participants with EASI-90 at Week 16 • Proportion of participants with both vIGA-AD of 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16

Objectives	Endpoints
	• Proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4
• To assess the safety and tolerability of bermekimab in participants with moderate to severe AD	• Number/proportion of participants with treatment-emergent adverse events (AEs) • Number/proportion of participants with treatment-emergent serious adverse events (SAEs)
• To evaluate the pharmacokinetics (PK) and immunogenicity of bermekimab in adult participants with moderate to severe AD	• Bermekimab concentration over time • The incidence of antibodies to bermekimab
Exploratory	
• To further characterize efficacy of bermekimab in participants with moderate to severe AD	• Improvement from baseline to Week 16 in Severity Scoring of Atopic Dermatitis (SCORAD) • Change from baseline to Week 16 in Dermatology Life Quality Index (DLQI) • Improvement from baseline to Week 16 in Patient-Oriented Eczema Measure (POEM) • Improvement from baseline to Week 8 in eczema-related itch NRS • Improvement from baseline to Week 8 in eczema-related pain NRS • Improvement from baseline to Week 16 in eczema-related pain NRS • Improvement from baseline to Week 16 in itch as measured by the Atopic Dermatitis Itch Scale (ADIS) • Proportions of participants with a Patient Global Impression of Severity (PGIS) score of 1 (none) or 2 (mild) at Week 16 • Change from baseline to Week 16 in Patient-Reported Outcomes Measurement Information System (PROMIS)-29 total score and sub-scores • Hand Dermatitis Investigator Global Assessment (IGA) at Week 16
• To assess the impact of treatment with bermekimab on selected biomarkers	• Changes in cellular and molecular biomarkers in skin and blood from baseline

Hypothesis

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

OVERALL DESIGN

This is a randomized, double-blind, placebo- and active-comparator-controlled, multicenter, interventional study to assess the efficacy, safety, PK, and immunogenicity of subcutaneous (SC) administered bermekimab for the treatment of moderate to severe AD in adult participants. The participant population will be comprised of men and women ≥18 years of age, with AD that is moderate to severe, and has been present for at least 1 year before the first administration of study intervention, as determined by the investigator through patient interview and/or review of the medical history. Participants must also have a history of inadequate response to treatment for AD with topical medications or for whom topical treatments are otherwise medically inadvisable, an EASI score ≥16, an IGA score ≥3, and an involved percent body surface area (BSA) ≥10% at both screening and at baseline. Participants must agree to apply moisturizers at least once daily for at least 7 days before randomization and continue the treatment throughout the study.

Two planned database locks (DBLs) will occur when all participants complete the Week 16 visit and at Week 36 (end of study).

The end of study is considered as the last visit for the last participant in the study.

An independent, external data monitoring committee (DMC), whose members are not directly involved in the conduct of study 77474462ADM2001, will review unblinded safety data to ensure the safety of the participants enrolled in this study.

NUMBER OF PARTICIPANTS

Approximately 200 participants are targeted for enrollment in Study 77474462ADM2001.

INTERVENTION GROUPS AND DURATION

Group 1: Placebo

- Participants will receive 2 placebo SC administrations weekly from Week 0 through Week 15.
- At Week 16, participants will crossover to receive 2 bermekimab 350 mg SC administrations weekly through Week 31.

Group 2: Bermekimab 350 mg SC every week (qw)

- Participants will receive 1 bermekimab 350 mg SC administration and 1 placebo SC administration at Week 0 and every week thereafter through Week 31.

Group 3: Bermekimab 700 mg SC qw

- Participants will receive 2 bermekimab 350 mg SC administrations at Week 0 and every week thereafter through Week 15.
- At Week 16, participants who achieve an EASI-75 response will be rerandomized in a 1:1 ratio either to continue to receive 2 bermekimab 350 mg SC administrations weekly, or to receive 1 bermekimab 350 mg SC administration and 1 placebo SC administration weekly, through Week 31.
- At Week 16, participants who do not achieve an EASI-75 response will continue to receive 2 bermekimab 350 mg SC administrations weekly through Week 31.

Group 4: Comparator/Reference Arm (Dupilumab)

- Participants will receive 2 dupilumab 300 mg SC administrations at Week 0. Participants will receive 2 placebo SC administrations every 2 weeks (q2w) beginning at Week 1 through Week 15. Participants will receive 1 dupilumab 300 mg SC administration and 1 placebo SC administration q2w beginning at Week 2 through Week 14.
- Participants who achieve an EASI-75 response at Week 16 will continue on 1 dupilumab 300 mg SC administration and 1 placebo SC administration q2w from Week 16 through Week 30, and 2 placebo SC administrations q2w from Week 17 to 31.
- At Week 16, participants who do not achieve an EASI-75 response will receive 2 placebo SC administrations weekly at Weeks 16 through 18 (ie, washout period), and 2 bermekimab 350 mg SC administrations weekly from Week 19 through Week 31.

Description of Interventions

Bermekimab will be supplied as a sterile liquid formulation of 350 mg (175 mg/mL) of bermekimab in a prefilled syringe (PFS) with an injectable volume of 2.0 mL. Bermekimab will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure for a list of excipients.

Commercially available dupilumab will be provided by the sponsor as a sterile liquid formulation of 300 mg (150 mg/mL) in a PFS with an injectable volume of 2.0 mL.

Placebo will be provided by the sponsor.

EFFICACY EVALUATIONS

Efficacy assessments (EASI, vIGA-AD™, percent BSA involvement, SCORAD, and Hand Dermatitis IGA) and patient-reported outcome (PRO) measures (DLQI, POEM, PGIS, PROMIS-29, Eczema Skin Pain and Itch NRS, and ADIS) will be performed at visits according to the Schedules of Activities. Serum samples for PK, immunogenicity, and biomarker analyses will be collected at the timepoints shown in the Schedules of Activities. Digital actigraphy and evaluation of EASI and SCORAD endpoints from digital photographs will be completed from a subgroup of participants who consent to these optional substudies at selected sites.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Venous blood samples will be collected for the measurement of serum bermekimab concentrations and detection of antibodies to bermekimab at the time points presented in the Schedule of Activities. Serum samples will also be collected at the final visit from participants who terminate study participation early.

BIOMARKER EVALUATIONS

Biomarker samples will be collected to evaluate the pharmacodynamics (PD) and mechanism of action of bermekimab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to the intervention.

PHARMACOGENOMIC (DNA) EVALUATIONS

A whole blood sample will be collected for pharmacogenomic research in participants who consent separately to this optional part of the study (where local regulations permit). Genotyping or sequencing techniques will be used to assess variation in the filaggrin (*FLG*) gene, a risk factor for AD, and interleukin-1 alpha gene (*IL1A*), the target of bermekimab. Additionally, genome-wide genotyping or sequencing will be used to assess variation genome-wide. Participants will have the option to participate in 1 or both of these studies.

SAFETY EVALUATIONS

Safety evaluations conducted at each study visit will include the assessment of AEs (at the visit and those occurring between evaluation visits), a tuberculosis evaluation and other infection assessment, clinical laboratory blood tests (complete blood count and serum chemistries), physical examinations, vital sign measurements, concomitant medication review, and observations for injection-site reactions and/or allergic reactions.

STATISTICAL METHODS

Sample Size Determination

This study is designed to enroll approximately 200 participants in order to have sufficient power to detect a difference between the bermekimab groups and the placebo group for the primary endpoint of the proportion of participants achieving EASI-75 at Week 16. The sample size was also chosen to have adequate confidence level for the difference between the bermekimab 700 mg group and the dupilumab group.

The EASI-75 response rate in the bermekimab 400 mg qw group was approximately 35% at Week 16 and 70% at Week 7 from the placebo-controlled study (77474462ADM2002) and the open-label study (2018-PT044), respectively. The EASI-75 response rates at Week 16 were 15% and 12% with placebo and 51% and 44% with dupilumab, respectively, in the two Phase 3 trials of dupilumab versus placebo in the treatment of adult participants with moderate to severe AD.

The EASI-75 response at Week 16 are assumed to be 15% for placebo, 45% to 50% for dupilumab, and 50% to 70% for the bermekimab 350 mg and 700 mg treatment groups, respectively. Based on these assumptions, approximately 200 participants are planned to be randomized in a 1:1:2:2 ratio to the placebo (n=33), bermekimab 350 mg (n=33), bermekimab 700 mg (n=67), or dupilumab (n=67) treatment groups. These sample sizes provide the study with at least 88% power to detect a treatment difference between the bermekimab treatment groups and the placebo group in EASI-75 at Week 16 based on a 2-sample Z-test at a Type I error rate of 0.05 (2-sided). These sample sizes also provide at least 88% power to detect a treatment difference between the dupilumab and placebo treatment group in EASI-75 at Week 16 at a 2-sided significance level of 0.05.

Efficacy Analyses

All randomized participants who received at least 1 dose of study intervention will be included in the efficacy analyses. Participants will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received.

The treatment comparisons for binary endpoints will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline EASI severity or Fisher's exact test in the case of rare events. The differences in binary endpoints between groups and the corresponding CIs will be presented. For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM will include treatment, visit, baseline EASI severity, baseline score, baseline score by visit interaction, baseline EASI severity by visit interaction, and the treatment-by-visit interaction, if applicable. The Least Square mean (LSmean) estimates and their corresponding 95% confidence interval (CI) will be provided at each time point. In addition, the estimates of LSmean difference and 95% CIs between treatment groups will be provided.

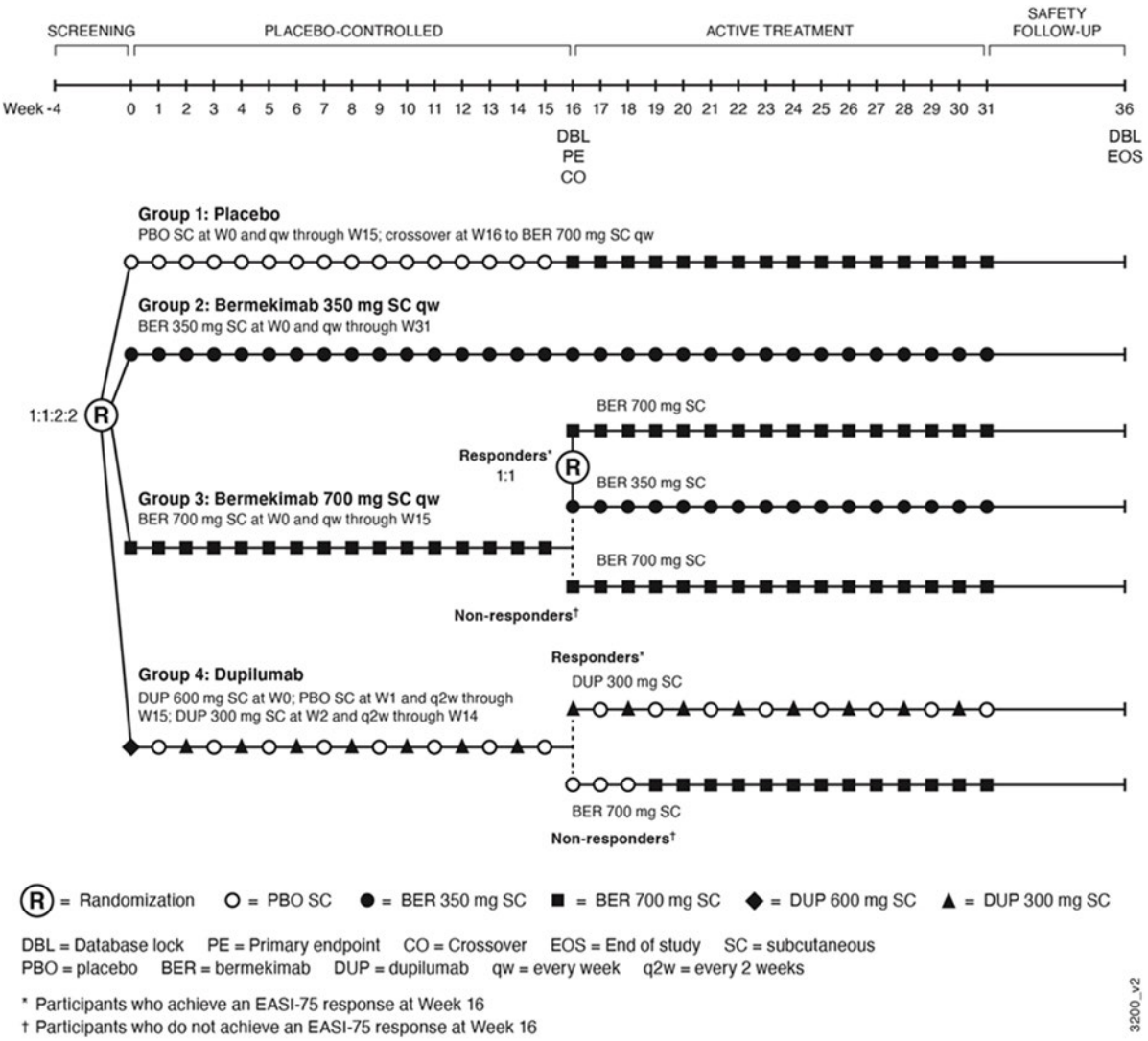
In general, all statistical testing will be performed at a significance level of 0.05 (2-sided) unless otherwise specified. Nominal p-values will be displayed for all treatment comparisons.

Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedules of Activities

Two Schedules of Activities (SoA) are presented below, the first for the study period from screening through Week 16 (Table 1) and the second from Week 17 through Week 36 (Table 2).

Table 1: Schedule of Activities From Screening through Week 16

Period	Screening[a]	Blinded, Placebo-controlled Period[m]																
Week[b]	(−28 Days to −7 Days)	0	1	2	3[t]	4	5[t]	6	7[t]	8	9[t]	10	11[t]	12	13[t]	14	15[t]	16
Study Procedure[c]																		
Screening/Administrative																		
Informed consent (ICF)[d]	X																	
ICF for optional pharmacogenomic research[d]	X																	
ICF for optional actigraphy substudy[d]	X																	
ICF for optional total body photography substudy[d]	X																	
ICF for optional biomarker substudy[d]	X																	
Medical History/ Demographics	X	X																
Inclusion/exclusion criteria	X	X																
Study Treatment Administration																		
Randomization		X																
Study intervention administration[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations																		
Physical examination	X																	X
Height		X																
Weight		X																X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph	X																	
12-lead ECG (triplicate)	X																	X
Urine pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy		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
Efficacy Evaluations																		
EASI	X	X		X		X		X		X		X		X				X
vIGA-AD	X	X		X		X		X		X		X		X				X
SCORAD	X	X		X		X		X		X		X		X				X
Hand dermatitis IGA		X				X				X				X				X
Total body photography[g]		X								X								X

Table 1: Schedule of Activities From Screening through Week 16

Period	Screening[a]	Blinded, Placebo-controlled Period[m]															
Week[b]	(−28 Days to −7 Days)	0	1	2	3[t]	4	5[t]	6	7[t]	8	9[t]	10	11[t]	12	13[t]	14	15[t]	16
DLQI[h]		X								X				X				X
POEM[h]		X								X				X				X
PGIS[h]		X								X				X				X
PROMIS-29[h]		X								X				X				X
Eczema Skin Pain and Itch NRS[i]	X	X----------																X
ADIS[i]	X	X----------																X
Actigraphy[i,j]	X	X----------																X
Clinical Laboratory Tests																		
QuantiFERON-TB® test (or T-SPOT® for sites in Japan)[k]	X																	
Hepatitis B and C serology	X																	
HIV antibody test	X																	
Hematology	X	X				X				X				X				X
Chemistry	X	X				X				X				X				X
Pharmacokinetics and Immunogenicity																		
Serum bermekimab concentration[l]		X	X			X				X				X				X
Population PK sample[l,m]				----------X[n]----------														
Antibodies to bermekimab[l]		X				X				X				X				X
Biomarkers																		
Serum Biomarkers		X				X				X								X
Blood sample for RNA[o]		X				X												X
Whole blood (PBMC)[o]		X				X												X
Whole blood (pharmacogenomics)[p,q]		X																
Skin biopsy[q,r]		X																X
Tape stripping[r]		X				X												X
Skin swab[q,s]		X				X												X

Table 1: Schedule of Activities From Screening through Week 16

Period	Screening[a]	Blinded, Placebo-controlled Period[m]																
Week[b]	(−28 Days to −7 Days)	0	1	2	3[t]	4	5[t]	6	7[t]	8	9[t]	10	11[t]	12	13[t]	14	15[t]	16

Abbreviations: ADIS = Atopic Dermatitis Itch Scale; DLQI = Dermatological Life Quality Index; EASI = Eczema Area and Severity Index; ECG= electrocardiogram; HIV = human immunodeficiency virus; ICF = informed consent; IGA = Investigator Global Assessment; NRS = numeric rating scale; PBMC= peripheral blood mononuclear cells; PGIS = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; PROMIS-29 = Patient-Reported Outcomes Measurement Information System-29; RNA = ribonucleic acid; SCORAD = Severity Scoring of Atopic Dermatitis; TB = tuberculosis; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.

Footnotes:

a. The screening visit should occur no more than 28 days prior to and no less than 7 days before the Week 0 (baseline) visit.
b. Study visit dates in Weeks 1 through 32 must be calculated from the first study intervention administration visit in Week 0. Visit and study intervention administrations should occur within ±3 days of scheduled visit.
c. All study procedures and evaluations are to be completed before study intervention is administered except where otherwise indicated.
d. Must be signed before first study-related activity. Separate informed consents are required for participants who chose to participate in the optional pharmacogenomic research, biomarkers, actigraphy, and total body photography substudies.
e. Study intervention administrations must occur no less than 4 days apart.
f. Women of childbearing potential must have a negative urine pregnancy test result before randomization and before receiving study intervention at all study intervention administration visits. This assessment can be performed any other time during the study visit including prior to PRO collection.
g. The optional total body photography for remote efficacy evaluations will be completed for a limited number of participants at some sites.
h. All PROs should be collected during the study visit prior to all other assessments, unless otherwise specified.
i. These assessments should be completed daily beginning at the screening visit.
j. The optional actigraphy substudy will be completed for a limited number of participants at some sites.
k. All participants will undergo QuantiFERON®-TB (or T-SPOT® for sites in Japan) testing. If the QuantiFERON®-TB test is not approved/registered in the country in which this protocol is being conducted or the tuberculin skin test is mandated by local health authorities, a negative tuberculin skin test result is also required. In Ukraine, while the QuantiFERON®-TB test is not approved/registered, it is accepted, and a tuberculin skin test is not required.
l. For all visits where study intervention will be administrated, all blood samples should be collected prior to study intervention administration for evaluation of serum concentration of bermekimab and/or antibodies to bermekimab.
m. Participants who discontinue study intervention but do not terminate study participation are strongly encouraged to return for all protocol-specified procedures and evaluations for approximately 5 weeks following the last dose of study intervention. The procedures and evaluations listed for the Early Termination visit in Table 2 should also be performed approximately 5 weeks after the last dose of study intervention. Participants who terminate study participation early should complete the procedures and evaluations listed for the Early Termination visit in Table 2 approximately 5 weeks after their last administration of study intervention.
n. A venous blood sample for population PK analysis will be collected from all participants at an additional study site visit and must occur on a random day between Week 2 and Week 12. This visit must not occur on the same day as the scheduled Week 4, Week 8, or Week 12 visits and cannot be collected within 24 hours (either prior to or after) of the actual time of study intervention administration at Week 4, Week 8, or Week 12.
o. Blood sample will be taken pre-dose
p. The whole blood (pharmacogenomics) sample is optional and should be collected at the specified time point; however, if necessary, it may be collected at a later time point without constituting a protocol deviation.
q. Participation is optional.
r. Biopsy and tape strip samples to be collected pre-dose. At Week 0, lesional and non-lesional skin samples will be collected. At later timepoints, lesional skin samples will be collected.
s. Skin swab will be collected before skin biopsy and/or tape stripping. Two swabs will be collected – one from the lesional skin from where skin biopsy will be taken and the second one from the adjacent non-lesional skin.
t. At Weeks 3, 5, 7, 9, 11, 13, and 15 there may be an option for a home health nurse visit instead of a site visit where feasible in the sponsor's opinion.

Table 2: Schedule of Activities From Week 17 through Week 36

Period	Blinded Active Treatment Phase																Safety Follow-up (EOS)[b]	Early Termination Visit (ET)[b,i]
Week[a]	17[k]	18	19[k]	20	21[k]	22	23[k]	24	25[k]	26	27[k]	28	29[k]	30	31[k]	32	36	
Study Procedure[c]																		
Study Treatment Administration																		
Study intervention administration[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Safety Evaluations																		
Physical examination																X	X	X
Weight																X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TB evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	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	X
Efficacy Evaluations																		
EASI		X		X		X		X		X		X				X	X	X
vIGA-AD		X		X		X		X		X		X				X	X	X
SCORAD		X		X		X		X		X		X				X		X
Hand dermatitis IGA				X				X				X				X		X
DLQI[f]				X				X				X				X		X
POEM[f]				X				X				X				X		X
PGIS[f]				X				X				X				X		X
PROMIS-29[f]				X				X				X				X		X
Eczema Skin Pain and Itch NRS[g]	X----------X																X	X
ADIS[g]	X----------X																	X
Clinical Laboratory Tests																		
Hematology				X				X				X				X	X	X
Chemistry				X				X				X				X	X	X
Pharmacokinetics and Immunogenicity																		
Serum bermekimab concentration[h]				X				X				X				X	X	X
Antibodies to bermekimab[h]								X								X	X	X

Table 2: Schedule of Activities From Week 17 through Week 36

Period	Blinded Active Treatment Phase																Safety Follow-up (EOS)[b]	Early Termination Visit (ET)[b,i]
Week[a]	17[k]	18	19[k]	20	21[k]	22	23[k]	24	25[k]	26	27[k]	28	29[k]	30	31[k]	32	36	
Biomarkers																		
Serum Biomarkers				X				X				X				X	X	X
Blood sample for RNA[j]				X												X		
Whole blood (PBMC)[j]				X												X		
Tape stripping																X		

Abbreviations: ADIS = Atopic Dermatitis Itch Scale; DLQI = Dermatological Life Quality Index; EASI = Eczema Area and Severity Index; EOS= end of study; ET = early termination; IGA = Investigator Global Assessment; NRS = numeric rating scale; PBMC= peripheral blood mononuclear cells; PGIS = Patient Global Impression of Severity; POEM = Patient-Oriented Eczema Measure; PROMIS-29 = Patient-Reported Outcomes Measurement Information System-29; RNA = ribonucleic acid; SCORAD = Severity Scoring of Atopic Dermatitis; TB = tuberculosis; vIGA-AD = validated Investigator Global Assessment for Atopic Dermatitis.

Footnotes:

a. Study visit dates in Weeks 1 through 32 must be calculated from the first study intervention administration visit in Week 0. Visit and study intervention administrations should occur within ±3 days of scheduled visit.
b. Study visit dates in for the Safety follow-up visit or Early Termination visit must be calculated from the date of the last administration of study intervention. The Safety follow-up visit should occur within -1 to +3 days of scheduled visit.
c. All study procedures and evaluations are to be completed before study intervention is administered except where otherwise indicated.
d. Study intervention administrations must occur no less than 4 days apart.
e. Women of childbearing potential must have a negative urine pregnancy test result before randomization and before receiving study intervention at all study intervention administration visits. This assessment can be performed any other time during the study visit including prior to PRO collection.
f. All PROs should be collected during the study visit prior to all other assessments, unless otherwise specified
g. Daily administration.
h. For all visits where study intervention will be administrated, all blood samples should be collected prior to study intervention administration for evaluation of serum concentration of bermekimab and/or antibodies to bermekimab.
i. Participants who discontinue study intervention but do not terminate study participation are strongly encouraged to return for all protocol-specified procedures and evaluations for approximately 5 weeks following the last dose of study intervention. The procedures and evaluations listed for the Early Termination visit should also be performed approximately 5 weeks after the last dose of study intervention. Participants who terminated study participation early should complete the procedures and evaluations listed for the Early Termination visit approximately 5 weeks after their last administration of study intervention.
j. Blood sample will be taken pre-dose.
k. At Weeks 17, 19, 21, 23, 25, 27, 29, and 31 there may be an option for a home health nurse visit instead of a site visit where feasible in the sponsor's opinion.

2. INTRODUCTION

JNJ-77474462 (bermekimab) is a recombinant human immunoglobulin G1 kappa monoclonal antibody (mAb) that binds with high affinity and selectivity for human interleukin-1 alpha (IL-1α) and is an effective blocker of IL-1α biological activity. IL-1α is a key mediator of sterile inflammatory responses. Skin is a significant reservoir of preformed IL-1α, and it has been postulated that IL-1α may play a role in the pathophysiology of multiple inflammatory skin disorders, including atopic dermatitis (AD).

Fourteen clinical studies to date have been conducted using bermekimab, including 12 completed studies in a wide range of therapeutic areas, and two Phase 2 studies currently ongoing, 1 in AD and 1 in hidradenitis suppurativa (HS). Bermekimab has been administered intravenously (IV) at doses ranging from 0.25 mg/kg to 7.5 mg/kg and subcutaneously (SC) at doses from 100 mg to 800 mg.

For the most comprehensive nonclinical and clinical information regarding bermekimab, refer to the latest version of the Investigator's Brochure (IB) for bermekimab.

The term “study intervention” throughout the protocol, refers to bermekimab, dupilumab, or placebo as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

This is a Phase 2 randomized, placebo- and active-comparator-controlled, multicenter study to assess the safety and efficacy of bermekimab in adult participants with moderate to severe AD using a placebo control and an active reference arm (DUPIXENT® [dupilumab]) by means of:

- Assessment of the efficacy of bermekimab through Week 16.
- Evaluating the longer-term efficacy resulting from the SC dose regimens of bermekimab through 32 weeks.
- Evaluating the efficacy of bermekimab relative to dupilumab
- Evaluating safety and tolerability data for bermekimab in these AD participants.

In addition, this study will evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of bermekimab therapy in participants with AD.

The scientific rationale in support of the study as well as relevant background information on nonclinical and clinical studies of bermekimab are summarized in Section 2.2.

An overview of the protocol design and supportive rationale is described in Section 4.

2.2. Background

Atopic dermatitis is an inflammatory skin disease that has been reported to affect up to 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.

Interleukin-1α plays a key role in the pathophysiology of a wide range of inflammatory skin disorders (Bou-Dargham 2017). Keratinocytes are a major reservoir of IL-1α and may be a key source of inflammatory stimulus in AD. Skin barrier defect and dysbiosis in AD stimulates keratinocytes to secrete chemokines and innate cytokines such as IL-1α, resulting in leukocyte infiltration and trafficking into skin to sustain chronic inflammation in AD. IL-1α is a key inducer of matrix metalloproteinases activity which could be directly involved in the epithelial barrier breakdown in AD (Han 2005). In addition, IL-1α, rather than IL-1β, was determined to be the primary driving force for inducing chronic skin inflammation (Archer 2019). 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 (eg, 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 (McAleer 2013). Filaggrin deficiencies are associated with changes in the composition of bacteria living on the skin of AD patients (Clausen 2017), whereby bacteria can colonize and infect the skin with greater success thereby exacerbating aberrant IL-1α secretion (Kezic 2012). In addition to being a driver of inflammation, IL-1α has been shown to induce pain mediator substance P secretion by neurons (Skoff 2009). Neutralizing IL-1α activity resolved chronic skin inflammation in the study by Skoff and strongly supported IL-1α as a key target for treating AD, along with other inflammatory skin diseases.

Endogenous anti-IL-1α antibodies are present in 5% to 28% of the general population (Gallay 1991; Miossec 2002; Saurat 1991; Suzuki 1991). 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 bermekimab targeting of IL-1α represents a safe treatment approach.

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

In previous dermatology studies, bermekimab demonstrated therapeutic activity and a well-tolerated safety profile.

Nonclinical Studies

A comprehensive overview of the nonclinical development program for bermekimab is available in Section 3 of the latest version of the bermekimab IB.

This section provides a summary of the sponsor's assessment of how the overall nonclinical data support the safety of the proposed dosing for bermekimab in this Phase 2 program in AD.

Bermekimab binds with high affinity and specificity to human IL-1α with a dissociation rate constant (K_D) of 0.14 nM. No binding to human IL-1β or interleukin-1 receptor antagonist (IL-1Ra) was detected up to the highest concentrations tested. In addition, bermekimab was shown to effectively neutralize the ability of human IL-1α to induce endothelial cell expression of adhesion molecules and fibroblast expression of interleukin-6 (IL-6). Bermekimab was bound by cynomolgus monkey IL-1α with a K_D of 3 nM and did not bind with mouse, rat, or pig IL-1α at the highest concentrations tested.

A 1-month repeat intraperitoneal dose mouse study tested bermekimab up to 3 doses of 312 mg/kg/week. No treatment-related adverse effects were observed.

Clinical Studies

Results from a Phase 2, open-label, dose escalation study of bermekimab in participants with moderate to severe AD showed that bermekimab appeared to be safe, well tolerated, and active at reducing the severity of AD, including reducing itch and pain (study 2018-PT044, NCT03496974). Thirty-eight patients across 9 clinical sites in 2 treatment groups received 1 of 2 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 Eczema Area and Severity Index (EASI), IGA, Numerical Rating Scale, Severity Scoring of Atopic Dermatitis (SCORAD), Patient-Oriented Eczema Measure (POEM), Dermatological Life Quality Index (DLQI), and Global Individual Signs Score from baseline to visit 9. The primary measure of efficacy was the EASI. In the study, 39% of participants in the 400 mg dose group achieved a 75% improvement in EASI score (EASI-75) after 4 weeks of therapy and 75% achieved EASI-75 at Week 8. An IGA score of 0 (clear) or 1 (minimal) and a ≥2-point decrease from baseline IGA at Week 7 was achieved by 25% of participants in the 400 mg dose group. In addition, 61% of participants in the 400 mg dose group achieved a 4-point or greater improvement in the Pruritus Numerical Rating Scale for overall itch; and 75% achieved a 4-point or greater improvement by Week 8. Furthermore, 80% of participants in the 400 mg dose group achieved a 4-point or greater improvement in the Numerical Rating Scale for pain by Week 8.

Preliminary internal company data from a Phase 2 study, 77474462ADM2002 (NCT04021862), have recently become available and were used to support decisions about the dose regimens and design of this study. Study 77474462ADM2002 is a double-blind, placebo-controlled study of bermekimab in adult participants with moderate to severe AD. The primary endpoint of this study

is the percentage of patients achieving EASI-75 (≥75% improvement from baseline) at Week 16. Preliminary results from this study are discussed in Section 4.3.

In other clinical studies completed to date in AD and HS, bermekimab was well tolerated and demonstrated therapeutic activity. For the most comprehensive clinical information regarding bermekimab, refer to the latest version of the IB for bermekimab.

2.2.1. Comparator/Active Reference Arm

DUPIXENT® (dupilumab)]

Dupilumab (DUPIXENT, Regeneron Pharmaceuticals, Inc.) is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Dupilumab was selected as the active reference arm for this study because it has demonstrated efficacy in patients with moderate to severe AD and serves as a useful efficacy benchmark. Dupilumab has been approved for treatment of moderate to severe AD in the adult and pediatric populations in the United States, Canada, the European Union, and the Asia-Pacific region.

For further information regarding dupilumab, refer to the current prescribing information.

2.3. Benefit-Risk Assessment

2.3.1. Bermekimab

Based on the available data and the proposed safety measures discussed below, the risks of the dose regimens of bermekimab to be investigated in this protocol appear to be acceptable relative to the potential benefit.

Bermekimab has undergone previous clinical evaluation in diseases such as psoriasis, AD, HS, acne vulgaris, pyoderma gangrenosum, and cancer, as summarized in the latest version of the IB. The collective efficacy and safety results of the Phase 1 and Phase 2 clinical studies in healthy volunteers and patients in dermatologic indications have indicated a favorable benefit-risk profile for bermekimab. In addition, nonclinical evidence suggests that IL-1α may be an important component for inducing chronic skin inflammation (Abdel-Razzak 1993, Murphy 2000).

Unblinded safety will be evaluated on an ongoing basis throughout this study by an independent external Data Monitoring Committee (DMC), in addition to the standard safety oversight performed by the sponsor. Details about the safety evaluations that will be utilized to continue or modify the protocol as the trial progresses are outlined in Section 9.6 and in the DMC charter.

The risks for bermekimab are infections, hypersensitivity reactions, and injection site reactions. More detailed information about the known and expected benefits and risks of bermekimab may be found in the IB.

The safety plan for bermekimab includes monitoring of AEs and safety laboratory results, using sites adequately prepared for managing hypersensitivity reactions and patient education for recognizing signs of a serious hypersensitivity reaction such as anaphylaxis. In addition, participants will be screened for tuberculosis (TB) prior to study entry (Section 8.2.8.1) and receive regular ongoing evaluation (Section 8.2.8.2).

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with bermekimab are justified by the anticipated benefits that may be afforded to participants with AD.

2.3.2. Dupilumab

The benefit:risk profile of dupilumab was established in multiple Phase 3 studies, which were the basis of global approvals for dupilumab in the treatment of moderate to severe AD in adult and pediatric populations. Warnings and precautions for dupilumab include hypersensitivity (including anaphylactic reaction, angioedema and serum sickness), conjunctivitis and keratitis, worsening of eosinophilic conditions (such as eosinophilic pneumonia and vasculitis consistent with eosinophilic granulomatosis with polyangiitis), exercising caution with reduction of corticosteroid dosage, and worsening of pre-existing parasitic infections. More detailed information about the known and expected benefits and risks of dupilumab can be found in the dupilumab prescribing information.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of bermekimab in participants with moderate to severe AD	• Proportion of participants with EASI-75 (≥75% improvement from baseline) at Week 16
Secondary	
• To characterize additional assessments of efficacy for bermekimab in participants with moderate to severe AD	• Proportion of participants with both validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) of 0 or 1 and a reduction from baseline of ≥2 points at Week 16 • Proportion of participants with improvement (reduction) of eczema-related itch numeric rating scale (NRS) ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 • Proportion of participants with EASI-90 at Week 16
• To evaluate the efficacy of bermekimab relative to dupilumab in participants with moderate to severe AD	• Proportion of participants with EASI-75 at Week 16 • Proportion of participants with EASI-90 at Week 16

Objectives	Endpoints
	• Proportion of participants with both vIGA-AD of 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 • Proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4
• To assess the safety and tolerability of bermekimab in participants with moderate to severe AD	• Number/proportion of participants with treatment-emergent adverse events (AEs) • Number/proportion of participants with treatment-emergent serious adverse events (SAEs)
• To evaluate the PK and immunogenicity of bermekimab in adult participants with moderate to severe AD	• Bermekimab concentration over time • The incidence of antibodies to bermekimab
Exploratory	
• To further characterize efficacy of bermekimab in participants with moderate to severe AD	• Improvement from baseline to Week 16 in SCORAD • Change from baseline to Week 16 in DLQI • Improvement from baseline to Week 16 in POEM • Improvement from baseline to Week 8 in eczema-related itch NRS • Improvement from baseline to Week 8 in eczema-related pain NRS • Improvement from baseline to Week 16 in eczema-related pain NRS • Improvement from baseline to Week 16 in itch as measured by the Atopic Dermatitis Itch Scale (ADIS) • Proportions of participants with a Patient Global Impression of Severity (PGIS) score of 1 (none) or 2 (mild) at Week 16 • Change from baseline to Week 16 in Patient-Reported Outcomes Measurement Information System(PROMIS)-29 total score and sub-scores • Hand Dermatitis IGA at Week 16
• To assess the impact of treatment with bermekimab on selected biomarkers	• Changes in cellular and molecular biomarkers in skin and blood from baseline

Other secondary analyses are listed in Section 9.4.3. Additional exploratory endpoints are listed in Section 9.4.4. Refer to Section 8, Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

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

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo- and active-comparator-controlled, multicenter, interventional study to assess the efficacy, safety, PK, and immunogenicity of SC administered bermekimab for the treatment of moderate to severe AD in adult participants. The participant population will comprise men and women who have had moderate to severe AD for at least 1 year.

A diagram of the study design (Figure 1) is provided in Section 1.2, Schema.

As depicted in Figure 1, approximately 200 participants who satisfy all inclusion and exclusion criteria will be randomly assigned in this study a 1:1:2:2 ratio to 1 of 4 treatment groups:

Group 1: Placebo

Participants will receive placebo weekly through Week 15. At Week 16, participants will crossover to receive bermekimab 700 mg weekly through Week 31.

Group 2: Bermekimab 350 mg SC every week (qw)

Participants will receive bermekimab 350 mg at Week 0 and every week thereafter through Week 31.

Group 3: Bermekimab 700 mg SC qw

Participants will receive bermekimab 700 mg at Week 0 and every week thereafter through Week 15. At Week 16, participants who achieve an EASI-75 response will be rerandomized in a 1:1 ratio either to continue to receive bermekimab 700 mg weekly, or to receive bermekimab 350 mg weekly, through Week 31. At Week 16, participants who do not achieve an EASI-75 response will continue to receive bermekimab 700 mg weekly through Week 31.

Group 4: Comparator/Reference Arm (Dupilumab)

Participants will receive a loading dose of dupilumab 600 mg at Week 0. Participants will receive dupilumab 300 mg every 2 weeks (q2w) beginning at Week 2 through Week 14. Participants who achieve an EASI-75 response at Week 16 will continue on dupilumab 300 mg q2w from Week 16 through Week 30. At Week 16, participants who do not achieve an EASI-75 response (ie, dupilumab nonresponders) will receive placebo weekly at Weeks 16 through 18 (ie, washout period), and bermekimab 700 mg weekly from Week 19 through Week 31.

Details on placebo SC administrations to maintain the blind are provided in Section 6.1.

A screening period will occur approximately 4 weeks before Week 0. All participants will enter the safety follow-up after Week 31 through Week 36. The total duration of study participation will be approximately 40 weeks.

Two planned database locks (DBLs) will occur when all participants complete the Week 16 visit and at Week 36 (end of study).

Efficacy assessments (EASI, vIGA-AD™, percent body surface area [BSA] involvement, SCORAD, and Hand Dermatitis IGA) and patient-reported outcome (PRO) measures (DLQI, POEM, PGIS, PROMIS-29, Eczema Skin Pain and Itch NRS, and ADIS) will be performed at visits according to the Schedules of Activities. Serum samples for PK, immunogenicity, and biomarker analyses will be collected at the timepoints shown in the Schedules of Activities (Section 1.3). Digital actigraphy and evaluation of EASI and SCORAD endpoints from digital photographs will be completed from a subgroup of participants who consent to these optional substudies at selected sites.

An interim analysis of data through Week 16 is planned for this study when approximately 50% of participants have completed the Week 16 visit. An independent, internal committee will review the results of the interim analysis. In addition, an independent, external DMC will review unblinded safety data to ensure the safety of the participants enrolled in this study. Refer to Section 9.5 (Interim Analysis) and Section 9.6 (Data Monitoring Committee) for details.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Dupilumab (DUPIXENT) is approved for the treatment of moderate to severe AD and was selected as a reference arm to benchmark bermekimab efficacy relative to dupilumab.

During the crossover period after Week 16, participants who received 700 mg bermekimab and are EASI-75 responders at Week 16 will be rerandomized 1:1 to either bermekimab 700 mg or 350 mg to explore the potential for a lower maintenance dosage of bermekimab. For the dupilumab group, EASI-75 nonresponders at Week 16 will receive bermekimab 700 mg to explore if dupilumab nonresponders can gain response after switching to bermekimab.

Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the PK, PD, efficacy, or safety of bermekimab and to identify genetic factors associated with AD.

Biomarker samples will be collected to evaluate the mechanism of action of bermekimab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the PD of bermekimab and aid in evaluating the intervention-clinical response relationship.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential AEs of the study, and provide their consent voluntarily will be enrolled.

The total blood volume to be collected from each participant in each group (approximately 294 mL over approximately 37 weeks) is far less than the American Red Cross standard limit for whole blood donation (approximately 475 mL every 8 weeks) and is therefore considered an acceptable amount of blood to be collected over this time period. For more details regarding blood collection, see Blood Sample Collection in Section 8.

4.3. Justification for Dose

Two bermekimab dose regimens were selected to be evaluated in this study: 350 mg SC qw and 700 mg SC qw. These dose regimens were chosen based on bermekimab PK, efficacy, and safety data from a Phase 2 open-label study (2018-PT044, NCT03496974) and a Phase 2 placebo-controlled study (77474462ADM2002, NCT04021862) in participants with AD.

Results from the open-label study (2018-PT044) of bermekimab demonstrated clinically meaningful activity in participants with AD. In the 400 mg SC qw group, 71% of participants achieved at least 75% improvement in EASI at Week 7, while none of the participants achieved EASI-75 at Week 4 in the 200 mg qw group. The study results suggested a possible dose response for the 400 mg SC qw compared with the 200 mg SC qw group. Based on these findings, a Phase 2 placebo-controlled study (77474462ADM2002) was conducted to further evaluate 400 mg SC qw

and 400 mg SC q2w. The Week 16 data from study 77474462ADM2002 showed significant effect of bermekimab 400 mg qw group relative to placebo (EASI-75: 34.5% vs. 13.8%, respectively), while the 400 mg q2w group showed numerically higher EASI-75 response relative to placebo (EASI-75: 24.1% vs 13.8%, respectively). Since 400 mg SC qw demonstrated meaningful clinical efficacy in these 2 AD studies, a similar dose regimen of 350 mg SC qw was selected to be evaluated in this Phase 2b study. The formulation for 350 mg SC (175 mg/mL in 2 mL) is less viscous compared to the formulation for 400 mg SC (200 mg/mL in 2 mL). Bermekimab 350 mg SC qw is expected to result in only slightly lower PK exposure compared to 400 mg SC qw.

In order to expand the dose range for treatment with bermekimab, a higher dose regimen of 700 mg SC qw was also selected to be evaluated in this Ph2b study. The dose regimen of 700 mg SC qw will provide 2-fold higher exposure than 350 mg qw and thus may achieve better efficacy in AD.

The weekly dosing frequency was selected based on bermekimab half-life ($T_{1/2}$). Bermekimab $T_{1/2}$ was estimated to be approximately 1 week so that weekly dosing is necessary in order to maintain adequate drug exposure over the entire dosing interval.

Bermekimab was well tolerated in AD study 2018-PT044 (200 mg SC qw and 400 mg SC qw) with no safety concerns. In ongoing Phase 2 AD and HS studies, 101 participants in 77474462HDS2002 (NCT04019041) and 29 participants in 77474462ADM2002 were dosed with an 800 mg SC loading dose followed by 400 mg qw of bermekimab with no safety concerns identified. The highest dose of bermekimab studied was 7.5 mg/kg IV q2w in HS (10 participants; Kanni 2018), also with no safety concerns. The 7.5 mg/kg IV dose is equivalent to 1,125 mg SC for a 90 kg (average body weight of HS patients) individual assuming a SC bioavailability of 60%.

Overall, the 2 proposed dose regimens are expected to be efficacious and would provide an opportunity to explore the dose response and PK/PD relationships to enable optimal dose selection for subsequent clinical trials in moderate to severe AD. These 2 dose regimens are also considered to be safe in participants with moderate to severe AD.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed all scheduled study interventions through Week 31 and has completed all assessments at Week 36 of the safety follow-up period.

5. STUDY POPULATION

A target sample size of 200 participants will be enrolled under the 77474462ADM2001 protocol.

Screening for eligible participants will be performed within 4 weeks before administration of the study intervention. Refer to Section 5.4, Screen Failures for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2, Sample Size Determination.

5.1. Inclusion Criteria

Each potential participant must satisfy all of the following criteria to be enrolled in the study:

Age and Sex

1. Be 18 (or the legal age of consent in the jurisdiction in which the study is taking place) years of age and be a male or female.

Type of Participant and Disease Characteristics

2. Be otherwise healthy on the basis of physical examination, medical history, vital signs, and 12-lead electrocardiograms (ECGs) performed at screening. Any abnormalities, must be consistent with the underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

3. Have AD for at least 1 year (365 days) prior to the first administration of study intervention as determined by the investigator through participant interview and/or review of the medical history.

4. Have a history of inadequate response to treatment for AD with topical medications or for whom topical treatments are otherwise medically inadvisable (eg, due to important side effects or safety risks).

5. Be considered, in the opinion of the investigator, a suitable candidate for dupilumab (DUPIXENT®) therapy according to their country's approved DUPIXENT product labeling.

6. Have an EASI score ≥16 at screening and at baseline.

7. Have an IGA score ≥3 at screening and at baseline.

8. Have an involved BSA ≥10% at screening and at baseline.

9. Have screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:

    a. Hemoglobin ≥10 g/dL (SI: ≥100 g/L)
    b. White blood cells ≥3.5 x 10^3/µL (SI: ≥3.5 GI/L)
    c. Neutrophils ≥1.5 x 10^3/µL (SI: ≥1.5 GI/L)
    d. Platelets ≥100 x 10^3/µL (SI: ≥100 GI/L)
    e. Serum creatinine ≤1.5 mg/dL (SI: ≤137 µmol/L)
    f. Aspartate aminotransferase ≤2 × upper limit of normal (ULN)
    g. Alanine aminotransferase ≤2 × ULN
    h. Alkaline phosphatase ≤2 × ULN

10. Criterion modified per Amendment 1.

    10.1 Agree to discontinue any topical medications/treatments/therapies (excluding non-prescription moisturizers, which are required for daily use per protocol, see Section 6.8.3) for AD within 1 week before the first administration of study intervention.

11. Criterion modified per Amendment 1.

    11.1 Agree not to receive a live virus or live bacterial vaccination during the study, and for 90 days after the last administration of study intervention.

12. Agree not to receive a Bacille Calmette-Guérin (BCG) vaccination during the study, and for 12 months after the last administration of study intervention.

TB screening

13. Are considered eligible according to the following TB screening criteria:

    a. Have no history of latent or active TB before screening. An exception is made for participants who have a history of latent TB and:
        - are currently receiving treatment for latent TB,

          OR

        - will initiate treatment for latent TB before the first administration of study intervention,

          OR

        - have documentation of having completed appropriate treatment for latent TB within 5 years before the first dose of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti tuberculous treatment and provide appropriate documentation. Participants with a history and documentation of having completed appropriate

treatment for latent TB more than 5 years before the first dose of study intervention are not eligible.

b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

c. Have had no known recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first administration of study intervention.

d. Within 2 months before the first administration of study intervention, have a negative QuantiFERON®-TB (or T-SPOT® for sites in Japan) test result, or have a newly identified positive QuantiFERON®-TB (or T-SPOT® for sites in Japan) test result (see laboratory manual) in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study intervention. Within 2 months before the first administration of study intervention, a negative tuberculin skin test, or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study intervention, is additionally required if the QuantiFERON®-TB test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

NOTE: A negative tuberculin skin test result (see Appendix 2 [Section 10.2]) is additionally required if the QuantiFERON-TB® test is not approved/registered in the country in which this protocol is being conducted. In Ukraine, while the QuantiFERON-TB® test is not approved/registered, it is acceptable, and an additional tuberculin skin test is not required. The QuantiFERON-TB® (or T-SPOT® for sites in Japan) test and the tuberculin skin test are not required at screening for participants with a history of latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed as described above in Inclusion Criterion #13a

e. Have a chest radiograph (both posterior-anterior and lateral views, or per country regulations where applicable), taken within 12 weeks before the first administration of study intervention and read by a radiologist or qualified pulmonologist, with no evidence of current, active TB or old, inactive TB. A chest CT scan is also acceptable if already available or obtained outside of the study protocol.

Contraceptive/Barrier Requirements

14. Before randomization, a woman must be (as defined in Appendix 3, Section 10.3, Contraceptive Guidance):

a. Not of childbearing potential

b. Of childbearing potential and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose - the end of relevant systemic

exposure. The investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first dose of study intervention. Examples of highly effective methods of contraception are located in Appendix 3, Section 10.3, Contraceptive Guidance.

NOTE: If a female participant's childbearing potential changes after start of the study (eg, a woman who is not heterosexually active becomes active, a premenarchal woman experiences menarche), she must begin practicing a highly effective method of birth control, as described above.

15. A woman of childbearing potential must have a negative urine pregnancy test (β-human chorionic gonadotropin [β-hCG]) at screening and at Week 0 prior to administration of study intervention.

16. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 12 weeks after receiving the last administration of study intervention.

17. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 12 weeks after receiving the last administration of study intervention.

18. All men must also agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of study intervention.

Informed Consent

19. Must sign an ICF indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

20. Must sign a separate informed consent form if he or she agrees to provide an optional DNA sample for research (where local regulations permit). Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

21. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

Medical Conditions

1. Has a current diagnosis or signs or symptoms of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances.

2. Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months.

3. Has as a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.

4. A history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with no evidence of recurrence for at least 3 months prior to the first administration of study intervention and with minimal risk of recurrence).

5. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (eg, bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers.

6. Has or has had a serious infection (eg, sepsis, pneumonia, or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before screening.

7. Has or has had herpes zoster within the 2 months before screening.

8. Has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

9. Has a history of being human immunodeficiency virus (HIV) antibody-positive, or tests positive for HIV at screening.

10. Tests positive for hepatitis B virus (HBV) infection (see Appendix 4, [Section 10.4]) or who are seropositive for antibodies to hepatitis C virus (HCV) at screening.

11. During the 6 weeks prior to baseline, have had any of (a) confirmed SARS-CoV-2 (Coronavirus Disease 2019; COVID-19) infection (test positive), **OR** (b) suspected SARS-CoV-2 infection (clinical features without documented test results), **OR** (c) close contact with a person with known or suspected SARS-CoV-2 infection.

    An exception to this criterion maybe granted if a participant has a documented negative result for a validated SARS-CoV-2 test:

    (i) Obtained at least 2 weeks after conditions (a), (b), (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND

    (ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit

    NOTES on COVID-19-related exclusion:

    - The field of COVID-19-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.
    - Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

12. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, prior to screening. Participants with radiographic evidence of possible prior histoplasmosis or coccidioidomycosis will be excluded. Refer to Inclusion Criterion 13 for information regarding eligibility with a history of latent TB.

13. Has a chest radiograph within 3 months before the first administration of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB. A chest CT scan is also acceptable if already available or obtained outside of the study protocol.

14. Has ever had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystis, aspergillosis).

15. Has 2 indeterminate (on repeat sampling) QuantiFERON®-TB test results.

16. Has had major surgery (eg, requiring general anesthesia and hospitalization) within 8 weeks before screening, or has not fully recovered from such surgery, or has such surgery planned during the time the participant is expected to participate in the study.

    NOTE: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

17. Has a transplanted organ (with exception of a corneal transplant >3 months before the first administration of study intervention).

18. Has known allergies, hypersensitivity, or intolerance to bermekimab or its excipients (refer to the IB) or to dupilumab or its excipients.

Prior/Concomitant Therapy

19. Has previously received dupilumab.

20. Has received an immunomodulating biologic therapy within the previous 3 months of study intervention administration (including, but not limited to, anti-cytokine, anti-complement antibodies, anti-Ig antibodies, etc).

21. Has received phototherapy or any systemic medications/treatments that could affect AD or IGA evaluations within 4 weeks of the first administration of any study intervention.

22. Initiation of treatment of AD with any prescription topicals including moisturizers during the screening period (see Section 6.8.4), or use of any prescription topical treatment for AD within 1 week of the baseline visit.

23. Has received systemic immunosuppressant, immunomodulatory, or cytotoxic treatments (including, but not limited to, oral or injectable corticosteroids, cyclosporin, or methotrexate) that could affect AD or IGA evaluations within 4 weeks before the baseline visit, or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment

24. Has ever received any IL-1 antagonist (eg, including but not limited to anakinra, rilonacept).

25. Has received natalizumab, belimumab, or agents that modulate B cells or T cells (eg, rituximab, alemtuzumab, abatacept, or visilizumab) within 12 months of the first administration of study intervention.

26. Has received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus) within 4 weeks of the first administration of study intervention.

Prior/Concurrent Clinical Study Experience

27. Has received any non-biologic investigational therapy within 30 days or 5 half-lives (whichever is longer) of any study intervention administration or is currently enrolled in another study using an investigational agent, device, or procedure

28. Has received, or is expected to receive, any live virus or bacterial vaccination within 12 weeks before the first administration of study intervention.

29. Has had a BCG vaccination within 12 months of screening.

30. Has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments.

31. Is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last dose of study intervention.

32. Plans to father a child while enrolled in this study or within 12 weeks after the last dose of study intervention.

Other Exclusions

33. Is known to have had a substance abuse (drug or alcohol) disorder within the previous 12 months.

34. Lives in an institution on court or authority order.

35. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

36. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first dose of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Appendix 5 (Section 10.5, Regulatory, Ethical, and Study Oversight Considerations.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (Inclusion Criterion 14) during the study and for at least 12 weeks after receiving the last administration of study intervention.

2. A woman must agree not to donate eggs (ova, oocytes) during the study and for a period of at least 12 weeks following the last administration of study intervention (Inclusion Criterion 16).

3. A man who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control (See Inclusion Criterion 17) during the study and for at least 12 weeks after receiving the last administration of study intervention.

4. A man must agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of study intervention (Inclusion Criterion 18).

5. Participants must comply with restrictions on concomitant medications and therapies specified in the protocol (see Section 6.8, Concomitant Therapy for details).

6. All patients are required to apply moisturizers at least once daily for at least 7 days before randomization and continue the treatment throughout the study (including the safety follow-up period; see Section 6.8.3, Required Treatment for details).

7. Participants must not receive a live virus or bacterial vaccination during the study and for 90 days after the last administration of any study intervention (Inclusion Criterion 11).

8. Participants must not receive a BCG vaccination during the study and for 12 months after the last administration of any study intervention (Inclusion Criterion 12).

9. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria.

10. It is recommended that participants are up-to-date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. For study participants who received locally-approved (and including emergency use-authorized) COVID-19 vaccines recently prior to study entry, follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrollment (see Section 6.8.6, Vaccinations [including COVID-19]).

5.4. Screen Failures

If, during the screening phase, the subject has not met all inclusion criteria or met any exclusion criteria, or is unable or unwilling to adhere to the prohibitions and restrictions of the study, the subject is considered to be a screen failure and is not eligible to be randomized at that time.

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the specified screening period of 4 weeks.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening period.

Completion of screening and randomization procedures within the specified screening window of approximately 4 weeks is required. No exceptions or waivers for screen failures are allowed.

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Appendix 6 (Section 10.6).

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention(s) Administered

The study intervention presentation to be used in this study is a sterile liquid formulation of 350 mg (175 mg/mL) of bermekimab in a prefilled syringe (PFS) with an injectable volume of 2.0 mL. Bermekimab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Commercially available dupilumab will be provided by the sponsor as a sterile liquid formulation of 300 mg (150 mg/mL) in a PFS with an injectable volume of 2.0 mL.

Placebo will be provided by the sponsor.

All participants will receive 2 SC injections at each visit every week from Week 0 through Week 31. Since 2 SC injections will be administered at each administration visit, each SC injection should be given at a different location of the body.

Group 1: Placebo

- Participants will receive 2 placebo SC administrations weekly from Week 0 through Week 15.
- At Week 16, participants will crossover to receive 2 bermekimab 350 mg SC administrations weekly through Week 31.

Group 2: Bermekimab 350 mg SC qw

- Participants will receive 1 bermekimab 350 mg SC administration and 1 placebo SC administration at Week 0 and every week thereafter through Week 31.

Group 3: Bermekimab 700 mg SC qw

- Participants will receive 2 bermekimab 350 mg SC administrations at Week 0 and every week thereafter through Week 15.
- At Week 16, participants who achieve an EASI-75 response will be rerandomized in a 1:1 ratio either to continue to receive 2 bermekimab 350 mg SC administrations weekly, or to receive 1 bermekimab 350 mg SC administration and 1 placebo SC administration weekly, through Week 31.
- At Week 16, participants who do not achieve an EASI-75 response will continue to receive 2 bermekimab 350 mg SC administrations weekly through Week 31.

Group 4: Comparator/Reference Arm (Dupilumab)

- Participants will receive 2 dupilumab 300 mg SC administrations at Week 0. Participants will receive 2 placebo SC administrations q2w beginning at Week 1 through Week 15. Participants will receive 1 dupilumab 300 mg SC administration and 1 placebo SC administration q2w beginning at Week 2 through Week 14.
- Participants who achieve an EASI-75 response at Week 16 will continue on 1 dupilumab 300 mg SC administration and 1 placebo SC administration q2w from Week 16 through Week 30, and 2 placebo SC administrations q2w from Week 17 to 31.
- At Week 16, participants who do not achieve an EASI-75 response will receive 2 placebo SC administrations weekly at Weeks 16 through 18 (ie, washout period), and 2 bermekimab 350 mg SC administrations weekly from Week 19 through Week 31.

Study intervention administration must be captured in the source documents and the case report form (CRF). Study-site personnel will instruct participants on how to store study intervention for at-home use when feasible as indicated in the Schedule of Activities (SoA).

For details on rescue medications, refer to Section 6.8.1. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Appendix 6 (Section 10.6).

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Bermekimab (JNJ-77474462) must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from light. Placebo must be stored at controlled temperatures, as indicated on the product-specific labeling.

Dupilumab must be stored as indicated on the product-specific labeling.

Refer to the Site Investigational Product Binder for additional guidance, including Instructions For Use, on study intervention preparation, handling, and storage.

Study intervention labels will contain information to meet the applicable regulatory requirements.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention.

If rescue medication or other medication is also supplied by the sponsor, inclusion of this medication on the intervention accountability form is required. The participants must return unused study intervention to the study site.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The study intervention boxes will be retained for inventory by the sponsor.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Dynamic central randomization will be implemented in this study. Participants will be randomly assigned to 1 of 4 intervention groups based on a minimization randomization algorithm implemented in the interactive web response system (IWRS) before the study under the supervision of the sponsor.

The randomization method will be a minimization procedure with biased-coin assignment, which minimizes the imbalance in the distribution of the number of participants across treatment groups within the levels of each individual stratification factor: investigational site and baseline EASI severity (<28, ≥28). Based on the algorithm, each participant will be assigned to the treatment group which will produce minimum total imbalance score with a high probability, where the total imbalance score is a weighted average of the imbalance scores for each stratification factor and for the whole study. The IWRS will assign a unique treatment code, which will dictate the treatment assignment and matching study drug for the participant. Approximately 200 participants with moderate to severe AD at Week 0 will be assigned to 1 of 4 treatment groups in a 1:1:2:2 ratio, resulting in approximately 33 participants to the placebo or bermekimab 350 mg treatment group, and approximately 67 participants to the bermekimab 700 mg or dupilumab treatment group.

At Week 16, participants randomized to bermekimab 700 mg who are EASI-75 responders will be rerandomized using the IWRS either to bermekimab 700 mg or 350 mg in a 1:1 ratio. Participants will be assigned to treatments groups using permuted block randomization and the randomization will be stratified by EASI-90 response status (<90%, ≥90% improvement from baseline) at Week 16.

The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

Active study intervention and placebo will be prepared by an unblinded pharmacist or an unblinded qualified member of the investigational staff. The volume of the placebo injections will match the volume of the active intervention injections within each group where placebo administration is required. Prepared doses will be covered to mask potential visual differences between the active

study intervention and placebo. The participants and other site staff members, including the investigator, will be blinded to study intervention allocation through study completion to reduce bias in the assessment of safety and tolerability data.

Sites must ensure that they have the ability to physically blind and/or separate the blinded participant from the unblinded administrator. A physical barrier must be used such that the study drug can be administered by the unblinded site personnel, and the participant and other site personnel remain blinded.

To ensure that no unintentional unblinding occurs during study intervention administration, at least one qualified site staff member will be designated to perform all SC injections of the investigational product. This unblinded administrator will have no other contact with the participant during the study and will not discuss the participant's treatment with the participant, the investigator, or other site personnel at any time. The unblinded administrator(s) will be documented in the source documents at each dosing day.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (ie, study intervention serum concentrations, antibodies to bermekimab, and intervention allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. However, selected sponsor personnel will be unblinded for analysis after the Week 16 DBL has occurred. All site personnel and participants will remain blinded to the treatment assignments until the last participant completes Week 36 evaluations and the database has been locked.

The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded by the investigator will not be eligible to receive further study intervention but should continue complete evaluations specified in the SoA (Section 1.3).

For the planned interim analyses and the DMC, the randomization codes and the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the interim analysis.

6.4. Study Intervention Compliance

Because study intervention will be administered at the investigational site for all randomized participants, intervention compliance will be ensured by site personnel. If study intervention is administered by a home health nurse, the sites will be instructed on modifications to ensure study intervention compliance.

The investigator or designated study personnel will maintain a log of all study intervention dispensed and returned. Study intervention supplies will be inventoried and accounted for throughout the study. Details of each administration will be recorded in the eCRF, including date, body location and time of SC injection.

All visits and study intervention administrations should occur ±3 days of scheduled visit throughout the study. Study intervention administration should occur not within 4 days of the prior administration of study intervention.

Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Source data will be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that intervention may be interrupted for many reasons, compliance with the intervention schedule is strongly encouraged.

6.5. Dose Modification

No treatment/dose adjustment will be permitted through the study.

6.6. Continued Access to Study Intervention After the End of the Study

No long-term extension is provided in this Phase 2 study. Participants will be instructed that study intervention will not be made available to them after they have completed/discontinued study intervention and that they should return to their primary physician to discuss treatment options.

6.7. Treatment of Overdose

For this study, any dose of bermekimab or dupilumab greater than the highest dose at a single dosing visit will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.

- Closely monitor the participant for AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.8. Concomitant Therapy

Prestudy therapies administered up to 30 days before first dose of study intervention must be recorded at screening.

Concomitant therapies must be recorded throughout the study from Week 0 through Week 36 or continuing until 5 weeks after the last dose of study intervention. Concomitant therapies on randomized participants should also be recorded beyond that point only in conjunction with SAEs that meet the criteria outlined in Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation) different from the study intervention must be recorded in the CRF. If a medication is temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly documented in the participant's medical records. Modification of an effective pre-existing therapy should not be made for the explicit purpose of entering a participant into the study.

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.8.1. Rescue Medication

In the event that a participant experiences any unacceptable or worsening symptoms of AD, investigators should first attempt to control symptoms in patients with moisturizers by increasing the frequency of use to at least twice a day and by reemphasizing other permitted skin care measures. However, if these measures are insufficient to control symptoms, investigators will have the option to treat with protocol-allowed rescue therapy (topical corticosteroid or topical calcineurin inhibitor). Investigators will be required to perform an IGA assessment prior to starting rescue treatment and initiate rescue treatment only in participants who either have an IGA score = 4, or have intolerable symptoms. Rescue therapy should not be initiated in the first 2 weeks after randomization. The rationale for rescue must be documented in source.

Participants using rescue by topical therapy will continue to receive investigational product and use of rescue therapy will be documented in the eCRF.

If topical rescue therapy as stipulated above fails to control AD symptoms sufficiently, the investigator should consider discontinuing the patient from the study.

6.8.2. Atopic Dermatitis Management

Investigators should counsel participants on expected management of their condition prior to randomization into the study. Participants should practice sensitive skin care measures as part of management of AD. These measures include taking infrequent (at most once daily) and brief showers or baths, using warm water (not hot) as tolerated. Moisturizer is best applied immediately after showering or bathing. Participants should use fragrance-free cleansers and avoid antibacterial or deodorant soaps, which may be more irritating to the skin. Participants should launder clothes with fragrance-free detergent and avoid fabric softeners. Participants should try to avoid fabrics that may be more irritating to the skin, such as wool or synthetic fabrics.

6.8.3. Required Treatment

All participants are required to apply moisturizers at least once daily for at least 7 days before randomization and continue the treatment throughout the study (including the safety follow-up period). All types of non-prescription moisturizers are permitted, excluding any moisturizer that contains a corticosteroid.

6.8.4. Prohibited Therapy

The following therapies will not be allowed during the course of the study.

- Topical corticosteroids, except for rescue therapy (see Section 6.8.1, Rescue Medication)
- Topical calcineurin inhibitors (eg, tacrolimus and pimecrolimus), except for rescue therapy (see Section 6.8.1, Rescue Medication)
- Topical PDE4 inhibitors (eg, crisaborole)
- Allergen immunotherapy
- Phototherapy (including PUVA, UVB, tanning beds, and excimer laser)
- Bleach baths
- Systemic corticosteroids (PO, IV, or IM)
  - The use of systemic corticosteroids for treatment of indications other than AD is permitted, but 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.
  - Other route of administration of corticosteroids including those inhaled, otic, ocular, nasal, or other routes of mucosal delivery of corticosteroids are allowed.
- Any systemic therapy, investigational or commercial (approved or off label use), used for the treatment of AD or symptoms of AD (eg, use of dupilumab outside of this protocol)
- Systemic and topical JAK inhibitors
- Systemic immunomodulatory agents, including, but not limited to, MTX, azathioprine, cyclosporine, mycophenolate mofetil. and immunomodulatory biologic therapies (eg, guselkumab, risankizumab, secukinumab)

- IL-1 inhibiting agents (eg, anakinra, rilonacept, canakinumab)
- Live vaccines

The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

6.8.5. Drugs Metabolized by Cytochrome P450

In vitro studies have shown that IL-1 could impact cytochrome (CYP) enzyme expression and activities (Renton 2005; Abdel-Razzak 1993). As such, suppression of IL-1α by bermekimab, a cytokine modulator, may potentially alter the hepatic metabolism and clearance of drugs that are substrates for CYP enzymes (FDA Guidance 2020). Therefore, upon initiation or discontinuation of bermekimab in patients being treated with CYP substrates with a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, theophylline) is recommended and the individual dose of the drug may be adjusted as needed.

6.8.6. Vaccinations (including COVID-19)

When considering use of locally approved non-live vaccines (including emergency use authorized COVID-19 vaccines) in study participants, follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy.

For study participants receiving a locally-approved COVID-19 vaccine (including emergency use authorized), in order to help identify acute reactions potentially related to COVID-19 vaccine, it is recommended where possible that vaccine and study drug be administered on different days, separated by as large an interval as is practical within the protocol.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention
- The participant or their legally acceptable representative withdraws consent/assent for administration of study intervention.
- The investigator believes that for safety reasons or tolerability reasons (eg, adverse event) it is in the best interest of the participant to discontinue study intervention
- The participant has a serious adverse reaction that is related to an injection including a hypersensitivity reaction. In general, discontinuation of study intervention administration must be considered for participants who develop a nonserious but severe injection-site reaction.
- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) after an injection of study intervention. These may be

accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

- The participant becomes pregnant or plans a pregnancy during the study period. Refer to Appendix 3 (Section 10.3), Contraceptive Guidance.
- The initiation of protocol-prohibited medications, treatments, or interventions (outlined in Section 6.8, Concomitant Therapy) that have an impact on AD efficacy evaluations.
- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allow participants, who develop ≤2 basal cell skin cancers and who are adequately treated with no evidence of residual disease, to continue to receive study intervention.
- A systemic opportunistic infection.
- A recurrent or chronic serious infection.
- The participant is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not undergo additional evaluation.
  - A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB test result and/or 2 indeterminate QuantiFERON®-TB test results on repeat testing (refer to Section 8.2.8, Tuberculosis Evaluations) (and/or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities).
  - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The participant is unable to adhere to the study visit schedule or comply with protocol requirements.
- The participant has his/her treatment assignment unblinded by the investigator.
- Sponsor decision.

Participants who decide to discontinue study intervention administration for reasons other than those outlined above must be interviewed by the investigator to determine if a specific reason for discontinuing study intervention can be identified. Participants should be explicitly asked about the possible contribution of AEs to their decision to discontinue study intervention; investigators should confirm that any AE information elicited has been documented. If a participant elects to discontinue study intervention due to an AE, the event should be recorded as the reason for study intervention discontinuation, even if the investigator's assessment is that the AE would not require study intervention discontinuation. The reason for study intervention discontinuation must be documented in the eCRF and in source documents. Study intervention assigned to a participant who discontinues may not be assigned to another participant.

A participant will not be automatically withdrawn from the study if he or she must discontinue treatment before the end of the treatment regimen. Participants who discontinue study intervention but do not terminate study participation are strongly encouraged to return for all protocol-specified procedures and evaluations for approximately 5 weeks following the last dose of study intervention. The procedures and evaluations listed for the Early Termination Visit should also be performed approximately 5 weeks after the last dose of study intervention.

All procedures and evaluations must be conducted prior to a participant's withdrawal of consent.

7.1.1. Liver Chemistry Stopping Criteria

Stopping of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Appendix 21 (Section 10.21) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the participant.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

To ensure access for participant follow-up, study sites should try to obtain both primary and secondary telephone contact numbers from participants (eg, home, work, and mobile phones), as well as other contact information such as email addresses, and emphasize the importance of follow-up information to the participant, before randomization. For participants who withdraw from study participation, every effort should be made to conduct the Early Termination Visit assessments, as indicated in the SoA (Section 1.3). If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of consent should be a very unusual occurrence in a clinical trial; the investigator should make every effort to maintain good participant relationships to avoid withdrawals of consent. For participants who truly request withdrawal of consent, it is recommended that the participant withdraw consent in writing; if the participant or the participant's representative refuses to do so or is physically unavailable, the study-site should document the reason for the participant's failure to withdraw consent in writing, sign the documentation, and maintain it with the participant's source records. When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Participants who withdraw will not be replaced.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Long-Term Retention of Samples for Additional Future Research in Appendix 5 (Section 10.5), Regulatory, Ethical, and Study Oversight Considerations). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, fax, and, if necessary, a certified letter to the participant’s last known mailing address, or local equivalent methods. These contact attempts should be documented in the participant’s medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, eg, for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The Schedule of Activities (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, pharmacogenomic, and safety measurements applicable to this study. It is strongly recommended that the same investigator perform the efficacy assessments at every visit.

During screening, each participant will be provided with an electronic device to enter PRO data. Study-site personnel will train the participants on how to use the electronic device (ePRO), including instructions to capture the data according to the study design and not to wait until the study-site visit to record information. Participants will be provided with written instructions on how to get 24-hour technical support, if needed, for operation of the ePRO device.

All visit-specific PRO assessments should be conducted/completed before any tests, procedures or other consultations, with the exception of a urine pregnancy test, to prevent influencing participant perceptions. Refer to the PRO completion guidelines for instructions on the administration of PROs.

Electrocardiograms should precede vital signs and both procedures should be completed prior to any invasive procedures. Vital signs should be recorded from the opposite arm from which blood samples are being taken.

All samples (including safety, efficacy, PK, and biomarkers) must be obtained after the PRO and ECG assessments but prior to study intervention administration. Blood collections for PK and biomarker assessments should be kept as close to the specified time as possible. Actual dates of all assessments will be recorded in the source documentation; in addition, times of all blood collections will be recorded in the source documentation (laboratory requisition form).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. Results of all pregnancy testing should be documented in the participants' source documents.

Guidelines for handling of assessments affected by the COVID-19 pandemic are found in Appendix 6 (Section 10.6).

Blood Sample Collection

The total blood volume to be collected from each participant through Week 36 of the study will be approximately 344 mL (Table 3). In addition, repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples.

Table 3: Volume of Blood to be Collected From Each Participant

Type of Sample	Volume per Sample (mL)	No. of Samples per Participant	Approximate Total Volume of Blood (mL)[a]
Safety (including screening and post-intervention assessments)			
- Hematology	2.0	11	22
- Serum chemistry	2.5	11	27.5
- Serology (HIV, HBV, HCV)	10	1	10
- HBV DNA testing[b]	6	1	6
- TB testing	4	1	4
Pharmacokinetic/Immunogenicity samples	7.5	11	82.5
Population PK sample	4.0	1	4.0
Serum Biomarker samples	8.5	9	76.5
PBMC Biomarker sample	16	5	80
Gene expression samples	2.5	10	25
Pharmacogenomic sample[c]	6	1	6
Approximate Total[d]			**344 mL**

a. Calculated as number of samples multiplied by amount of blood per sample.
b. Performed only in participants who test positive for core HBV antibody.
c. A blood sample will be collected only from participants who have consented to provide an optional DNA sample for research.
d. Repeat or unscheduled samples may be taken for safety reasons or technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the SoA (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Protocol
- Investigator's Brochure for bermekimab
- Country-specific package insert for dupilumab
- Site Investigational Product Binder
- Laboratory Manual
- Laboratory Kits
- IWRS Manual
- Sample CRF
- eCRF Completion Guidelines

- ePRO equipment (tablet device questionnaires, completion instructions)
- Patient Diary
- Actigraphy devices and instruction for use manual (at participating sites)
- Digital photographic equipment and instructions manual (at participating sites)
- Participant Study Participation Card
- Investigative Site File
- Recruitment materials, as needed

8.1. Efficacy Assessments

Investigator assessments and PROs of efficacy are included in this section.

- The PRO instrument will be provided in the local language in accordance with local guidelines.
- The PRO instrument must be available for regulators and for IRB/ERC submissions.
- The PRO and AE data will not be reconciled with one another.

8.1.1. 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 (Hanifin 2001). The EASI is a composite index with scores ranging from 0 to 72. Four AD disease characteristics (erythema, thickness [induration, papulation, edema], scratching [excoriation], and lichenification) will each 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, upper limbs, and lower limbs, and converted to a score of 0 to 6. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%). The EASI will be collected at time points according to the SoA. See Appendix 7 (Section 10.7) for a representative example of the index.

8.1.2. Validated Investigator Global Assessment for Atopic Dermatitis

The vIGA-AD™ developed by Eli Lilly and Company is an assessment instrument used in clinical studies to rate the severity of AD, based on a 5-point scale ranging from 0 (clear) to 4 (severe; Simpson 2020). The IGA score is selected using the morphological descriptors that best describe the overall appearance of the AD lesions at a given time point. The IGA score will be assessed at time points according to the SoA. See Appendix 8 (Section 10.8) for a representative example of the assessment.

8.1.3. Severity Scoring of 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 visual analog scale, 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.

See Appendix 9 (Section 10.9) for a representative example of the assessment.

8.1.4. Hand Dermatitis Investigator Global Assessment

The Hand Dermatitis IGA is a measurement of severity of dermatitis localized to the hands. The measurements include evaluation of 7 features, erythema, edema, scaling, vesiculation, erosion, lichenification (skin thickening), and fissuring, graded from clear to severe on a scale from 0 to 4. The investigator will complete the assessment at timepoints according to the SoA. See Appendix 10 (Section 10.10) for a representative example of the assessment.

8.1.5. Patient-Reported Dermatology Life Quality Index

The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a participant's quality of life (Finlay 1994). It is a 10-item questionnaire that assesses quality of life (QoL) over the past week and in addition to evaluating overall quality of life, can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The total score ranges from 0 to 30 with a higher score indicating greater impact on QoL. See Appendix 11 (Section 10.11) for a representative example of the index.

8.1.6. 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 (Charman 2004). 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 and a higher score indicates greater severity. See Appendix 12 (Section 10.12) for a representative example of the questionnaire.

8.1.7. Patient Global Impression of Severity

The PGIS of AD is a one-item questionnaire that measures participants' perceived severity of AD. Participants will rate the severity of their AD using a 5-point scale ranging from "none" to "very severe". PGIS will be used as an anchor to establish a clinical response criterion of other patient or physician reported outcomes for future reference. The questionnaire will be administered at time points according to the SoA. See Appendix 13 (Section 10.13) for a representative example of the questionnaire.

8.1.8. Patient-Reported Outcomes Measurement Information System-29

The PROMIS-29 is a 29-item generic health-related quality of life survey, assessing each of the 7 PROMIS domains (depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities) with 4 questions. The questions are ranked on a 5-point Likert Scale. There is also one 11-point rating scale for pain intensity (Cella 2010). Participants will undergo this assessment at time points according to the SoA. See Appendix 14 (Section 10.14) for a representative example of the questionnaire.

8.1.9. Eczema Skin Pain and Itch Numeric Rating Scale

The Eczema Skin Pain and Itch NRS is a 2-item patient-reported outcome developed by the sponsor that participants will use to rate the severity of their eczema-related skin pain and eczema-related itch daily. Participants will be asked the following questions:

- Please rate the severity of your eczema-related **skin pain** at its worst in the past 24 hours.
- Please rate the severity of your eczema-related **itch** at its worst in the past 24 hours.

Each item is on a 0 to 10 NRS ranging from 0 "none" to 10 "worst possible" and will be scored separately. Participants will complete the rating scale daily from the screening visit through the last study visit as detailed in the SoA. See Appendix 15 (Section 10.15) for a representative example of the scale.

8.1.10. Atopic Dermatitis Itch Scale

The ADIS will be used to assess pruritus (itching) among patients with AD, a condition commonly referred to as eczema. It will be evaluated by patient a twice-daily diary, in the morning and evening diary. The start-of-day item set consists of 4 items evaluating itching at the time of morning diary completion, the presence of itching at last night, itching at its worst at night, and the impact of itching on sleep at night. The end-of-day item set also consists of 4 items evaluating itching at the time of evening diary completion, the presence of itching during the day, itching at its worst during the day, and the amount of time the patient experienced eczema-related itching. The ADIS utilizes an 11-point scale which ranges from 0 (No itching at all) to 10 (Worst possible itching) with the presence of itching during the day or the evening (Yes/No).

Participants will complete the rating scale daily from the screening visit through the last study visit as detailed in the SoA. See Appendix 16 (Section 10.16) for a representative example of the scale.

8.1.11. Digital Actigraphy

Clinical features of AD vary by age, duration, and severity but can include papules, vesicles, erythema, exudate, xerosis, scaling, and lichenification. However, the most defining and universal symptom of AD is pruritus. Pruritus or itch, defined as an unpleasant urge to scratch, is problematic for many reasons, particularly its negative impact on QoL. Despite the profoundly negative impact of pruritus on patients with AD, clinicians and researchers lack standardized and validated methods to objectively measure pruritus (Smith 2019). In addition, pruritus in AD patients leads to sleep disturbances, fatigue and altered physical activity patterns. A wrist actigraph is a portable device that uses a micro-accelerator to measure nocturnal wrist movement as a proxy for scratching activity that is correlated to itch in patients with AD (Price 2014). Furthermore, actigraphy has been used in several systemic autoimmune disease studies to document the differences in quality of the sleep and physical activity.

The current study includes an optional substudy that will combine an ePRO and wearable actigraphy devices (worn by a limited number of participants at some clinical sites) with clinical and biomarker assessments to identify patterns or signatures that are indicative of clinical disease and potentially demonstrate clinical benefit of bermekimab in patients with AD. Details are provided in Appendix 17 (Section 10.17) and additional instructions about the actigraphy substudy are provided in the actigraphy manual. The results of these analyses will be presented in a separate report.

8.1.12. Remote Endpoint Assessment Using Total Body Photography

Participation in clinical studies can be a burden on participants as well as investigators due to time constraints and the need to access a participating study site. Total body photography (TBP) has long been employed in dermatology for the process of “mole mapping,” ie, monitoring the development or change of nevi on the skin over time. As such a standardized photographic series has been established to capture the entirety of the skin surface for visual evaluation. As part of Study 77474462ADM2001, standard AD severity assessments (eg, EASI) will be completed using digital photographs and compared with results from in-person investigator assessments for a limited number of participants who consent to this optional substudy at some clinical sites. Details are provided in Appendix 18 (Section 10.18) and instructions for acquiring photographs and completing assessments are provided in the TBP manual. The results of these analyses will be presented in a separate report.

8.2. Safety Assessments

Details regarding the independent Data Monitoring Committee are provided in Committees Structure in Appendix 5 (Section 10.5), Regulatory, Ethical, and Study Oversight Considerations.

Adverse events will be reported and followed by the investigator as specified in Section 8.3, Adverse Events, Serious Adverse Events, and Other Safety Reporting, and Appendix 19 (Section 10.19, Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA.

8.2.1. Physical Examinations

Physical Examination

Physical examinations will be performed by the investigator or designated physician, nurse practitioner or physician assistant as specified in the SoA (Section 1.3). Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

Height and Weight

Height and weight will be measured as specified in the SoA (Section 1.3). Participants will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

8.2.2. Vital Signs

Vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained before prior to study intervention administration at visits specified in the SoA (Section 1.3).

8.2.3. Electrocardiograms

A triplicate 12-lead ECG will be performed during screening to serve as a baseline reference for comparison and at Week 16, should a cardiovascular related safety event occur. The 3 individual ECG tracings should be obtained as closely as possible in succession about 2 minutes apart. The full set of triplicates should be completed in about 5 minutes.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Appendix 20 (Section 10.20), Clinical Laboratory Tests. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The tests that will be performed by the central laboratory unless otherwise specified or approved by the medical monitor are specified in Appendix 20 (Section 10.20), Clinical Laboratory Tests.

Female participants of childbearing potential will undergo a urine pregnancy test at screening, before each study intervention administration, and at the Week 36 or early termination visit

8.2.5. Concomitant Medication

Concomitant medications will be reviewed at each visit and recorded in the source documents and eCRF.

8.2.6. Allergic Reactions

Before any SC injection, appropriately trained personnel and medications must be available to treat allergic reactions, including anaphylaxis. All participants must be observed carefully for symptoms of an allergic reaction (eg, urticaria, itching, hives). If a mild or moderate allergic reaction is observed, acetaminophen, non-steroidal anti-inflammatory drugs, and/or diphenhydramine may be administered.

In the case of a severe allergic reaction (eg, anaphylaxis), IM or SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures may be essential and must be available at the location where the injections are being administered.

Participants who experience serious adverse reactions related to an injection should be discontinued from further study intervention administrations.

Participants who experience reactions following an injection that result in bronchospasm, wheezing and/or dyspnea that requires ventilatory support, or that results in symptomatic hypotension with a decrease in systolic blood pressure of 30% from a participant's baseline value blood or systolic blood pressure <90 mm Hg will not be permitted to receive additional study intervention (Sampson 2006).

Participants who experience reactions suggestive of serum sickness-like reactions (resulting in symptoms such as myalgia and/or arthralgia with fever and/or rash that are not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention, should be discontinued from further study intervention administrations. Note that these symptoms may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.

8.2.7. Injection-site Reactions

A study intervention injection-site reaction is any adverse reaction at an SC study intervention injection-site. The injection sites will be evaluated for reactions and any injection-site reactions will be recorded as an AE. Participants should be monitored for the occurrence of injection-site reactions for 30 minutes after the study intervention administration.

8.2.8. Tuberculosis Evaluation(s)

8.2.8.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB (refer to Appendix 2 [Section 10.2]) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON-TB® (or T-SPOT® for sites in Japan) test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated to evaluate a participant who is high risk of having latent TB. If either the QuantiFERON-TB® (or T-SPOT® for sites in Japan) test or the tuberculin skin test is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON-TB® (or T-SPOT® for sites in Japan) test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB® test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with pre-randomization procedures. Participants with a newly identified positive QuantiFERON-TB® (or T-SPOT® for sites in Japan or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study.

A participant whose first QuantiFERON-TB® test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB® test result is also indeterminate, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. For sites in Japan, a participant whose first T-SPOT® test result is borderline should have the test repeated. In the event that the second T-SPOT® (for sites in Japan) test result is also borderline, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

8.2.8.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the Schedule of Activities in Section 1.3). The following series of questions is suggested for use during the evaluation:

- "Have you had a new cough of >14 days' duration or a change in a chronic cough?"
- "Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?"
- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB (or T-SPOT® for sites in Japan) test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment is warranted. Study intervention administration should be interrupted during the investigation. A positive QuantiFERON®-TB (or T-SPOT® for sites in Japan) test or tuberculin skin test result should be considered detection of latent TB. Participants with a newly identified positive QuantiFERON-TB® (or T-SPOT® for sites in Japan or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study. If the QuantiFERON-TB® test result is indeterminate, the test should be repeated. For sites in Japan, a participant whose first T-SPOT® test result is borderline should have the test repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the Schedule of Activities (Section 1.3).

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including adverse events, serious adverse events, and product quality complaint (PQC), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established Standard Operating Procedures in

conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Further details on adverse events, serious adverse events, and PQC can be found in Appendix 19 (Section 10.19), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All serious adverse events, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last dose of study intervention, must be reported. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

A possible Hy's Law case is defined by the occurrence of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3xULN together with total bilirubin ≥ 2xULN or international normalized ratio (INR) > 1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported to the sponsor in an expedited manner using the Serious Adverse Event form, even before all other possible causes of liver injury have been excluded.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting adverse events or serious adverse events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about adverse event occurrence.

Solicited Adverse Events

Solicited adverse events are predefined local at the injection site and systemic events for which the participant is specifically questioned and which are noted by participants in their diary (see Section 8, Study Assessments and Procedures).

Unsolicited Adverse Events

Unsolicited adverse events are all adverse events for which the participant is not specifically questioned in the participant diary.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the adverse event, serious adverse event, or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

Adverse events, including pregnancy, will be followed by the investigator as specified in Appendix 19 (Section 10.19), Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of adverse events to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an adverse event that commonly occurs in the study population independent of exposure to the drug under investigation. No anticipated events have been identified for this study.

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using a serious adverse event reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention (see Section 7.1, Discontinuation of Study Intervention).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in participants participating in this clinical study must be reported by the investigator according to the procedures in Appendix 19 (Section 10.19). Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Pharmacokinetics and Immunogenicity

Blood samples will be collected for the measurement of serum bermekimab concentrations and antibodies to bermekimab at the timepoints presented in the Schedules of Activities.

At visits in which serum bermekimab concentration and/or antibodies to bermekimab will be evaluated, 1 venous blood sample of sufficient volume should be collected, and each serum sample should be divided into 3 aliquots: 1 for serum concentration of bermekimab and a back-up. Each serum sample will be divided into 3 aliquots: 1 for serum concentration of bermekimab, 1 for antibodies to bermekimab, and 1 back-up.

Blood samples should also be collected at the final visit or at the Early Termination Visit from participants who are discontinued from intervention or withdrawn from the study. Blood samples collected for serum bermekimab concentrations may also be used for exploratory biomarker analyses.

A random venous blood sample for population PK analysis will be collected from all participants on any day between Weeks 2 to 12, except on the days of the scheduled study visits. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study intervention administration. Each population PK serum sample will be divided into 2 aliquots: 1 for serum concentration of bermekimab and a back-up.

The exact dates and times of blood sample collection must be recorded in the laboratory requisition form. See the laboratory manual for further information regarding collection, handling, and shipment of biological samples. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Pharmacokinetic Analytical Procedures

Serum samples will be analyzed to determine serum bermekimab concentrations using a validated, specific, and sensitive immunoassay method under the supervision of the sponsor. The sponsor, or its designee, under conditions in which the participants' identity remains blinded, will assay these samples.

Immunogenicity Analytical Procedures

The detection and characterization of antibodies to bermekimab will be performed using a validated immunoassay method by or under the supervision of the sponsor. Serum samples will be screened for antibodies binding to bermekimab and the titer of confirmed positive samples will be reported. Antibodies to bermekimab may be further characterized and/or evaluated for their ability to neutralize the activity of bermekimab.

8.5. Pharmacogenomics

Genetic variation can be an important contributory factor to interindividual differences in drug disposition and response and may also serve as a marker for disease susceptibility and prognosis. Here, pharmacogenomic research refers to the analysis of 1 or more candidate genes or of the analysis of markers throughout the genome in relation to bermekimab and AD clinical endpoints. The goal of the pharmacogenomic research component is to explore factors that may influence the PK, PD, efficacy, or tolerability of bermekimab and to evaluate genetic factors previously reported to be associated with AD or to identify new associations with disease. These DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and more precisely applied therapies.

A whole blood sample will be collected for pharmacogenomic research in participants who consent separately to this optional part of the study (where local regulations permit). Genotyping or sequencing techniques will be used to assess variation in the filaggrin (*FLG*) gene, a risk factor for AD, and interleukin-1 alpha gene (*IL1A*), the target of bermekimab. Additionally, genome-wide genotyping or sequencing will be used to assess variation genome-wide. Participants will have the option to participate in 1 or both of these studies.

8.6. Biomarkers

Biomarker samples will be collected to evaluate the PD and mechanism of action of bermekimab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to the intervention. The goal of the biomarker analyses is to evaluate the PD of and aid in evaluating the intervention-clinical response relationship.

Biomarker assessment will include the evaluation of relevant markers in serum, blood, and tape strips for all participants. Skin biopsies or skin swabs, or both, will also be collected in participants that consent to this optional part of the study. The samples will be used to better understand the biology of AD; to provide biological assessment of the response of participants to treatment with bermekimab; to analyze differences between responders and nonresponders; and to determine if the markers can be used to classify participants as potential responders prior to treatment. Blood

samples will be separated into serum and PBMCs for biomarker analysis. Samples for serum biomarkers, flow cytometry and gene expression from blood will be collected at time points according to the SoA. Instructions for the collection and shipment of these samples are found in the Laboratory Reference Manual and Biopsy Collection Manual.

8.6.1. Skin Biomarkers

Non-invasive skin sampling through tape stripping is mandatory and will be collected from all participants at time points specified in the SoA. At baseline, tape strips will be collected from both lesional and adjacent non-lesional areas; at Weeks 4, 16, and 32, only lesional areas will be sampled. Tape stripping allows for the measurement of gene expression as well as levels of proteins or other biomarkers in the stratum corneum.

Skin swabs on lesional and non-lesional skin will be collected from participants that consent to this part of the study at time points specified in the SoA. A skin swab will be collected to study the effects of intervention on microbiome composition on affected skin.

Skin biopsy samples will be collected from participants that consent to this part of the study at time points specified in the SoA. At the baseline sampling time point, biopsy samples will be collected from both lesional and adjacent non-lesional areas; at Week 16 two lesional areas will be sampled. Gene expression analysis of skin biopsy samples will be performed to investigate differential gene expression during treatment compared with baseline to explore PD, mechanism of action, and differences in responders versus nonresponders. At Week 16, a whole biopsy will be dedicated for proteomic analysis. In addition, the tissue biopsies may be analyzed for histological readouts and immunohistochemistry to explore the effects of study intervention on cellular composition and PK/PD within skin tissue.

Participants may consent to participate in either collection of skin biopsies or skin swabs (which is a less invasive collection method than a biopsy), or both of these methods for skin sampling.

8.6.2. Serum Biomarkers

Serum samples will be collected from all participants at time points specified in the SoA. Potential circulating factors to be evaluated may include cytokines and other inflammatory markers (eg, CCL17/TARC), and other categories of biomarkers potentially associated with AD or related to the mechanism of action of bermekimab.

8.6.3. Flow Cytometry Analysis

Whole blood samples will be collected from all participants at time points specified in the SoA, and peripheral blood mononuclear cells (PBMC) will be isolated. Flow cytometry analysis of blood cell samples will be utilized to monitor the effects of bermekimab on circulating immune cell populations. Cell surface markers such as, but not limited to, those for T cell subsets (eg, Th1, Th2), dendritic cells (DCs), and B cells will be assessed.

8.6.4. Gene Expression Analysis in Whole Blood

Whole blood samples will be collected from all participants at time points specified in the SoA. Total RNA will be isolated and used for differential gene expression analyses to better understand the pathologic mechanisms involved in AD and to potentially identify a treatment response signature to bermekimab.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.7. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data are outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP).

9.1. Statistical Hypotheses

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

The null hypothesis to be tested to address the primary objective of this study is that there is no difference between any of the bermekimab doses (350 mg or 700 mg) and placebo treatment as measured by the proportion of participants achieving EASI-75 at Week 16.

9.2. Sample Size Determination

This study is designed to enroll approximately 200 participants in order to have sufficient power to detect a difference between the bermekimab groups and the placebo group for the primary endpoint of the proportion of participants achieving EASI-75 at Week 16. The sample size was also chosen to have adequate confidence level for the difference between the bermekimab 700 mg group and the dupilumab group.

The EASI-75 response rate in the bermekimab 400 mg qw group was approximately 35% at Week 16 and 70% at Week 7 from the placebo-controlled study (77474462ADM2002) and the open-label study (2018-PT044), respectively. The EASI-75 response rates at Week 16 were 15% and 12% with placebo and 51% and 44% with dupilumab, respectively, in the two Phase 3 trials

of dupilumab versus placebo in the treatment of adult participants with moderate to severe AD (Simpson 2016).

Therefore, based on the data from these studies, various assumptions to calculate sample size and power are shown in Table 4. The EASI-75 response at Week 16 are assumed to be 15% for placebo, 45% to 50% for dupilumab, and 50% to 70% for the bermekimab 350 mg and 700 mg treatment groups, respectively. Based on these assumptions, approximately 200 participants are planned to be randomized in a 1:1:2:2 ratio to the placebo (n=33), bermekimab 350 mg (n=33), bermekimab 700 mg (n=67), or dupilumab (n=67) treatment groups. These sample sizes provide the study with at least 88% power to detect a treatment difference between the bermekimab treatment groups and the placebo group in EASI-75 at Week 16 based on a 2-sample Z-test at a Type I error rate of 0.05 (2-sided). These sample sizes also provide at least 88% power to detect a treatment difference between the dupilumab and placebo treatment group in EASI-75 at Week 16 at a 2-sided significance level of 0.05 (Table 4).

Table 4: Power to Detect a Treatment Difference in EASI-75 at Week 16

Placebo	Treatment Group	Difference	Power
bermekimab 700 mg (n=67) vs placebo (n=33)			
15%	50%	35%	95%
15%	60%	45%	>99%
15%	70%	55%	>99%
12%	50%	38%	98%
12%	60%	48%	>99%
12%	70%	58%	>99%
bermekimab 350 mg (n=33) vs placebo (n=33)			
15%	50%	35%	88%
15%	55%	40%	94%
15%	50%	38%	93%
12%	55%	43%	97%
dupilumab (n=67) vs placebo (n=33)			
15%	45%	30%	88%
15%	50%	35%	95%
15%	55%	40%	99%
12%	45%	33%	94%
12%	50%	38%	98%
12%	55%	43%	>99%

Note: The power calculation is based on two-sample Z-test (pooled variance) under the normal distribution approximation.

In addition, a sample size of 67 participants in each of the bermekimab 700 mg and dupilumab groups produce a 2-sided 80% confidence interval for the difference in 2 groups with a width of

22.9% when the assumed EASI-75 response is 60% and 50% in the bermekimab 700 mg and the dupilumab group, respectively. Assuming a EASI-75 response is 50% in both the bermekimab 350 mg and dupilumab groups, a sample size of 33 participants in the 350 mg group and 67 participants in the dupilumab group would provide a 2-sided 80% confidence interval of difference with a width of 27.3% (Table 5).

Table 5: Confidence Interval for the Treatment Difference in EASI-75 at Week 16

EASI-75 Response (P1)	EASI-75 Response (P2)	Difference (P1 − P2)	Width	Confidence Limit	Confidence Level
bermekimab 700 mg (n=67; P1) vs dupilumab (n=67; P2)					
60%	50%	10%	22.9%	(−1%, 21%)	80%
65%	50%	15%	21.6%	(4%, 26%)	80%
70%	50%	20%	21.2%	(9%, 31%)	80%
bermekimab 350 mg (n=33; P1) vs dupilumab (n=67; P2)					
50%	50%	0%	27.3%	(−14%, 14%)	80%
55%	50%	5%	27.2%	(−9%, 19%)	80%
60%	50%	10%	26.9%	(−3%, 23%)	80%
bermekimab 700 mg (n=67; P1) vs bermekimab 350 mg (n=33; P2)					
60%	50%	10%	27.1%	(−4%, 24%	80%
65%	50%	15%	26.8%	(2%, 28%)	80%
70%	50%	20%	26.5%	(7%, 33%)	80%

9.3. Populations for Analysis Sets

For the efficacy analyses in this study, the full analysis set (FAS) will be used according to the participants' assigned treatment to which they were randomized, regardless of the treatment they actually received. The FAS includes all randomized participants who receive at least one administration of study intervention. The FAS will be used for all primary and secondary efficacy analyses.

Safety analyses will include all participants who received at least 1 dose (complete or partial) of study intervention and participants will be analyzed based on the treatment they actually received, regardless of the treatment groups to which they were assigned.

Pharmacokinetics analyses for bermekimab will include participants who receive at least one complete dose of bermekimab and have at least one post-dose sample collection. Antibodies to bermekimab will be analyzed for participants who receive at least one dose of bermekimab and have at least one post-dose sample collection.

9.4. Statistical Analyses

9.4.1. General Considerations

Simple descriptive summary statistics, such as n, mean, standard deviation (SD), median, inter quantile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data.

The treatment comparisons for binary endpoints will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline EASI severity or Fisher's exact test in the case of rare events. The differences in binary endpoints between groups and the corresponding CIs will be presented. For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM will includes treatment, visit, baseline EASI severity, baseline score, baseline score by visit interaction, baseline EASI severity by visit interaction, and the treatment-by-visit interaction, if applicable. The Least Square mean (LSmean) estimates and their corresponding 95% confidence interval (CI) will be provided at each time point. In addition, the estimates of LSmean difference and 95% CIs between treatment groups will be provided.

In general, all statistical testing will be performed at a significance level of 0.05 (2-sided) unless otherwise specified. Nominal p-values will be displayed for all treatment comparisons.

9.4.2. Primary Endpoint

The primary efficacy endpoint is the proportion of participants with EASI-75 (≥75% improvement from baseline) at Week 16.

Primary Estimand: The primary estimand (ie, a precise definition of the primary targeted treatment effect) is defined by the following 5 attributes:

- **Population:** adult participants with moderate to severe AD
- **Variable/endpoint:** EASI-75 binary responder variable at Week 16, where participants are considered nonresponders if they experience any of the following intercurrent events post treatment initiation and prior to Week 16:
  - discontinuation of study intervention due to lack of efficacy or an AE of worsening of AD
  - initiation of a protocol-prohibited medication or therapy during the study that could improve AD
  - initiation of rescue medication for AD
- **Treatment:**
  - Experimental: Bermekimab 350 mg, 700 mg
  - Control: Placebo
- **Intercurrent Events:** the composite strategy is used to address this trial intercurrent events; as reflected in the variable definition, a participant with any intercurrent event is not considered an EASI-75 responder after that event.
- **Population level summary:** Difference in the proportions of participants achieving an EASI-75 response at Week 16 between the bermekimab and placebo treatment groups.

Primary Endpoint Analysis

In the primary efficacy analysis, data from all randomized participants who received at least 1 administration of study intervention will be analyzed according to their assigned treatment group.

The primary endpoint will be analyzed at Week 16 based on the primary estimand and the number and proportion of participants who achieve an EASI-75 response at Week 16 will be summarized for each treatment group. To address the primary objective, a CMH chi-square statistic stratified by baseline EASI severity (less severe [EASI <28] or more severe [EASI ≥28]) at an alpha level of 0.05 will be used to compare each bermekimab group separately with placebo. The proportion difference between each bermekimab group and placebo group and its 2-sided 95% CI will be provided based on normal approximation with Mantel-Haenszel weights adjusting for baseline EASI severity.

The study would be considered as positive if any of the comparisons for primary endpoint analysis (bermekimab 700 mg vs placebo, and bermekimab 350 mg vs placebo) is less than or equal to p-value of 0.05. Therefore, an overall Type I error rate will be maintained at 0.1 or less for the primary endpoint analysis.

In addition, the comparison between dupilumab and placebo for the primary endpoint will also be performed at a 2-sided significance level of 0.05. Nominal p-values will be reported.

For the analyses described above, participants with any intercurrent event before Week 16 will be considered as EASI-75 nonresponders at Week 16. In addition, participants who do not return for evaluation or have missing components of EASI will also be considered as nonresponders at Week 16.

To examine the robustness of the primary endpoint analysis, additional analyses of the primary endpoint will be conducted using different missing data approaches; these analyses will be described in the SAP. In addition, sensitivity analyses will be performed for the primary endpoint using the per-protocol population, which includes participants who are generally compliant with the protocol.

To evaluate the consistency of the efficacy, subgroup analysis of the primary endpoint will be performed.

9.4.3. Secondary Endpoints

The major secondary analyses are:

- The proportion of participants with both vIGA-AD 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- Proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 will be compared between each of the bermekimab groups and the placebo group.
- The proportion of participants with EASI-90 response at Week 16 will be compared between each of the bermekimab groups and the placebo group.

- The difference in the EASI-75 response rate between each of the bermekimab treatment groups and the dupilumab treatment group and the corresponding 80% CIs will be calculated at Week 16.
- The difference in the EASI-90 response rate between each of the bermekimab treatment groups and the dupilumab treatment group and the corresponding 80% CIs will be calculated at Week 16.
- The difference and 2-sided 80% CIs in the proportion of participants with both vIGA-AD 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 between each of the bermekimab groups and the dupilumab treatment group will be calculated.
- The difference and 2-sided 80% CIs in the proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 will be calculated between each of the bermekimab groups and the dupilumab group.

Other secondary analyses include:

- The improvement from baseline in EASI score at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- The percent improvement from baseline in EASI score at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- The improvement from baseline in eczema-related itch NRS at Week 16 will be compared between each of the bermekimab groups and the placebo group.

In addition, comparisons between dupilumab and placebo for the secondary endpoints will also be performed.

No adjustments for multiple comparisons will be made for the secondary endpoints.

9.4.4. Exploratory Endpoints

- The improvement from baseline in SCORAD at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in DLQI at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- The improvement from baseline in POEM at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- The improvement from baseline in eczema-related itch NRS at Week 8 will be compared between each of the bermekimab groups and the placebo group.
- The improvement from baseline in eczema-related pain NRS at Week 8 will be compared between each of the bermekimab groups and the placebo group.
- The improvement from baseline in eczema-related pain NRS at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- The improvement from baseline in ADIS itch at Week 16 will be compared between each of the bermekimab groups and the placebo group.

- The proportions of participants with a PGIS score of 1 (none) or 2 (mild) at Week 16 will be compared between each of the bermekimab groups and the placebo group**.**
- The change from baseline in PROMIS-29 total score and sub-scores at Week 16 will be compared between each of the bermekimab groups and the placebo group.
- Hand Dermatitis IGA will be compared between each of the bermekimab groups and the placebo group.
- The improvement and percent improvement in EASI score will be summarized by treatment group over time.
- The proportion of participants who achieve EASI-50, EASI-75, EASI-90, and EASI-100 will be summarized by treatment group over time. The improvement from baseline and percent improvement from baseline in EASI total score will be summarized by treatment group over time.
- The proportions of participants who achieve a vIGA-AD 0 or 1 and a reduction from baseline of ≥2 points over time will be summarized by treatment group.
- The proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline will be summarized by treatment group over time among participants with a baseline itch NRS value ≥4.
- The improvement from baseline in eczema-related itch NRS will be summarized by treatment group over time.
- The improvement from baseline in eczema-related pain NRS will be summarized by treatment group over time.
- In addition, the EASI-50, EASI-75, EASI-90, EASI-100, vIGA-AD 0 or 1 and a reduction from baseline of ≥2 points after Week 16 will be summarized by different subpopulations (eg, dupilumab EASI-75 nonresponders, dupilumab EASI-75 responders, EASI-75 responders to bermekimab 700 mg, EASI-75 nonresponders to bermekimab 700 mg).

Additional analyses through Week 36 will be specified in the SAP.

9.4.5. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, infections, serious infections, mortality, changes in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Details will be specified in the SAP.

Safety Definition

Injection-Site Reactions

An injection-site reaction is any unfavorable or unintended sign that occurs at an injection-site and will be recorded as an AE. Detailed instructions for the evaluation of injection-site reactions are in the Trial Center File.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA. Treatment-emergent AEs are AEs with onset during the intervention period or that are a consequence of a pre-existing condition that has worsened since baseline. All treatment-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

The following analyses will be used to assess the safety of participants in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of severe AEs.
- The incidence and type of infections.
- The incidence and type of reasonably related AEs as assessed by the investigator.
- The incidence and type of injection-site reactions.
- The incidence and type of AEs leading to discontinuation of study.

Listings of participants with SAEs, severe AEs, AEs leading to discontinuation of study intervention, and anaphylactic reaction/serum sickness reactions will also be provided. All safety analyses will be based on the population of participants who received at least 1 administration of study intervention; participants will be summarized by the intervention they received.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test (eg, hematology, clinical chemistry). Selected laboratory parameters will be summarized by treatment groups. Common Terminology Criteria (CTC) will be used to identify abnormal laboratory test results, and the incidence and severity of abnormal laboratory parameters (hematology and chemistry) will be summarized by treatment group.

In addition, a listing of participants with grade 2 or higher laboratory test results (based on the CTC criteria) will also be provided.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized.

Weight

Descriptive statistics of changes from baseline will be summarized at selected scheduled time points.

9.4.6. Other Analyses

Pharmacokinetic Analyses

The PK evaluable population is defined as all the participants who received at least 1 complete dose of bermekimab and had at least 1 valid blood sample drawn for PK analysis after their first dose of bermekimab.

Serum bermekimab concentrations will be summarized by visit and treatment group. Descriptive statistics will be calculated at each sampling timepoint. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. Pharmacokinetic data may also be displayed graphically.

If feasible, population PK analysis of serum concentration-time data of bermekimab may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, race, etc) will be tested as potential covariates affecting PK parameters. The results of the population PK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum bermekimab concentration and efficacy may be examined when appropriate. If a relationship is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship and will be presented in a separate technical report.

Immunogenicity Analyses

The incidence and titers of antibodies to bermekimab will be summarized for all participants who receive at least 1 dose of bermekimab and have appropriate samples for detection of antibodies to bermekimab (ie, participants with at least 1 sample obtained after their first dose of bermekimab).

A listing of participants who are positive for antibodies to bermekimab will be provided. The maximum titers of antibodies to bermekimab will be summarized for participants who are positive for antibodies to bermekimab.

The incidence of neutralizing antibodies (NAbs) to bermekimab will be summarized for participants who are positive for antibodies to bermekimab and have samples evaluable for NAbs to bermekimab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Biomarker Analyses

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the biomarker analysis.

Changes in serum analytes obtained over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in selected markers and response to treatment will be explored. The analyses will aim to identify biomarker relevant to treatment. Results of serum biomarker analyses will be reported in separate technical reports.

Additional analyses related to data collected using digital actigraphy are specified in the biomarker analysis plan and results will be reported in a separate technical report.

Pharmacogenomic Analyses

DNA samples will be used for research related to bermekimab or AD. They may also be used to develop tests/assays related to bermekimab and AD. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to bermekimab or AD clinical endpoints.

Results will be presented in a separate report.

9.5. Interim Analysis

An interim analysis will be conducted prior to the Week 16 DBL when approximately 50% of participants have completed their Week 16 visit. The interim analysis will be used to inform the future development planning of bermekimab for AD based on the data accrued up to the interim analysis. No changes to the current study are planned. Details of the plan for the interim analysis will be specified in a separate interim analysis plan before the time at which the interim analysis is performed. An independent, internal committee will review the results of the interim analysis.

9.6. Data Monitoring Committee

An independent, external DMC, whose members are not directly involved in the conduct of study 77474462ADM2001, will review unblinded safety data to ensure the safety of the participants enrolled in this study. The committee will meet regularly to review unblinded safety data. After the review, the DMC will make recommendations to the study team regarding the conduct of the study. The DMC will consist of at least one clinical physician and one statistician, not involved in the conduct of the study. DMC responsibilities, authorities, and procedures will be documented in the DMC charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AD	atopic dermatitis
ADIS	Atopic Dermatitis Itch Scale
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacille Calmette-Guérin
BSA	Body Surface Area
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRF	case report form(s) (paper or electronic as appropriate for this study)
CTC	Common Terminology Criteria
CYP	cytochrome
DBL	database lock
DLQI	Dermatological Life Quality Index
DMC	Data Monitoring Committee
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HS	hidradenitis suppurativa
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IGA	Investigator Global Assessment
IL-1α	interleukin-1 alpha
IP	Investigational Product
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
LSmean	Least Square mean
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
MTX	methotrexate
NAbs	neutralizing antibodies
NRS	numeric rating scale
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PFS	prefilled syringe
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
POEM	Patient-Oriented Eczema Measure
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
PROMIS-29	Patient-Reported Outcomes Measurement Information System-29

QoL	quality of life
qw	every week
q2w	every 2 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	Severity Scoring of Atopic Dermatitis
SD	standard deviation
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBP	Total body photography
ULN	upper limit of normal
vIGA-AD	validated Investigator Global Assessment for Atopic Dermatitis

10.2. Appendix 2: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

Local country guidelines **for immunocompromised patients** should be consulted for acceptable antituberculous treatment regimens for latent TB. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.3. Appendix 3: Contraceptive Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 19 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, or bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective - failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Male or female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier methods)[c]
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor or designee by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.4. Appendix 4: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Subjects must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Subjects who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Subjects who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Subjects who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Subjects who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the subject ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is NOT eligible*** for this study.

For subjects who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended.

Eligibility based on hepatitis B virus test results

	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+	—
	—	+	+
Exclude	+	— *or* +	— *or* +
Require testing for presence HBV DNA*	—	—	+

* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.

For Japan sites only: For subjects with surface antigen (HBsAg) negative, core antibody (anti-HBc), and/or surface antibody (anti-HBs) positive must undergo further HBV DNA test. If the HBV DNA test is negative, the subject is eligible for this study and the HBV DNA test should be performed every 4 weeks.

10.5. Appendix 5: Regulatory, Ethical, and Study Oversight Considerations

10.5.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Clarification Communications

If text within a final approved protocol requires clarification (eg, current wording is unclear or ambiguous) that does not change any aspect of the current study conduct, a protocol clarification communication (PCC) may be prepared. The PCC Document will be communicated to the Investigational Site, Site Monitors, Local Trial Managers (LTMs), Clinical Trial Managers (CTMs), and/or Contract Research Organizations (CROs) who will ensure that the PCC explanations are followed by the investigators.

The PCC Document may be shared by the sites with Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) per local regulations.

The PCC Documents must NOT be used in place of protocol amendments, but the content of the PCC Document must be included in any future protocol amendments.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor, and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the

situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable
- Documentation of investigator qualifications (eg, curriculum vitae)
- Completed investigator financial disclosure form from the principal investigator, where required
- Signed and dated clinical trial agreement, which includes the financial agreement
- Any other documentation required by local regulations

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable

- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)
- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda

- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site
- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.5.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.5.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations, and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

Completion of screening and randomization procedures within the specified approximately 4-week window is required. If a participant is approaching the completion of that period, the medical monitor can be contacted to discuss eligibility.

If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph), the participant will be considered a screen failure because he/she will not meet eligibility criteria, and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening

10.5.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, biomarker, PK, and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.5.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand bermekimab, to understand atopic dermatitis, to understand differential intervention responders, and to develop tests/assays related to bermekimab and atopic dermatitis. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.5.6. Committees Structure

Data Monitoring Committee

Details regarding the DMC are presented in Section 9.6.

10.5.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding bermekimab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of bermekimab, and thus may be disclosed as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will

not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.5.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.5.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.5.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that patient-reported outcomes (PROs) are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source (eSource) system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source

documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

10.5.11. Monitoring

The sponsor designee will perform on-site monitoring visits as frequently as necessary. This will include blinded site monitors who will perform source data verification and review drug preparation and dispensation. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site, as allowed by local regulation. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF (as defined in the monitoring guidelines) with the source documents (eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

10.5.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.5.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an 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.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.5.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.6. Appendix 6: 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 participants 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 participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgement of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention 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, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants 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 participants on study intervention, including follow-up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the case report form (CRF).

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 participant has tested positive for COVID-19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention 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:

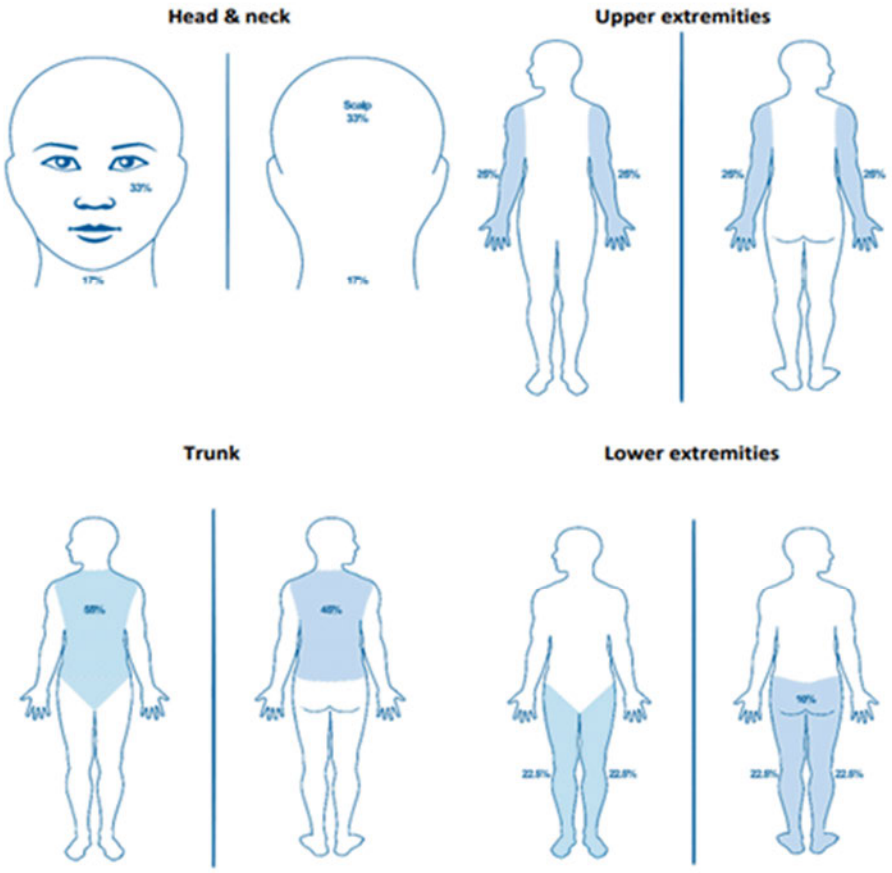
- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those 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 eg, those related to safety monitoring / efficacy evaluation / study drug storage and administration (including training where pertinent)

  - procurement of study drug by patients (or designee) or shipment of study drug from the study site directly to patients for at-home administration (including the potential for patient self-administration of study drug)
  - 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 clinical trial management system for protocol deviations. Discontinuations of study interventions 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 of enrolling in the study, and during participation in the study.

10.7. Appendix 7: Eczema Area and Severity Index

EASI Score Calculation: Assessment is performed on the indicated body regions, with each component (erythema, induration/papulation, excoriation, lichenification) graded on a scale of 0-3 and summed. The component score is then multiplied by the area score corresponding to the degree of body area involvement, followed by the weighting factor for the particular body region. (diagram from francefoundation.com and table excerpted from Hanifin 2001)



cation. The average degree of severity of each sign in each of the four body regions was assigned a score of 0 to 3 (none, mild, moderate, and severe, respectively) with half-steps allowed. It should be

Table 1. Eczema area and severity index: calculation for patients 8 years of age and older[1]

Body region	EASI Score[2,3]
Head/Neck (H)	(E+I+Ex+L)×Area×0.1
Upper limbs (UL)	(E+I+Ex+L)×Area×0.2
Trunk (T)	(E+I+Ex+L)×Area×0.3
Lower limbs (LL)	(E+I+Ex+L)×Area×0.4
EASI =	*Sum of the above 4 body region scores*

[1]For children aged 0–7 years, proportionate areas were head/neck, 20%; upper limbs, 20%; trunk, 30%; and lower limbs, 30%.
[2]E=Erythema, I=induration/papulation, Ex=excoriation, L=lichenification.
[3]Where area is defined on a 7-point ordinal scale: 0=no eruption; 1=<10%; 2=<10%–29%; 3=<30%–49%; 4=<50%–69%; 5=<70%–89%; and 6=>90%–100%.

10.8. Appendix 8: Validated Investigator Global Assessment for Atopic Dermatitis

Validated Investigator Global Assessment scale for Atopic Dermatitis

vIGA-AD™

Instructions:

The IGA score is selected using the descriptors below that best describe the overall appearance of the lesions at a given time point. It is not necessary that all characteristics under Morphological Description be present.

Score	Morphological Description
0 – Clear	No inflammatory signs of atopic dermatitis (no erythema, no induration/papulation, no lichenification, no oozing/crusting). Post-inflammatory hyperpigmentation and/or hypopigmentation may be present.
1 – Almost clear	Barely perceptible erythema, barely perceptible induration/papulation, and/or minimal lichenification. No oozing or crusting.
2 – Mild	Slight but definite erythema (pink), slight but definite induration/papulation, and/or slight but definite lichenification. No oozing or crusting.
3 – Moderate	Clearly perceptible erythema (dull red), clearly perceptible induration/papulation, and/or clearly perceptible lichenification. Oozing and crusting may be present.
4 – Severe	Marked erythema (deep or bright red), marked induration/papulation, and/or marked lichenification. Disease is widespread in extent. Oozing or crusting may be present.

Notes:

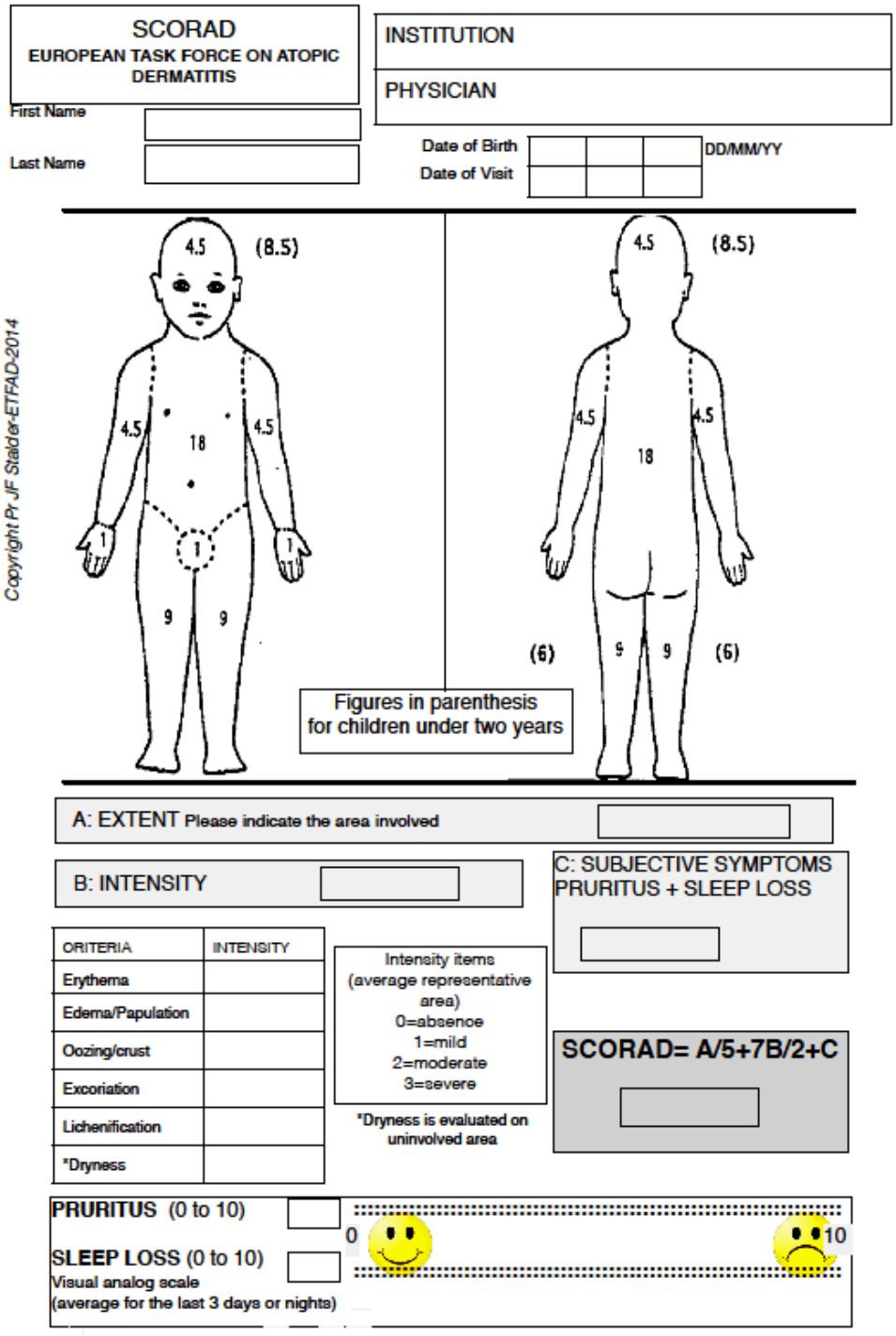
1. In indeterminate cases, please use extent to differentiate between scores.

For example:

- *Patient with marked erythema (deep or bright red), marked papulation and/or marked lichenification that is limited in extent, will be considered "3 – Moderate".*

2. Excoriations should not be considered when assessing disease severity.

10.9. Appendix 9: Severity Scoring of Atopic Dermatitis



10.10. Appendix 10: Hand Dermatitis Investigator Global Assessment

4-Severe: Severe erythema (deep intense red color), scaling, vesiculation (with or without erosion), and/or edema (swelling). Prominent lichenification (thickening with accentuated normal skin markings) and/or deep fissuring (causing bleeding or severe pain).

3-Moderate: Moderate erythema (prominent redness), scaling, vesiculation, and/or edema. Palpable skin thickening and/or visible fissuring affecting multiple areas of the hand.

2-Mild: Faint but definite erythema, slight but definite flaking, scattered vesicles without erosion, and/or slight but definite swelling over limited areas of the hands. Slight but definite skin thickening and/or cracked skin affecting limited areas of the hands.

1-Almost Clear: Barely perceptible erythema, flaking, and/or swelling. Minimal vesicles. Barely perceptible skin thickening and/or minimal cracked skin over limited areas of the hands.

0-Clear: No erythema, scaling, vesiculation, edema, lichenifcation, or fissuring. Post-inflammatory pigment alteration (either hyper- or hypopigmentation) may be present.

10.11. Appendix 11: Patient-Reported Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick one box for each question.

1.	Over the last week, how **itchy, sore, painful or stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed or self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home or garden**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social or leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working or studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work or studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends or relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

10.12. Appendix 12: Patient-Oriented Eczema Measure

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM • CHINA • MALAYSIA

POEM for self-completion

Patient Details: _____

_____

_____

_____ Date: _____

Please circle one response for each of the seven questions below about your eczema. Please leave blank any questions you feel unable to answer.

1. Over the last week, on how many days has your skin been itchy because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

2. Over the last week, on how many nights has your sleep been disturbed because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

3. Over the last week, on how many days has your skin been bleeding because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

4. Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

5. Over the last week, on how many days has your skin been cracked because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

6. Over the last week, on how many days has your skin been flaking off because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

7. Over the last week, on how many days has your skin felt dry or rough because of your eczema?

No days 1-2 days 3-4 days 5-6 days Every day

Total POEM Score (Maximum 28): .....

POEM
Patient-Oriented Eczema Measure

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

POEM for self-completion

How is the scoring done?

Each of the seven questions carries equal weight and is scored from 0 to 4 as follows:

No days	= 0
1-2 days	= 1
3-4 days	= 2
5-6 days	= 3
Every day	= 4

Note:

- If one question is left unanswered this is scored 0 and the scores are summed and expressed as usual out of a maximum of 28
- If two or more questions are left unanswered the questionnaire is not scored
- If two or more response options are selected, the response option with the highest score should be recorded

What does a poem score mean?

To help patients and clinicians to understand their POEM scores, the following bandings have been established (see references below):

• 0 to 2	= Clear or almost clear
• 3 to 7	= Mild eczema
• 8 to 16	= Moderate eczema
• 17 to 24	= Severe eczema
• 25 to 28	= Very severe eczema

Do I need permission to use the scale?

Whilst the POEM scale is protected by copyright, it is freely available for use and can be downloaded from: www.nottingham.ac.uk/dermatology
We do however ask that you register your use of the POEM by e-mailing cebd@nottingham.ac.uk with details of how you would like to use the scale, and which countries the scale will be used in.

References

Charman CR, Venn AJ, Williams HC. The Patient-Oriented Eczema Measure: Development and Initial Validation of a New Tool for Measuring Atopic Eczema Severity From the Patients' Perspective. Arch Dermatol. 2004;140:1513-1519

Charman CR, Venn AJ, Ravenscroft JC, Williams HC. Translating Patient-Oriented Eczema Measure (POEM) scores into clinical practice by suggesting severity strata derived using anchor-based methods. Br J Dermatol. Dec 2013; 169(6): 1326–1332.

10.13. Appendix 13: Patient Global Impression of Severity

Patient's Global Impression of Severity (PGIS)
of Eczema

Overall, how would you rate the severity of your eczema currently? (Please select one response)

- ☐ 1. None
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Very Severe

10.14. Appendix 14: Patient-Reported Outcomes Measurement Information System-29

PROMIS–29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AND	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

07 February 2018
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PROMIS–29 Profile v2.1

	Fatigue In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER45_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAINN9	How much did pain interfere with your day to day activities?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINN22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINN31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAINN34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

PROMIS–29 Profile v2.1

Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 No pain	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 Worst pain imaginable

10.15. Appendix 15: Eczema Skin Pain and Itch Numeric Rating Scale

Eczema Skin Pain and Itch Numeric Rating Scale

Individuals with eczema may experience skin pain and itch. Please indicate how severe your skin pain and itch were in the past 24 hours. Please select only one number for each item on the 0 to 10 scale (0=none and 10=worst possible).

1. Please rate the severity of your eczema-related **skin pain** at its worst in the past 24 hours.

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
0	1	2	3	4	5	6	7	8	9	10
None										Worst possible

2. Please rate the severity of your eczema-related **itch** at its worst in the past 24 hours.

❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑
0	1	2	3	4	5	6	7	8	9	10
None										Worst possible

10.16. Appendix 16: Atopic Dermatitis Itch Scale

Eczema Itching Severity Diary

[Morning Administration]

1. How would you rate your eczema-related itching **right now**?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No itching at all					Moderate itching					Worst possible itching

2. Did you have **any** eczema-related itching last night? (since you last completed the diary)

☐ Yes
☐ No *[End of morning administration]*

3. At its **worst**, how would you rate your eczema-related itching last night?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No itching at all					Moderate itching					Worst possible itching

4. To what extent did eczema-related itching impact your sleep last night?

☐ No impact: itching did not affect sleep
☐ Mild impact: a little difficulty falling or staying asleep due to itching
☐ Moderate impact: a moderate amount of difficulty falling or staying asleep due to itching
☐ Severe impact: a great deal of difficulty falling or staying asleep due to itching

Eczema Itching Severity Diary

[Evening Administration]

1. How would you rate your eczema-related itching **right now**?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No itching at all					Moderate itching					Worst possible itching

2. Did you have **any** eczema-related itching today? (since you last completed the diary)

☐ Yes
☐ No *[End of evening administration]*

3. At its **worst**, how would you rate your eczema-related itching today?

☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
0	1	2	3	4	5	6	7	8	9	10
No itching at all					Moderate itching					Worst possible itching

4. How much of the time did you experience eczema-related itching today?

☐ A little of the time (less than 20% of the day)
☐ Some of the time (20% to 40% of the day)
☐ About half of the time (40% to 60% of the day)
☐ Most of the time (60% to 80% of the day)
☐ All or nearly all of the time (more than 80% of the day)

10.17. Appendix 17: Digital Actigraphy

Pruritus or itch is the most defining and universal symptom of AD. Pruritus is defined as an unpleasant urge to scratch and is problematic for many reasons, particularly its negative impact on quality of life (QoL). Despite the profoundly negative impact of pruritus on patients with AD, clinicians and researchers lack standardized and validated methods to objectively measure pruritus (Smith 2019). In addition, pruritus in AD patients leads to sleep disturbances, fatigue and altered physical activity patterns.

A wrist actigraph is a portable device that uses a micro-accelerator to measure nocturnal wrist movement as a proxy for scratching activity that is correlated to itch in patients with AD (Price 2014). Furthermore, actigraphy has been used in several systemic autoimmune disease studies to document the differences in quality of the sleep and physical activity.

A recently published study presents an algorithm to detect nocturnal scratching events based on tri-axial wrist actigraphy data sampled at ≥20 Hz (Moreau 2018). The algorithm showed good performance with an F1 score of 0.68, sensitivity of 0.66, and precision of 0.71. The algorithm was trained on manually labeled scratching events from infrared video data collected from 24 subjects (6 healthy controls and 18 AD patients). In this study, the published algorithm will be applied to actigraphy data collected on a subset of patients in order to assess treatment effects on nocturnal scratching.

For the optional digital actigraphy assessments, a subgroup of participants across treatment arms from selected sites will be provided 2 wrist actigraphs from screening through Week 16. Study participants will be instructed to wear 2 devices (1 on each wrist) before going to sleep and wear one device on the non-dominant wrist during the day.

For analysis of results, scratching events will be quantified by night into 2 endpoints: normalized scratch duration (nightly scratch duration normalized by total sleep time) and normalized scratch rate (number of scratching events normalized by total sleep time). These nocturnal scratch endpoints will be correlated with self-reported itch, disease severity, and other efficacy assessments.

10.18. Appendix 18: Remote Endpoint Assessment Using Total Body Photography

A previous study (Hughes 2019) has described the capture of digital images of subjects by site personnel, with subsequent analysis of the on-site investigator who also performed the in-person assessment. In addition, total body photography (TBP) has long been employed in dermatology for the process of "mole mapping," ie, monitoring the development or change of nevi on the skin over time (Rice 2010, Truong 2016). As such a standardized photographic series has been established to capture the entirety of the skin surface for visual evaluation (Shriner 1990).

In the assessment of atopic dermatitis, the well-established and validated scoring systems of the Eczema Area and Severity Index (EASI; Appendix 7 [Section 10.7]) and Severity Scoring of Atopic Dermatitis (SCORAD; Appendix 9 [Section 10.9]) are particularly well-suited for the use of photographic evaluation. Both scoring systems use regional component assessments (eg, arms, legs, chest, extremities) that correspond well to the photographic series proposed. Furthermore, the percentage of BSA involvement, itself a criterion for defining moderate to severe disease in AD, can be calculated separately (eg, rule of 9's approximation) or extracted from the SCORAD system.

In this study, standard atopic dermatitis severity assessments captured and analyzed via digital photographs will be compared with in-person investigator assessments. In addition, comparisons at 3 time points and across the treatment groups in this study will allow assessment of the utility of digital photography in the measurement of treatment effects.

For the optional digital photographic assessments, a subgroup of participants across dose groups from selected sites will provide a series of digital total body photographs at the baseline, Week 8, and Week 16 visits.

Participants will agree to take multiple series of total body photographs with assistance and with the provided device. Instructions and photographic guides will be provided to the participant. On the same day as a scheduled site visit, the participant will obtain the set of digital images. During the same visit, the investigator will also capture a corresponding set of images. Captured images will be transferred and stored in a secure manner. The site investigator (at some point after the Week 16 visit), will access the images for the subjects at their site and will assess the subjects' severity according to the specified analyses. A central reader(s) will be selected to evaluate and score the images for all participants within the substudy.

For analysis of results, a comparison will be performed of the correlation of efficacy measures between the in-person site visit, site investigator assessment by images (including those captured by the participant and those captured by the site), and central reader assessment by images.

10.19. Appendix 19: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.19.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Conference on Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For bermekimab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB. For dupilumab, the expectedness of an adverse event will be determined by whether or not it is listed in the package insert.

10.19.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.19.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.19.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention

- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson & Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)
- Exposure to a sponsor study intervention from breast-feeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

10.19.5. Procedures

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available

- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct
- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study within 4 weeks of the last dose of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

Information regarding serious adverse events will be transmitted to the sponsor using a serious adverse event reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site, and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.19.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory

requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.19.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.20. Appendix 20: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities by the central laboratory:

Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th colspan="3">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet count
Red blood cell count
Hemoglobin
Hematocrit</td><td><u>RBC Indices:</u>
MCV
MCH</td><td><u>White Blood Cell (WBC) count with Differential:</u>
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils
Bands</td></tr>
<tr><td rowspan="2">Clinical Chemistry</td><td colspan="2">Sodium
Potassium
Chloride
Blood urea nitrogen (BUN)
Creatinine
Glucose
Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic
Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic</td><td>Total bilirubin
Indirect bilirubin
Alkaline phosphatase
Calcium
Phosphate
Albumin
Total protein</td></tr>
<tr><td colspan="3">Details of liver chemistry stopping criteria and required actions and follow-up are provided in Section 10.21: Liver Safety.

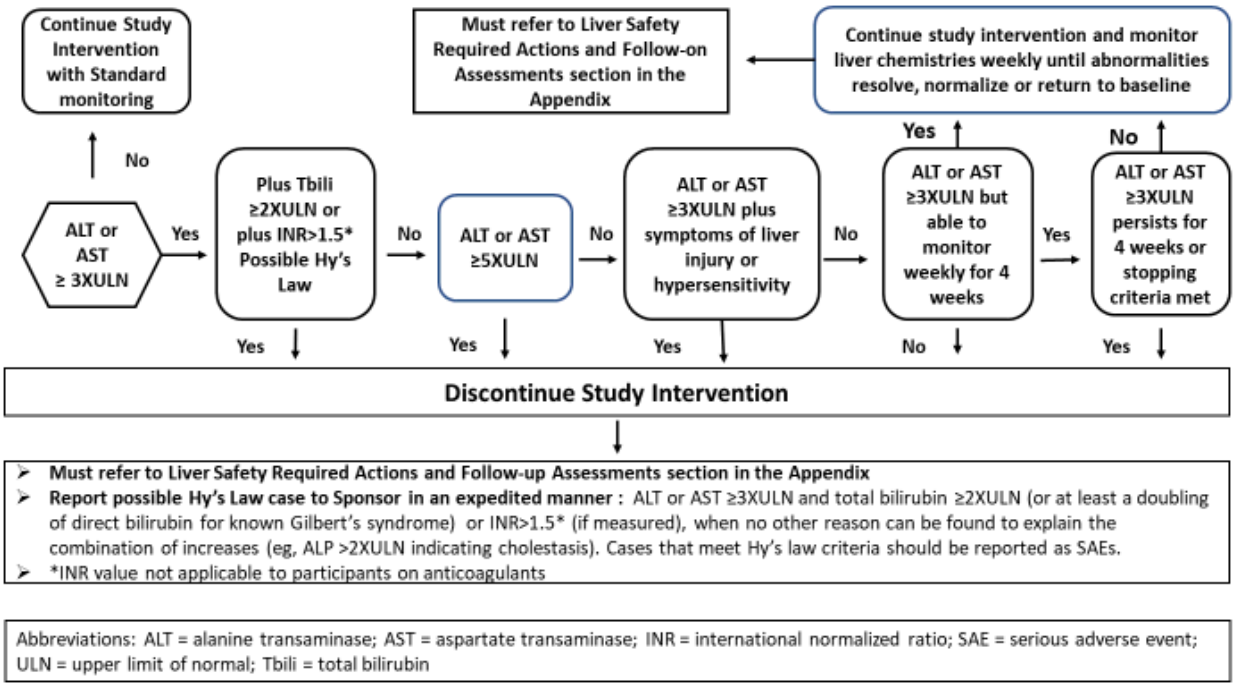
Potential Hy’s Law case reporting requirements are defined in Section 8.3.1</td></tr>
<tr><td>Other Laboratory Tests</td><td colspan="3">• Urine pregnancy testing for women of childbearing potential only
• Lipids (Week 0 only)
• High-sensitivity C-reactive protein
• Serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc], and hepatitis C virus antibody</td></tr>
</table>

10.21. Appendix 21: Liver Safety: Suggested Actions and Follow-up Assessments

10.21.1. Stopping Algorithm

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



10.21.2. Follow-up Assessments

10.21.2.1. Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology.

Liver Chemistry Stopping Criteria	
ALT/AST--absolute	ALT **or AST-** ≥5xULN
ALT/AST-Increase	**If cannot monitor:** ALT **or AST-** ≥3 xULN and cannot be monitored weekly for 4 weeks **Or if able to monitor:** ALT **or AST-** ≥3xULN persists for ≥4 weeks
Total bilirubin[1, 2]	ALT **or AST-** ≥3xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome)
INR[2]	ALT **or AST-** ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[3]	ALT **or AST-** ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring and Follow-up Assessments

Actions	Follow-up Assessments
• **Immediately** stop study intervention • Report the event to the sponsor **within 24 hours** • Complete an SAE form • Perform follow-up assessments as described in the Follow Up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) **MONITORING:** **If ALP <2xULN, ALT or AST- ≥3xULN AND total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 (if measured):** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT or AST- ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) within 1 week of the event of ALT or AST ≥3×ULN[5] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF as per CRF completion guidelines • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) • Record alcohol use on the CRF as per CRF completion guidelines

bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participant weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **If liver event causality is determined to be "not related", restart may be permitted upon written approval of the sponsor**. See restart guidelines	**If ALT or AST- ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured)** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete CRF as per CRF completion guidelines • Liver biopsy may be considered and discussed with local specialist if available: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation • If liver biopsy conducted complete CRF as per CRF completion guidelines

1.Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT **or AST** ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

2.All events of ALT **or AST-** ≥3 xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome), ALT **or AST-** ≥3 xULN **and** INR >1.5 (if measured) may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner as an SAE**. The INR stated threshold value will not apply to participants receiving anticoagulants.

3.New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

4.Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAg and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

5.PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual.

10.22. Appendix 21: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

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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 study intervention, 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

Signature: [electronic signature appended at the end of the protocol] Date: _____

(Day Month Year)

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