Janssen Research & Development *

Clinical Protocol

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

Protocol 77474462ADM2003**;** Phase 2
Amendment 1
Bermekimab (JNJ-77474462)

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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

Registry	**ID**
IND	112459
EudrCT	2020-005900-21

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EDMS Number: EDMS-RIM-280762, 4.0

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	23-Nov-2021
Original Protocol	17-Jun-2021

Amendment 1 (23 November 2021)

Overall Rationale for the Amendment: To add additional sample collections for lipid panels in order to provide a more robust safety check for participants. In addition, grammar and inconsistencies have been amended throughout the protocol.

Section Number and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	• Added "fasting" to lipid panel and added additional collections at Weeks 1 and 8 for participants in Parts B and C. • Footnote 'aa' added for clarity.	To provide a more robust safety profile.
	Realigned the parameters under "Whole blood (Pharmacogenomics)" under the 'Pharmacogenomics' heading from previously under 'Biomarker' heading.	Grammatical error.
	• Collection of Total body photography at Week 20 was deleted. • Footnote 'c' added to ICF for skin barrier function substudy. • The footnote was updated to remove biomarkers and added '***optional skin barrier function assessments****, and* ***optional*** *total body photography*'.	To align with amended footnote. The final collection timepoint is Week 16 (end of treatment).
	Removed informed consent form for optional biomarker sample collection since this is being removed from the study.	Skin swabs will no longer be collected as part of the study.
	Vital signs collection removed for Week 16. The corresponding footnote 'w'was updated to state Week 15 since the last dose is on Week 15 not Week 16.	Fixed numerical error.
	Added visit window ±3 days for all visits to match footnote 'y'	Added to provide clarity
	Removed height collection at Week 0	Redundant since collected at screening and unnecessary at Week 0.
	Added electrocardiogram at Week 16 timepoint.	To provide more comprehensive safety review.
1.3. SoA 8.6.1. Skin Biomarkers	Removed the row corresponding to 'skin swab-optional' since there were no longer plans to collect and analyze biomarkers samples; corresponding footnote 'o' was deleted. Removed paragraph pertaining to skin swab collection and analysis.	Skin swabs will no longer be collected as part of the study.
2.2. Background	Updated wording (~~**deleted text**~~ and **revised text**) in clinical studies to match the achieved Eczema Area and Severity Index (EASI)-75	To provide clarity.

Section Number and Name	Description of Change	Brief Rationale
	results after 4 weeks of therapy at Week 7 updated to match study results ie, "~~75~~**71**% achieved EASI-75 at Week **8**~~7~~" reported in the clinical study report.	
	Nonclinical Pharmacology: The K_D for human IL-1α was updated from 0.14 nM to 0.029 nM and for cynomolgus monkey from 3 nM to 1.3 nM.	To align with the latest information in the investigator's brochure.
2.3. Benefit-Risk Assessment	Updated to remove injection site reactions pertaining to risks in this study.	This study is IV infusion so there is no risk for injection site reactions.
2.3.1. Benefit Risk Assessment for Study Participation	Updated with the addition of "approximately" for infusion and monitoring in the *Infusion related reactions* subsection of Table 1.	To provide flexibility around timing of monitoring
1.1. Synopsis (Objectives and Endpoints) 3. Objectives and Endpoints	Abbreviations updated to include pharmacodynamics.	For consistency with the table.
4.1. Overall Design	Added 'approximately' to all timepoints and number of participants.	To provide flexibility around timing and number of participants
4.2. Scientific Rationale for Study Design	Removed placeholder of "insert text here".	Fixed error.
4.4. End of Study Definition	Updated the wording for the definition of EOS.	To provide more clarity.
	Updated the wording for the definition of Study completion ie, included completion of all study interventions at Week 15.	
5.1. Inclusion Criteria; 5.3. Lifestyle Considerations	Criteria 17: Updated the laboratory values with appropriate superscripts ($\times 10^3$).	Fixed formatting errors.
	Criteria 19: was updated to include 'strongly' for recommendation and "including COVID-19 vaccines prior to screening". In addition, the updated criteria was moved to Section 5.3: Lifestyle Considerations.	To provide clarity.
	Criteria 20: fixed incorrect reference to inclusion criterion 21b which was changed to 20a.	
5.2. Exclusion Criteria	Criteria 24: updated timeline pertaining to the use of any prescription topical treatment for atopic dermatitis from within ~~**1 week**~~ to **4 weeks** of the baseline visit.	Clarification and to align with inclusion criteria 18 for consistency.
	Criteria 25: was amended to reflect 4 weeks prior to the first administration of study intervention.	To provide consistency with the rest of the criterion.
	Criteria 27: was deleted as it has been captured in exclusion criterion 25.	Redundant exclusion criteria.
	Criteria 35: was deleted as it has been captured in exclusion criterion 16.	Redundant exclusion criteria.
	Criteria 38: was deleted as it has been captured in exclusion Criteria 9.	Redundant exclusion criteria.
	Criteria 10: was updated to reflect hepatitis B surface antigen (HBsAg) or hepatitis C antibody (anti-hepatitis C virus) which was originally part of a separate Criteria 37 which	Redundant exclusion criteria.

Section Number and Name	Description of Change	Brief Rationale
	has now been deleted. Conditions for participants with antibodies to HCV have been included.	
	Criteria 39: updated wording since drug and alcohol use are not being test at screening.	To provide clarity.
5.3. Lifestyle Considerations	Updated points 1 and 3 to reflect correct inclusion criterion numbering.	Align with amended inclusion criteria and numbering.
6.3. Measures to Minimize Bias: Randomization and Blinding	Under 'Blinding'- Language was amended to clarify blinded versus unblinded participants. In addition, wording around emergency unblinding was added.	Clarification of blinding criteria.
	Under 'Procedures for Randomization' – the sentence was revised as, "…*randomly assigned to* ***either the bermekimab or placebo*** ~~***1 of 2***~~ *intervention groups*"	To be more specific.
6.8.3. Prohibited Therapies/Medications	Text added for oral corticosteroid use to indicate 'for conditions other than AD'.	To provide clarity around use of oral corticosteroids during the study
6.8.4. Rescue Medication	Wording was added for clarity regarding use of hydrocortisone.	To provide clarity.
6.8. Concomitant Therapy; 6.8.6. Vaccinations (including COVID-19)	Paragraphs pertaining to concomitant use of COVID-19 or influenza vaccine was moved from Concomitant Therapy to a dedicated subsection pertaining to vaccinations.	To provide more clarity around vaccinations in a dedicated subsection.
7.1. Discontinuation of Study Intervention	Removed '>' symbol for oral corticosteroids since it was redundant when used along with the wording "more than".	Redundant text.
	Discontinuation criteria pertaining to serious adverse reactions was updated to include infusions.	To correctly align with the route of administration of study treatment in this study.
1.1. Synopsis (Efficacy Evaluations); 8.1. Efficacy Assessments	vIGA was added to list of endpoints.	Consistency with objectives and efficacy endpoints.
8.2.3. Electrocardiograms	Week 16 timepoint was added.	To align with the SoA.
8.2.4. Clinical Safety Laboratory Assessments 8.2.5. Pregnancy Testing	• Serum pregnancy testing was added alongside urine pregnancy test; timeline for testing was amended from Week 22 to Week 20. • The aforementioned, amended paragraph was also moved from clinical laboratory assessment section to pregnancy testing section as it was better placed under the latter heading ie, Section 8.2.5.	Clarification of language and relocation to a more appropriate section.
8.5. Pharmacogenomics	Statement regarding option to participate in either or both studies was deleted as it was a carry-over from a different study protocol.	Language correction to apply to this study.
8.6.4. Gene Expression Analysis in Whole Blood	Total ribonucleic **acid**.	Completion of the term.

Section Number and Name	Description of Change	Brief Rationale
9.4.2. Primary Endpoint Analyses	• Section and Table 4 updated for primary endpoint wherein intercurrent events (ICEs) were updated to include 'prior to Week 16' timeline and definition/criteria for EASI-75 non-responders was clarified. • It was also indicated that, "***No adjustment for multiple comparisons will be made for primary.***" • Variable/endpoint was reformatted as it is 1 of 5 attributes. • ICEs were updated to include 1 through 4.	To provide more clarity. To align with Table 4.
	'Missing data' was updated to 'data handling'.	
10.2. Appendix 2: Clinical Laboratory Tests	Changed alanine aminotransferase (ALT)/serum glutamic "~~**oxaloacetic**~~" to alanine aminotransferase (ALT)/Serum glutamic-"**pyruvic**".	To provide clarity.
	Lactic acid dehydrogenase (LDH) was added to the Chemistry panel	Was missed in the original draft and is required for disease monitoring.
10.3.6. Committees Structure	Fixed repetitive phrase placeholder.	To provide clarity.
10.3.7. Publication Policy/Dissemination of Clinical Study Data	Deleted duplicate phrases.	Typographical errors corrected
10.5. Appendix 5: Contraceptive and Barrier Guidance	Updated wording around tubal ligation based on European Medicines Agency guidance ie, tubal closure eg, bilateral tubal ligation has been added.	Updated EMEA guidance
10.7. Appendix 7: Liver Safety: Suggested Actions and Follow Up Assessments	Fixed incorrect symbol from £ to ≤ for international normalized ratio criteria.	Typographical errors corrected
	Under Phase 2 Liver Chemistry Stopping Criteria and Follow Up Assessments, table title was revised from ~~**Suggested**~~ to **Required** Actions	To clarify that these actions are mandatory and not suggested as an option.
10.8. Appendix 8: Hepatitis B Virus (HBV) Screening with HBV DNA Testing	In the "Require testing for presence HBV DNA*" changed it from positive (+) to negative (-).	To provide clarity.
10.19. Appendix 19: Remote Endpoint Assessment Using Total Body Photography	Language was updated to specify 4 visits, including Week 20 and that total body photography will only be performed at the sites and not at home by participants. In addition, Week 0 was added in parenthesis to baseline and the Week 16 visit was updated to Week 20.	To provide clarity.
Throughout the protocol	• Added "approximately" to numerical values for infusion times, observation times, and number of participants. • Removed the term "~~injection~~" from document and replaced with "infusion" where appropriate.	• Minor errors were noted • Grammatical errors were corrected. • Edits were made to accommodate revisions

Section Number and Name	Description of Change	Brief Rationale
	• The full form of 'ET' was corrected from "~~end of treatment~~" to "early termination" including Appendix 1: Abbreviations • Corrected bermekimab capitalization and lower case, as applicable. • Inclusion and exclusion criteria were renumbered to accommodate additions and deletions under respective categories. Subsequently, cross-referenced criteria were also appropriately renumbered. • Minor grammatical, formatting, or spelling changes were made.	for consistency and accuracy

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1. PROTOCOL SUMMARY

1.1. Synopsis

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

DESCRIPTION OF COMPOUND

Bermekimab (also known as JNJ-77474462 and monoclonal antibody protein-1 [MABp1]) is a recombinant human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) specific for human interleukin-1 alpha (IL-1α). Interleukin-1 alpha is a key mediator of cutaneous inflammation and is constitutively and inducibly expressed by several cell types, including keratinocytes where high levels of IL-1α are present in healthy individuals, these data suggest that IL-1α has the potential to mediate inflammation in the skin.

OBJECTIVES AND ENDPOINTS

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

Objectives	Endpoints
	• Proportion of participants with Clinically significant abnormalities in vital signs and laboratory tests.
To characterize additional assessments of efficacy of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in participants with moderate-to-severe AD	Analyses of the following at applicable visits through Week 16 by visit, respectively: • Proportion of participants with both vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points • Proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline among participants with a baseline itch value ≥4 • Proportion of participants with EASI-90
Exploratory	
To further characterize efficacy of 16 weeks of multiple IV doses of bermekimab, compared with placebo, 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 ADIS • Proportions of participants with a PGIS score of 1 (none) or 2 (mild) at Week 16 • Change from baseline to Week 16 in PROMIS-29 total score and sub-scores • Improvement in Hand Dermatitis IGA from baseline to Week 16.
To assess the impact of treatment with 16 weeks of multiple IV doses of bermekimab, compared with placebo, on selected biomarkers.	Analyses of the following at all applicable visits from Week 0 through Week 16: • Changes in cellular and molecular PD biomarkers levels in skin and blood from baseline compared with placebo. • Changes in skin barrier function from baseline compared with placebo.

Abbreviations: AD=atopic dermatitis; ADIS=Atopic Dermatitis Itch Scale; AE=adverse event; DLQI=Dermatological Life Quality Index; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; -IV=intravenous; NRS=numeric rating scale; PD=pharmacodynamics; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; PROMIS=Patient-Reported Outcomes Measurement Information System; POEM=Patient-Oriented Eczema Measure; SAE=serious adverse event; SCORAD=Severity Scoring of Atopic Dermatitis; TEAE=treatment-emergent adverse event; vIGA-AD=validated Investigator Global Assessment for Atopic Dermatitis.

HYPOTHESIS

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

OVERALL DESIGN

This is a Phase 2, double-blind, randomized, placebo-controlled, multicenter, interventional study designed to assess the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), biomarkers, and immunogenicity of multiple doses of bermekimab administered via IV infusion for the treatment of moderate-to-severe AD in adult participants.

The study has 3 phases that will include: a screening phase of up to 4 weeks, a double-blinded, placebo-controlled phase of 16 weeks, and a safety follow-up phase of 4 weeks. The study will have 3 treatment parts which will run in parallel and/or staggered during the active treatment or placebo-controlled phase, namely Parts A, B, and C.

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

The study also includes 4 mandatory skin biopsies (2 at baseline and 2 post-dosing). All participants of Part A and the first 10 participants of Part B will have skin biopsies done at Week 0 (1 lesional and 1 non-lesional), and at Week 6 (2 lesional). The rest of the participants will be biopsied at Week 0 (1 lesional and 1 non-lesional), and at Week 16 (2 lesional).

All participants will have an extended in-clinic observation period of approximately 4 hours during the first 2 infusions. In this period, vital signs will be taken at the following time points: 0 hour (start of infusion), 30 minutes (mins), 1 hour, 1 hour and 30 mins, 2 hours (end of infusion), 2 hours and 30 mins, 3 hours, 3 hours and 30 mins, and 4 hours (post-infusion). Beyond the first 2 infusions, all participants will have approximately a 1 hour infusion period and at least a 1 hour observation post infusion, as well as vital signs taken approximately every 30 minutes.

An internal and Independent Data Review Committee (DRC) will be commissioned for this study.

NUMBER OF PARTICIPANTS

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

INTERVENTION GROUPS AND DURATION

Approximately, 10 participants are planned to receive weekly 800 mg of IV bermekimab or placebo in Part A. Approximately, 30 participants are planned to receive weekly dose of 1200 mg of IV bermekimab or

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

EFFICACY EVALUATIONS

Efficacy assessments (EASI, validated Investigator Global Assessment for Atopic Dermatitis [vIGA AD™], percent body surface area [BSA] involvement, Severity Scoring of Atopic Dermatitis (SCORAD), and Hand Dermatitis Investigator Global Assessmen [IGA]) and electronic patient reported outcome (ePRO) measures (Dermatological Life Quality Index [DLQI], Patient Oriented Eczema Measure [POEM], Patient Global Impression of Severity [PGIS], Patient Reported Outcomes Measurement Information System [PROMIS]-29, Eczema Skin Pain and Itch numeric rating scale [NRS], and Atopic Dermatitis Itch Scale [ADIS]) will be performed at visits according to the Schedules of Activities. Evaluation of EASI, SCORAD, and validated investigator global assessment (vIGA) 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 (SoA). Serum samples will also be collected at the final visit from participants who terminate study participation early.

PHARMACODYNAMIC AND BIOMARKER EVALUATIONS

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.

Biomarker assessment will include the evaluation of relevant markers in serum, blood, skin biopsies, and tape strips for all participants. Blood samples will be separated into serum and peripheral blood mononuclear cell (PBMC) for biomarker analysis. Samples for serum biomarkers, flow cytometry, and gene expression from blood will be collected at time points according to the SoA.

PHARMACOGENOMIC (DNA) EVALUATIONS

A whole blood sample will be collected to allow for pharmacogenomic research, from which the genes for filaggrin and IL-1α alpha will be evaluated in participating volunteers. Participation in additional whole genome research analyses is optional.

SAFETY EVALUATIONS

Safety data, including but not limited to, adverse events (AEs), serious adverse events (SAEs), infections, mortality, changes in laboratory assessments, 12-lead electrocardiogram, allergic reactions, infusion-related reactions, and changes in vital signs will be summarized. The treatment-emergent adverse events (TEAEs) will be summarized by treatment groups and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

STATISTICAL METHODS

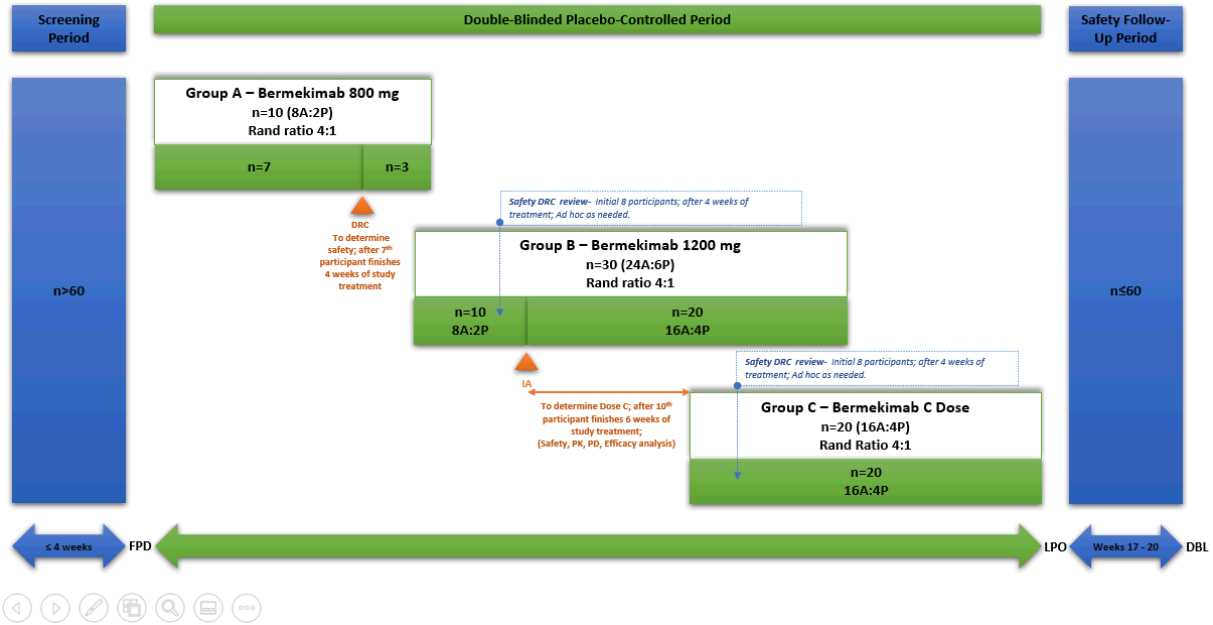
Safety Analyses

All safety analyses will be made on the Safety Population, which include all participants who received at least 1 dose of study intervention. Safety data, including but not limited to, AEs, SAEs, infections, changes

in laboratory assessments, and changes in vital signs will be summarized. Treatment-emergent AEs will be summarized by treatment group and MedDRA system organ class and preferred terms.

1.2. Schema

Figure 1 Schematic Overview of the Study



DBL database lock; DRC Data Review Committee; FPD first participant dosed; LPO last participant out; n number of participants; PD pharmacodynamics; PK pharmacokinetics; Rand randomization.

The DRC in Part A is planned to review unblinded safety data after the 7th participant has completed Week 4 dose administration, and it will include the first 7 participants in Part A.

The DRC in Part B is planned to review unblinded safety data after the 8th participant has completed Week 4 dose administration, and it will include the first 8 participants in Part B.

The DRC in Part C is planned to review unblinded safety data after the 8th participant has competed week 4 of dose administration, and it will include the first 8 participants in Part C.

Ad hoc DRC may also convene as requested by the clinical team.

1.3. Schedule of Activities (SoA)

Period	Screening (-28 to -2 days)	Double-blinded – Placebo-controlled Period[x]																Safety Follow-up[x]				ET[o]
																					EOS	
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[y]**	**18[y]**	**19[y]**	**20**	-
Visit Windows (days)[x]		±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3		
Study Procedure																							
Screening/ Administrative																							
ICF[a]	X																						
ICF for optional pharmacogenomic research[c]	X																						
ICF for optional total body photography substudy[c]	X																						
ICF for skin barrier function substudy[c]	X																						
FSH (post menopausal females only)	X																						
Review medical history requirements	X	X																					
Inclusion/ exclusion criteria[b]	X	X																					
Study Treatment Administration																							
Randomization		X																					
Dispense/administer study intervention[d,t]		X[s]	X[s]	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				X	X
vIGA AD	X	X		X		X		X		X		X		X				X				X	X
SCORAD	X	X		X		X		X		X		X		X				X				X	X
Hand dermatitis IGA		X				X				X				X				X				X	X
Total body photography (if available/applicable)[c]		X								X								X					X
DLQI[f]		X								X				X				X				X	X
POEM[f]		X								X				X				X				X	X
PGIS[f]		X								X				X				X				X	X
PROMIS 29[f]		X								X				X				X				X	X

Eczema Skin Pain and Itch NRS[g]	X	X																			X	X
ADIS[g]	X	X																			X	X
Period	**Screening (-28 to -2 days)**	**Double-blinded Placebo-controlled Period[x]**																**Safety Follow-up[x]**				**ET[o]**
																					EOS	
Week		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17[y]**	**18[y]**	**19[y]**	**20**	**-**
Visit Windows (days)[x]		**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		
Study Procedure																							
Safety Evaluations																							
Physical examination	X	X																				X	X
Height	X																						
Weight	X	X																				X	X
Vital signs[v (except Weeks 0 and 1)]	X	X[s]	X[s]	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	X	X	X	X	X
Chest radiograph	X																						
12 lead ECG (triplicate)	X	X[u]																X					
Serum pregnancy test	X																						
Urine pregnancy test[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X
Clinical Laboratory Tests																							
QuantiFERON TB® test[i]	X																						
Hepatitis B and C serology	X																						
HIV antibody test	X																						
Hematology	X	X	X	X	X	X		X		X		X		X		X		X				X	X
Chemistry	X	X	X	X	X	X		X		X		X		X		X		X				X	X
Fasting Lipid panel[z]	X		X							X								X					
Pharmacokinetics/ Immunogenicity																							
Serum bermekimab concentration[j]		X	X			X				X				X				X				X	X
Population PK sample[j,k]									X														
Antibodies to bermekimab[j]		X				X				X				X				X				X	X
Pharmacodynamics and Biomarkers (eg, plasma, serum, urine, biopsy sample collection)																							
Serum Biomarkers[l]		X	X			X				X								X					X
Blood sample for RNA[l]		X				X												X					
Whole blood (PBMC)[l]		X				X												X					
Pharmacogenomics																							
Whole blood (pharmacogenomics)[m]		X																					
Biomarkers																							
Tape stripping[n,r]		X				X												X					

Skin biopsy schedule 1[n,p]		X						X															
Skin biopsy schedule 2[n,q]		X																X					
Skin barrier assessment[h,r]		X[w]	X	X	X	X[w]	X	X	X	X	X	X	X	X	X	X	X	X[w]					
Ongoing Participant Review																							
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Footnotes:

a. Must be signed before first study related activity.

b. Minimum criteria for the availability of documentation supporting the eligibility criteria are described in Source Documentation in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations (Study Governance Considerations). Check clinical status again before first dose of study medication.

c. Must be signed before first study related activity. Separate informed consents are required for participants who chose to participate in the optional pharmacogenomic research, optional skin barrier function assessments, and optional total body photography substudies.

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. These assessments should be completed once and twice daily for NRS and ADIS, respectively, beginning at the screening visit.

h. The optional skin barrier function substudy will be completed for a limited number of participants at some sites. This assessment includes TEWL, SCH, and EIS, which will be measured at each visit (Weeks 0 through 16) in both lesional and non lesional skin of participants.

i. All participants will undergo QuantiFERON TB 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 still acceptable to use, and a tuberculin skin test is not required.

j. For all visits where study intervention will be administered, all blood samples should be collected prior to (pre dose) and immediately after (within 15 minutes from end of infusion) study intervention administration for evaluation of serum concentration of bermekimab and/or antibodies to bermekimab. Pre dose samples will be used for evaluation of serum concentration of bermekimab and antibodies to bermekimab. Post dose samples should be drawn from a different arm than the IV infusion line and will be used for evaluation of serum concentration of bermekimab only.

k. A venous blood sample for population PK analysis will be collected from the first 20 participants (all 10 participants from Part A plus the first 10 participants from Part B) 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 weekly infusion visits and cannot be collected within 24 hours (either prior to or after) of the actual time of study intervention administration. If possible, we would prefer this sample to be taken between Week 2 and Week 6, although if it is done after Week 6, it would not constitute a protocol deviation. All other participants (last 20 participants of Part B, and all 20 participants of Part C) may also participate in the collection of this sample as optional, and they should follow the same schedule as the first 20 participants.

l. Blood sample will be taken pre dose.

m. 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.

n. 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.

o. Participants who discontinue study intervention but do not terminate study participation are strongly encouraged to return for all protocol specified procedures for the safety follow up period and also for the ET Visit 5 weeks after last dose was administered. The procedures and evaluations listed for the ET visit 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 ET visit approximately 5 weeks after their last administration of study intervention.

p. Skin biopsy for all 10 participants of Part A and first 10 participants of Part B. At Week 0, lesional and non lesional skin samples will be collected. At Week 6, lesional skin samples will be collected.

q. Skin biopsy for no participants in Part A, 20 last participants in Part B, and all participants in Part C. At Week 0, lesional and non lesional skin samples will be collected. At Week 16, lesional skin samples will be collected.

r. Skin barrier function assessment should be evaluated together with tape stripping. Skin barrier function evaluation before tape stripping and after every 5 tapes.
s. Vital signs (Heart rate, respiratory rate, temperature, blood pressure) to be collected every 30 mins between 0 to 4 hrs. This applies to the first 2 infusions only.
t. For the first 2 doses, the study drug will be infused over approximately 2 hours to reduce the risk for IRR, followed by at least approximately a 2 hour observation. For the subsequent infusions, the infusion time may be decreased to approximately one hour with a minimum of approximately 1 hour observation period.
u. Triplicate ECG to be done pre dose and post end of first infusion (after approximately 2 hours), at Week 0 only.
v. Vital signs (heart rate, respiratory rate, temperature, blood pressure) to be collected approximately every 30 mins between 0 to 2 hours for infusions 3 through 15. This does ***not*** apply to the first 2 infusions.
w. Additional serial TEWL, SCH, and EIS measurements will be acquired after every 5 tape strips at Weeks 0, 4, and 16.
x. Study visits in Weeks 1 through 19 must be calculated from the first study intervention administration visit in Week 0. Visit and study intervention administrations should occur within ±3 days of the scheduled visit.
y. These Safety Follow Up visits can be performed via phone calls and must be documented in the source document. Should the participant present any issue deemed clinically significant, they must be bought in to the clinic for follow up consultation.
z. Fasting lipid panel at Screening and Weeks 1, 8, and 16 are for participants in Parts B and C only. Participants in Part A do not need to fast for lipid panel collection and only need samples collected at Screening and Week 16.

Abbreviations: ADIS Atopic Dermatitis Itch Scale; DLQI Dermatological Life Quality Index;EASI Eczema Area and Severity Index; ECG electrocardiogram; EIS Electrical Impedance Spectroscopy; FSH follicle stimulating hormone; HIV human immunodeficiency virus; EOS end of study; ET early termination; ICF informed consent form; IGA Investigator Global Assessment; IRR infusion related reaction; NRS numeric rating scale; PBMC peripheral blood mononuclear cells; PGIS Patient Global Impression of Severity; POEM Patient Oriented Eczema Measure; PK pharmacokinetic; PROMIS 29 Patient Reported Outcomes Measurement Information System 29; RNA ribonucleic acid; SCH Stratum Corneum Hydration; SCORAD Severity Scoring of Atopic Dermatitis; TB tuberculosis; TEWL Transepidermal Water Loss; vIGA AD validated Investigator Global Assessment for Atopic Dermatitis.

2. INTRODUCTION

Bermekimab (also known as JNJ-77474462 and MABp1) is a recombinant human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (mAb) specific for human interleukin-1 alpha (IL-1α). Interleukin-1 alpha is a key mediator of cutaneous inflammation and is constitutively and inducibly expressed by several cell types, including keratinocytes where high levels of IL-1α are present in healthy individuals, these data suggest that IL-1α has the potential to mediate inflammation in the skin.

Bermekimab has been investigated in dermatologic clinical studies and other indications. Two Phase 2 studies are currently ongoing: one in atopic dermatitis (AD; Study 2018-PT044 [NCT03496974]) and one in hidradenitis suppurativa (HS; Study 2018-PT045). Bermekimab has been administered intravenously (IV) at doses ranging from 0.25 mg/kg to 7.5 mg/kg and subcutaneously (SC) at doses ranging 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) and Addenda for Bermekimab.

The term "study intervention" throughout the protocol, refers to study drug as defined in Section 6.1. Study Intevention Administered. For the purpose of this study protocol, the study intervention will be referred to as 'bermekimab'.

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

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (ie, itchiness), xerosis (skin dryness), and eczematous lesions whose features include erythema, infiltration/papulation, oozing with crusting, excoriations, and lichenification. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QoL) that lead to a high socioeconomic cost. An estimated 2% to 10% of adults are affected by AD (Bieber 2008).

Inhibition of IL-1α has been shown clinically to resolve chronic skin inflammation. However, it is not fully known what levels of IL-1α are present in active skin lesions from patients with AD and what dose level of bermekimab would maximally neutralize IL-1α in active lesions. Evaluating this question in the context of clinical response would improve our understanding of the role of IL-1α in AD disease pathophysiology.

Efficacy results from 2 open label studies (2018 PT-044 and PT-045), and preliminary results from an ongoing randomized phase 2 trial (77474462ADM2002, NCT04021862) of bermekimab SC 400 mg weekly show a dose-response relationship. However, the data suggests additional room for improvement in efficacy outcomes.

Given the favorable safety profile observed to date in multiple trials including at the highest dose (1200 mg IV) in a single dose evaluation, this study has been designed to evaluate the efficacy of

higher doses of bermekimab, which need to be administered as weekly in IV infusions, coupled with detailed tissue evaluations. The purpose is to provide a comprehensive analysis of safety, pharmacokinetics (PK), pharmacodynamics (PD), including target engagement, and efficacy, in patients with moderate-to-severe AD, to understand the full potential of IL-1α inhibition in AD.

In summary, this is a Phase 2a, randomized, adaptive, placebo-controlled, double-blind, multicenter, interventional study to assess the safety, efficacy, PK, and immunogenicity of multiple IV doses of bermekimab in adult participants with moderate-to-severe AD using a placebo control by means of:

- Assessment of the efficacy of multiple IV infusions of bermekimab through Week 16
- Evaluating safety and tolerability data for bermekimab in these participants with AD.

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

An overview of the protocol design, supportive rationale, and justification for dose are described in Sections 4.1 (Overall Design), 4.2 (Scientific Rationale for Study Design), and 4.3 (Justification for Dose), respectively.

2.2. Background

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. Interlukin-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 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.

Clinical evidence generated to date suggests that targeting IL-1α maybe 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

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.

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

Nonclinical Pharmacology

Bermekimab binds with high affinity and specificity to human IL-1α with a dissociation rate constant (K_D) of 0.029 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 1.3 nM and did not bind with mouse, rat, or pig IL-1α at the highest concentrations tested.

Toxicology

A 1-month single- and repeat-intraperitoneal (IP) dose mouse study tested JNJ-77474462 up to 3 doses of 312 mg/kg/week. There were no treatment-related deaths following the single- or short-term repeat-dose administration. There were no treatment effects on clinical observation, body weight, food consumption, body temperature, clinical pathology, and histopathology evaluations. Mice that received a single high dose or 2 intermediate doses had minimal, but statistically significant decreases in blood urea nitrogen (BUN) which were attributed to intergroup variation since no similar decrease was observed in the mice that received 3 high doses. Slight increases in total protein and globulin seen in the high dose animals were likely due to the administration of the protein test article.

The potential toxicity of bermekimab was evaluated in a 6-week repeat IV and SC exploratory and tolerability study with toxicokinetics in female cynomolgus monkey, at dose levels of 0, 50 (IV), 300 (IV), and 300 (SC) mg/kg/week for 6 weeks. The toxicology evaluations included mortality, clinical observation, body weight, food consumption, veterinary physical examination, ophthalmology, clinical pathology (hematology, chemistry, coagulation, and urinalysis), organ weight, gross necropsy, and histopathology. In addition, safety pharmacology and physiology endpoints (electrocardiogram, blood pressure, heart rate, respiratory rate, and body temperature) were evaluated. There was a transient decrease in blood pressure only at the high dose for both IV and SC administrations on Day 6 and the values returned to baseline at the end of dosing period (Day 37). There were no other treatment-related findings at any dose levels. The no observed adverse effect level (NOAEL) was 300 mg/kg for both IV and SC administrations. At the NOAEL dose, the exposures maximum serum concentration (C_{max}) and area under the curve (AUC) for IV administration were 9048.26 µg/mL and 26032.83 µg·day/mL respectively and C_{max} and AUC for SC administration were 4482.98 µg/mL and 22623.84 µg·day/mL respectively following dosing on Day 36.

Clinical Studies

Results from a Phase 2, open label, dose escalation study of bermekimab in participants with moderate-to-severe atopic dermatitis showed that bermekimab appeared to be safe, well tolerated, and active at reducing the severity of atopic dermatitis, 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, and hematology), allergic reaction monitoring, and adverse event monitoring. Efficacy was assessed by change in Eczema Area and Severity Index (EASI), Investigator Global Assessment (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 71% achieved EASI-75 at Week 7. 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 at Week 16. Preliminary results from this study are discussed in Section 4.3. Justification for Dose.

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.

2.3. Benefit-Risk Assessment

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 (PG), 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).

As of 26 February 2020, unblinded data is available from 911 patients treated with JNJ-77474462 in patients with advanced solid tumors, advanced hematologic malignancies, metastatic colorectal cancer, peripheral vascular disease, type II diabetes, acne vulgaris, plaque psoriasis, PG, AD, and HS. To date there has been little evidence of drug-related toxicity, with most adverse events (AEs) appearing to be secondary to worsening of patients' underlying disease states.

An Independent Data Review Committee (DRC) with at least 3 members external to the study team and consisting of a statistician and 2 physicians from clinical science and medical safety will be established to review unblinded safety data at pre-specified timepoints during the study. The DRC may also convene on Ad Hoc basis at the request of the Study Team. The DRC unblinded

safety data review and recommendation will be required for the study to proceed to the higher doses of IV bermekimab in patients with AD. Details will be further described in the DRC Charter. The potential risks for bermekimab in this study are infections, hypersensitivity reactions, and infusion-related 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 to the safety laboratory and physical examinations, the Sponsor will implement the additional measures to ensure the safety of the study participants. These additional measures include: 1) a 2-hour, extended infusion time for the first 2 doses to reduce the risk of infusion-related reaction (IRR; 2) a 2-hour post dose observation time for the first 2 doses to ensure tolerability; 3) weekly visits to the investigative site for close monitoring; 4) the establishment of a DRC to review the unblinded safety data at prespecified timepoints in Parts A, B, and C as well as on an ad hoc basis.

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 moderate-to-severe AD.

2.3.1. Benefit-Risk Assessment for Study Participation

Table 1: Benefit-Risk for Study Participants (Bermekimab)

Potential Risks of Clinical Significance	Summary of Data/ Rationale for Risk	Mitigation Strategy
Risks Due to Study Intervention		
Increased risk of infection.	JNJ-77474462 is a recombinant human IgG1k mAb specific for human IL-1α. As such, it is considered to be an immunomodulator. Other agents that could be considered in the same pharmacologic class include biologic agents that target IL-1Ra and IL-1β. Bacterial infections have been reported in clinical trials using JNJ-77474462; however, the infections vary based upon the disease being treated and do not appear to be related to blockade of IL-1α. No opportunistic infections have been reported.	In this study participants with a history of, or ongoing, chronic or recurrent infectious disease, evidence of active or untreated latent opportunistic infections including TB, will be excluded from the study. As a precaution, participants should be evaluated for TB before administration of study intervention. In addition, participants will be screened for TB prior to study entry and receive regular ongoing evaluation. Participants will be instructed to seek medical attention if they develop signs or symptoms suggestive of an infection, and investigators are instructed in the protocol to monitor for signs or

Table 1: Benefit-Risk for Study Participants (Bermekimab)		
Potential Risks of Clinical Significance	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
		symptoms of infections, including TB (Section 8.2.9, Tuberculosis Evaluations). A participant's study intervention must be discontinued if an opportunistic infection including TB develops, and study intervention must be interrupted if the participant develops a serious infection, and continuation or discontinuation of study intervention should be discussed and decided with the Medical Monitor or designee
Infusion-related reactions	IRR have been reported with the first or second IV infusions of bermekimab. In the largest oncology study, PT023 Version 3, there were reports of infusion reaction in 2.6% (11 of 430) participants compared to 0% in placebo. The majority (n=10) were mild to moderate (Grade 1 to 2) and did not result in discontinuation. There was one Grade 3 infusion reaction, an SAE that resulted in patient discontinuation.	In order to mitigate the risk of IRRs, the study drug will be infused over approximately 2 hours for the first 2 doses in the study followed by close monitoring for approximately 2 hours at the investigative site. Availability of resuscitation equipment must be ensured. Any participant who has experienced a Grade 2 IRR, will continue with the 2-hour infusion regimen (and a 2-hour post infusion observation) for the duration of the study. Participants who experience a Grade ≥3 IRR should be discontinued from the study. Pre-medication with antihistamines or corticosteroids is not recommended at this time as a lower risk of occurrence for IRR is expected with the approximately 2-hour infusion time. However, based on emerging clinical experience, the sponsor may implement a premedication regimen for all future participants if >1 incidents of IRR Grade 2 is observed in Part A, or ≥1 incidents of IRR Grade 2 is observed in Parts B or C. Such a premedication regimen would be administered approximately 30 minutes before the infusion of the study drug and will consist of an oral non-sedating H1 histamine blocker (eg, loratadine 10 mg orally or

Table 1: Benefit-Risk for Study Participants (Bermekimab)		
Potential Risks of Clinical Significance	**Summary of Data/ Rationale for Risk**	**Mitigation Strategy**
		equivalent) and oral paracetamol (eg, acetaminophen 650 mg orally or equivalent).
Serious hypersensitivity reactions (including anaphylaxis and serum sickness).	Serious hypersensitivity reactions (including anaphylaxis and serum sickness) may occur at any time and not only during administration of bermekimab.	Study intervention must not be administered to individuals with known or suspected intolerance or hypersensitivity to any biologic medication or known allergies or clinically significant reactions to any components of the formulation used in this study.

IgG immunoglobulin G; IL interleukin; IRR infusion related reactions; TB tuberculosis.

More detailed information about the known and expected benefits and risks of bermekimab may be found in the IB.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To evaluate the efficacy of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in participants with moderate-to-severe AD	• Proportion of participants with EASI-75 (≥75% improvement from baseline) at Week 16
Secondary	
To evaluate the PK and immunogenicity of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in adult participants with moderate-to-severe AD	Analyses of the following at all applicable visits from Week 0 through Week 16: • Serum concentrations of bermekimab over time, including steady-state trough serum concentrations. • The incidence and titers of antibodies to bermekimab
To assess the safety and tolerability of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in participants with moderate-to-severe AD	• Proportion of participants with TEAEs • Proportion of participants with treatment-emergent SAEs • Proportion of participants with AEs leading to discontinuation of study intervention. • Proportion of participants with AEs reasonably related to study intervention. • Proportion of participants with AEs of infusion-related reactions. • Proportion of participants with AEs of infections, including serious infections and infections requiring oral or parenteral antimicrobial treatment. • Proportion of participants with Clinically significant abnormalities in vital signs and laboratory tests.
To characterize additional assessments of efficacy of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in participants with moderate-to-severe AD	Analyses of the following at applicable visits through Week 16 by visit, respectively: • Proportion of participants with both vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points • Proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from

Objectives	Endpoints
	baseline among participants with a baseline itch value ≥4 • Proportion of participants with EASI-90
Exploratory	
To further characterize efficacy of 16 weeks of multiple IV doses of bermekimab, compared with placebo, 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 ADIS • Proportions of participants with a PGIS score of 1 (none) or 2 (mild) at Week 16 • Change from baseline to Week 16 in PROMIS-29 total score and sub-scores • Improvement in Hand Dermatitis IGA from baseline to Week 16.
To assess the impact of treatment with 16 weeks of multiple IV doses of bermekimab, compared with placebo, on selected biomarkers.	Analyses of the following at all applicable visits from Week 0 through Week 16: • Changes in cellular and molecular PD biomarkers levels in skin and blood from baseline compared with placebo. • Changes in skin barrier function from baseline compared with placebo.

Abbreviations: AD=atopic dermatitis; ADIS=Atopic Dermatitis Itch Scale; AE=adverse event; DLQI=Dermatological Life Quality Index; EASI=Eczema Area and Severity Index; IGA=Investigator Global Assessment; IRR=infusion-related reaction; IV=intravenous; NRS=numeric rating scale; PD=pharmacodynamics; PGIS=Patient Global Impression of Severity; PROMIS=Patient-Reported Outcomes Measurement Information System; POEM=Patient-Oriented Eczema Measure; SAE=serious adverse event; SCORAD=Severity Scoring of Atopic Dermatitis; TEAE=treatment-emergent adverse event; vIGA-AD=validated Investigator Global Assessment for Atopic Dermatitis.

Refer to Section 8., Study Assessments and Procedures for evaluations related to endpoints.

HYPOTHESIS

The hypothesis for this study is that IV 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 Phase 2, double-blind, randomized, placebo-controlled, multicenter, interventional study designed to assess the efficacy, safety, PK, biomarkers, and immunogenicity of multiple doses of bermekimab administered via IV infusion for the treatment of moderate-to-severe AD in adult participants. The participant population will be comprised of men and women ≥18 years of age, with moderate-to-severe AD, that has been present for at least 1 year before the first administration of study intervention, as determined by the investigator through participant 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.

A target of approximately 60 participants will be randomly assigned in this study. The study has 3 periods namely: a screening period of up to 4 weeks, a double-blinded placebo-controlled period of 16 weeks, and a Safety Follow-Up period of 4 weeks, which includes an End of Study (EOS) visit. The study will have 3 parts within the double-blinded placebo-controlled period that will run in parallel and/or staggered: A, B, and C.

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

The study also includes 4 mandatory skin biopsies (2 at baseline and 2 after dosing). All participants of Part A and the first 10 participants of Part B will have skin biopsies done at Week 0 (1 lesional and 1 non-lesional), and at Week 6 (2 lesional). The rest of the participants will be biopsied at Week 0 (1 lesional and 1 non-lesional), and at Week 16 (2 lesional). Instructions for the collection and shipment of these samples can be found in the biopsy collection manual.

All participants will have an extended in-clinic observation period of approximately 4 hours during the first 2 infusions. In this period, vital signs will be taken at the following time points: 0 hour (start of infusion), 30 minutes, 1 hour, 1 hour and 30 mins, 2 hours (end of infusion), 2 hours and 30 mins, 3 hours, 3 hours and 30 mins, and 4 hours (post-infusion). Beyond the first 2 infusions, all participants will have approximately a 1 hour infusion period and at least a 1 hour observation post infusion, as well as vital signs taken approximately every 30 minutes.

An internal and independent DRC will be commissioned for this study. Refer to Committees Structure in Section 10.3, Appendix 3: Regulatory, Ethical, and Study Oversight Considerations for details.

One planned database lock (DBL) will occur at the end of the study. Additional DBLs could be considered.

A diagram of the study design is provided in Section 1.2, Schema.

4.2. Scientific Rationale for Study Design

This Phase 2a study is an Experimental Medicine trial designed to evaluate a study intervention (JNJ-77474462/bermekimab) that has a scientific rationale to benefit AD participants through inhibition of IL-1α. This study is designed to better understand what levels of IL-1α are present in active skin lesions from patients with AD and what dose level of bermekimab would maximally neutralize IL-1α in active lesions. By evaluating this question in the context of clinical response it would help us better understand the role of IL-1α in AD disease pathophysiology.

JNJ-77474462 efficacy and safety data from 2 open label studies (2018 PT-044 and PT-045), along with preliminary results from an ongoing randomized phase 2 trial (77474462ADM2002, NCT04021862) of bermekimab SC 400 mg weekly, have shown a dose-response relationship and a favorable safety profile. However, the data suggests additional room for improvement in efficacy outcomes and the possibility of having more target engagement. As such, this study is designed to evaluate the efficacy of higher doses of bermekimab administered by weekly IV infusions, along with detailed skin tissue evaluations.

Blinding, Control, Study Phase/Periods, Intervention Parts

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. Randomization will be used to minimize bias in the assignment of participants to intervention parts, 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.

Selection of Dose for Part C

An interim analysis will be conducted when the 10th participant of Part B completes dose administration at Week 6. The interim analysis will be used to inform the dose decision for Part C based on the safety, preliminary efficacy, PK and PD data accrued up to the interim analysis from both Parts A and B. Safety review will be conducted by an internal and independent DRC. Preliminary analyses will be performed to evaluate dose-response and exposure-response relationship for the efficacy and PD (including target engagement). The dose for Part C will be determined based on the totality of the available data and the preliminary analyses conducted thereof, but it will not be higher than 2400 mg.

Deoxyribonucelic Acid 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, and 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 inter-individual 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.

Deoxyribonucleic acid 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 primary ethical concern is that the IV dose levels of the interventional therapy and frequency evaluated in this study will be higher than what has previously been studied in patients and/or healthy volunteers. In Part A, a starting dose level of 800 mg IV dose was selected, as this dose constitutes a 1.9-fold exposure increase to the 7.5 mg/kg dose administered in the oncology studies with bermekimab. Furthermore, the advancement to higher doses will be based on safety reviews by the DRC.

As with all clinical and PK studies, there are risks associated with venipuncture and multiple blood sample collection. To avoid multiple venipunctures, which cause additional discomfort and other potentially toxic effects, the use of IV indwelling catheters is permitted in this study. The blood sample collection scheme was designed to collect the blood samples that accurately and completely describe the PK and the study intervention. This minimizes the number of venipunctures and the total volume of blood collected from each participant during the study.

The total blood volume to be collected from each participant in each part is far less than the American Red Cross standard limit for whole blood donation (approximately 475 mL once 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, Study Assessments and Procedures.

4.3. Justification for Dose

In this study, bermekimab dose regimens of 800 and 1200 mg IV qw will be evaluated in Parts A and B, respectively. Following the interim analysis, and for the purpose of analyzing target coverage at a higher dose of bermekimab in this population, a bermekimab dose regimen of up to 2400 mg IV qw (Part C) may be evaluated. These dose regimens were chosen to build upon the bermekimab PK, efficacy and safety data from a Phase 2 placebo-controlled study in participants with AD (77474462ADM2002, NCT04021862), a Phase 1 open-label study in healthy volunteers (77474462ADM1001, NCT04544813), and a Phase 2 placebo-controlled study in participants with HS (Kanni 2018, NCT02643654). Additionally, safety margins derived from predicted human exposure and the exposure observed during preclinical toxicity studies in cynomolgus monkeys were also considered in selection of the dose regimens.

The Week 16 data from study 77474462ADM2002 (NCT04021862) in patients with AD showed significant effect of bermekimab 400 mg SC qw group relative to placebo (EASI-75: 34.5% vs 13.8%, respectively), while the 400 mg SC once every 2 weeks (q2w) group showed numerically higher EASI-75 response relative to placebo (EASI-75: 24.1% vs 13.8%, respectively). The dose-response observed between 400 mg SC qw and 400 mg SC q2w (EASI-75: 34.5% vs 24.1%) warranted additional dose-ranging studies in order to expand the dose range to explore target engagement in skin tissue and maximize efficacy in AD. A Phase 2 placebo-controlled study (77474462ADM2001) is being conducted with SC administration of bermekimab at doses of 350 and 700 mg qw.

In this current Phase 2 study, IV infusion will be utilized in order to further expand the dose range potentially up to 2400 mg qw. The dose regimens of 800, 1200 and 2400 mg IV qw are predicted to provide 1.9-, 2.9- and 5.7-fold higher exposure (AUC) at steady-state compared to 700 mg SC qw (assuming 60% bioavailability), respectively. Overall, the IV doses proposed in this current study is expected to maximize the target coverage in the skin tissue and potentially contribute to improved 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 necessitating weekly dosing to maintain adequate drug exposure over the entire dosing interval.

Bermekimab was well tolerated with no safety concerns following single administration of 800 and 1200 mg IV in study 77474462ADM1001 (NCT04544813) in healthy volunteers. The highest multiple IV dose of bermekimab studied was 7.5 mg/kg IV q2w in HS patients (equivalent to 675 mg IV dose for 90 kg body weight which is the average body weight of HS patients) where no AE was related to bermekimab (Kanni 2018, NCT02643654). The 7.5 mg/kg IV dose is equivalent to 675 mg IV dose for a 90 kg individual (average body weight of HS patients). The 800 and 1200 mg IV qw dose regimens proposed in this study (Parts A and B) are predicted to result in 2.4- and 3.6-fold higher AUC compared to 7.5 mg/kg IV q2w, while the 2400 mg IV qw, which is proposed as the maximum dose for Part C, is predicted to result in a 7.1-fold higher AUC. Bermekimab was also well tolerated with no safety concerns in 2 studies in AD patients (77474462ADM2002 [NCT04021862] and 2018-PT044 [NCT03496974]). In these studies, a loading dose of up to 800 mg SC was studied and the highest maintenance dose regimen studied was 400 mg SC qw. In this study, dose escalation from 800 mg IV to 1200 mg IV, and from

1200 mg IV to up to 2400 mg IV will be performed after safety review by the DRC. This internal and independent DRC will be commissioned to actively monitor unblinded safety data after a limited number of participants reach Week 4 in Parts A, B, and C.

Further details about the pre-specified timepoints and ad-hoc reviews by the DRC are provided in Section 9.6, Data Review Committee.

In addition, to predict the safety margins up to 2400 mg IV qw, a population PK model for bermekimab was used to simulate human serum concentration-time profiles of bermekimab. The safety margins for predicted human exposure at 800, 1200, and up to 2400 mg IV qw was 34.3-, 22.8-, and 11.4-fold for $C_{max,ss}$ and 21.3-, 14.2-, and 7.1-fold for $AUC_{1week,ss}$, respectively, relative to the cynomolgus monkey NOAEL (300 mg/kg IV qw, Section 2.2, Background). Therefore, it was modeled that dose regimens of up to 2400 mg IV qw proposed in this Phase 2 study would have adequate safety margins.

Overall, the high doses delivered via IV infusion in this study would provide the opportunity to explore the potential maximum efficacy, dose-response and PK/PD relationships of bermekimab while maintaining safety of participants. The findings from this study will contribute to optimal dose selection for subsequent clinical trials in participants with moderate-to-severe AD.

For more details, refer Section 2.1, Study Rationale.

4.4. End of Study Definition

End of Study Definition

The EOS is considered as the last scheduled study assessment shown in the SoA 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 assessment 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 15 and has completed all assessments at both Week 16 and Week 20 of the safety follow-up period.

5. STUDY POPULATION

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 is 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 9.1, Sample Size Determination.

5.1. Inclusion Criteria

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

Age

1. ≥18 to ≤65 years (or the legal age of consent in the jurisdiction in which the study is taking place).

Type of Participant and Disease Characteristics

2. be otherwise healthy on the basis of physical examination, medical history, vital signs, and 12-lead electrocardiogram (ECG) 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. have an EASI score ≥16 at screening and at baseline.
6. have an IGA score ≥3 at screening and at baseline.
7. have an involved BSA ≥10% at screening and at baseline.

Sex and Contraceptive/Barrier Requirements

8. male or female (according to their reproductive organs and functions assigned by chromosomal complement)
9. all woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at pregnancy test at screening and a negative urine pregnancy test at Week 0 prior to administration of study intervention.

10. A woman must be (as defined in Section 10.5, Appendix 5: Contraceptive and Barrier Guidance)
    a. Not of childbearing potential, OR
    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 Section 10.5, Appendix 5: Contraceptive and Barrier Guidance. However, the method selected must meet local/regional regulations/guidelines for highly effective contraception.
11. a woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 12 weeks after the last dose of study intervention.
12. a male 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
13. a male participant must agree not to donate sperm for the purpose of reproduction during the study and for a minimum 12 weeks after receiving the last dose of study intervention

Informed Consent

14. must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.
15. must sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit) or any other samples for optional substudies. Refusal to give consent for the optional DNA research sample and/or other optional substudies does not exclude a participant from participation in the study.
16. willing and able to adhere to the lifestyle restrictions specified in this protocol.

Laboratory Parameters:

17. 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 (Système Internationale [SI]: ≥100 g/L)
    b. White blood cells ≥3.5 × 10^3/μL (SI: ≥3.5 GI/L)
    c. Neutrophils ≥1.5 × 10^3/μL (SI: ≥1.5 GI/L)
    d. Platelets ≥100 × 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.

Other Therapies and Vaccines

18. agree to discontinue any topical medications/treatments/therapies (excluding non-prescription moisturizers, which are required for daily use per protocol, see Section 6.8.2, Required Treatment) and/or ultraviolet (UV) therapy for AD within 4 weeks before the first administration of study intervention.

Tuberculosis

19. are considered eligible according to the following tuberculosis (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.

- 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.

- Within 2 months before the first administration of study intervention, have a negative QuantiFERON-TB test result, or have a newly identified positive QuantiFERON-TB 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 Section 10.6, Appendix 6: Tuberculin Testing) 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 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 20a.

a. 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 computed tomography (CT) scan is also acceptable if already available or obtained outside of the study protocol.

Miscellaneous

20. must be willing and able to complete electronic patient reported outcome (ePRO) questionnaires and diaries (Section 8.1, Efficacy Assessments) per the Schedule of Activities (SoA; Section 1.3).
21. willing and able to adhere to the lifestyle restrictions specified in this protocol.
22. must be willing to undergo 4 skin biopsies.

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; has a QT corrected according to Fridericia's formula (QTcF) interval >450 msec for males, and >470 msec for females, has a complete left or right bundle branch block, or has a history or current evidence of additional risk factors for torsades de pointes (eg, heart failure, hypokalemia, family history of Long QT Syndrome) at screening or at Day 1/Week 0 (baseline).
3. Criterion modified per Amendment 1

   has 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. Criterion modified per Amendment 1

    tests positive for hepatitis B virus (HBV) infection (see Section 10.8, Appendix 8: HBV Screening with HBV DNA Testing) or has clinically active liver disease, or is seropositive for antibodies to hepatitis C virus (HCV) at screening unless they satisfy one of the following conditions:

    - have a history of successful treatment (defined as being negative for HCV ribonucleic acid [RNA] at least 6 months after completing antiviral treatment) and have a negative HCV RNA test result at screening,

      OR

    - while seropositive, have a negative HCV RNA test results at least 6 months prior to screening and a negative HCV RNA test result at screening regardless of vaccination status.

11. During the 6 weeks prior to baseline, have had any of (a) confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; Coronavirus Disease 2019 [COVID-19]) infection (test positive), OR (b) suspected serious adverse reactions (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:

    a. 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

    b. 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:

a. 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.

b. 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. Criterion modified per Amendment 1

    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 20 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.

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

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

Prior/Concomitant Therapy

19. has taken any of the medications or therapies outlined in the inclusion/exclusion criteria within the specified period, or has plans to receive any disallowed therapies as noted in Section 6.8, Concomitant Therapy throughout the study.

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

21. has previously received dupilumab.

22. 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).

23. 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.

24. Criterion modified per Amendment 1

use of any prescription topical treatment for AD within 4 weeks of the baseline visit, including prescription moisturizer, unless the prescribed moisturizer can be obtained over the counter (OTC) and it doesn't require a prescription.

25. Criterion modified per Amendment 1

    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 other than AD that, in the opinion of the investigator, is likely to require such treatment(s) within 4 weeks before the baseline visit.

26. 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.

27. has received, or is expected to receive, any live virus or bacterial vaccination within 12 weeks before the first administration of study intervention. Non-live vaccines approved or authorized for emergency use (eg, COVID-19) by local health authorities are allowed.

28. has had a Bacille Calmette-Guerin (BCG) vaccination within 12 months prior to screening.

Prior/Concurrent Clinical Study Experience

29. has received any non-biologic investigational intervention (including investigational vaccines) 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

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.

33. 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.

Diagnostic Assessments – Not applicable

Other Exclusions

34. 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

35. Criterion modified per Amendment 1

history of drug or alcohol abuse according to Diagnostic and Statistical Manual of Mental Disorders (5th edition) criteria within 12 months before screening.

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 Section 10.3, Appendix 3, 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 10) 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.
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 12) 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.
5. Participants must comply with restrictions on concomitant medications and therapies specified in the protocol (refer to Section 6.8, Concomitant Therapy, for details).
6. 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; see Section 6.8, Concomitant Therapy, for details).
7. Participants must not receive a live virus or bacterial vaccination during the study and for 3 months after the last administration of any study intervention. See lifestyle consideration for information regarding BCG vaccination.
8. Participants must not receive a BCG vaccination during the study and for 12 months after the last administration of any study intervention.
9. Agree to follow all requirements that must be met during the study as noted in the inclusion and exclusion criteria (eg, contraceptive requirements).
10. Criterion modified per Amendment 1

    It is strongly recommended that participants are up-to-date on age-appropriate vaccinations including COVID-19 vaccines 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 enrolment (see also Section 6.8 Concomitant Therapy).

5.4. Screen Failures

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.

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

5.5. Criteria for Temporarily Delaying Administration of Study Intervention

Guidelines for study intervention administration affected by the COVID-19 pandemic are found in Section 10.9, Appendix 9: Study Conduct During A Natural Disaster.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Intervention Administered

Study intervention administration must be captured in the source documents and the electronic case report form (eCRF).

Bermekimab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

For details on rescue medications, refer to Section 6.8.4, Rescue Medication. For a definition of study intervention overdose, refer to Section 6.7, Treatment of Overdose.

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

Table 2: Description of Interventions

Part Name	Part A	Part B	Part C	N/A
Intervention Name	bermekimab	bermekimab	bermekimab	Placebo
Dose Formulation	sterile liquid formulation of 350 mg (175 mg/mL) of bermekimab in a prefilled syringe (PFS) with an injectable volume of 2.0 mL.	sterile liquid formulation of 350 mg (175 mg/mL) of bermekimab in a PFS with an injectable volume of 2.0 mL.	sterile liquid formulation of 350 mg (175 mg/mL) of bermekimab in PFS with an injectable volume of 2.0 mL.	Saline vials
Unit Dose Strength(s)	175 mg/mL	175 mg/mL	175 mg/mL	N/A
Dosage Level(s)	800 mg intravenous (IV) infusion weekly from Week 0 through Week 15	1200 mg IV infusion weekly from Week 0 through Week15	TBD mg IV infusion weekly from Week 0 through Week 15	IV infusion weekly from Week 0 through Week 15
Route of Administration	IV infusion	IV Infusion	IV Infusion	IV Infusion
Use	Experimental	Experimental	Experimental	Placebo comparator
Investigational Medicinal Product	Yes	Yes	Yes	No
Non-Investigational Medicinal Product /Auxiliary Medicinal Product	No	No	No	No
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the Sponsor
Packaging and Labeling	The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. Study intervention labels will contain information to meet the applicable regulatory requirements	The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. Study intervention labels will contain information to meet the applicable regulatory requirements	The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. Study intervention labels will contain information to meet the applicable regulatory requirements	The investigational supplies will be uniquely packaged to assure that they are appropriately managed throughout the supply chain process. Study intervention labels will contain information to meet the applicable regulatory requirements
Delivery instructions	See Investigational Product Preparation Instructions (IPPI)	See IPPI	See IPPI	See IPPI
Current/Former Name or Alias	JNJ-77474462	JNJ-77474462	JNJ-77474462	N/A

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

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

Refer to the IPPI for additional guidance on study intervention preparation, handling, and storage.

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.

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 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 intervention accountability purposes.

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 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

Central randomization will be implemented in this study. Participants in Part A, Part B, and Part C will be randomly assigned to either the bermekimab or placebo intervention groups (4:1 ratio) based on a computer-generated randomization schedule prepared before the study by or under the supervision of the sponsor. The randomization will be balanced by using randomly permuted blocks. The interactive web response system (IWRS) will assign a unique intervention code, which

will dictate the intervention assignment and matching study intervention kit for the participant. 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 while the remainder of site personnel will remain blinded. The volume of the placebo will match the volume of the active intervention in each cohort. Prepared doses may 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. Administration of study intervention to the participants will be performed by a blinded, qualified healthcare provider. Independent drug monitors will be used to monitor drug accountability and all unblinded study data.

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, anti-JNJ-77474462 antibodies, study intervention preparation/accountability data, 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 DBL and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. Otherwise, the blind should be broken only if specific emergency intervention/course of action would be dictated by knowing the intervention status of the participant. In such cases, 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.

For the purpose of the interim analysis of safety data and preliminary PK, efficacy, and PD analysis, designated sponsor personnel will be unblinded to the relevant data as is required (Section 8.4, Pharmacokinetics and Immunogenicity). The randomization code will be disclosed to those authorized and only for those participants included in the interim analysis. All site personnel and participants will remain blinded to the treatment assignments until the last participant completes the Week 20 evaluations and the final database is locked.

Participants who have had their intervention assignment unblinded should continue to return for scheduled evaluations and are not eligible to receive further study intervention.

Additionally, a given participant's treatment assignment may be unblinded to the sponsor, the Independent Ethics Committee/Institutional Review Board (IEC/IRB), and site personnel to fulfill regulatory reporting requirements for suspected unexpected serious adverse reactions (SUSARs).

A separate code break procedure will be available for use by the sponsor's Global Medical Safety group to allow for unblinding of individual participants to comply with specific requests from regulatory or health authorities.

6.4. Study Intervention Compliance

Study intervention will be administered by IV infusion by blinded qualified study-site personnel and the details of each administration will be recorded in the eCRF (including date and time of study intervention administration).

The investigator or designated study-site personnel will maintain a log of all study interventions dispensed and returned. Intervention supplies for each participant will be inventoried and accounted for throughout the study. At all times, study intervention under preparation/administration must be supervised to ensure proper handling and to avoid potential dosing errors or tampering.

Any accidental administration of study intervention to a non-study participant must be reported immediately to the sponsor's medical monitor.

Additional details are provided in the instructions provided by the sponsor (IPPI).

6.5. Dose Modification

No treatment or dose adjustment will be permitted throughout the study.

6.6. Continued Access to Study Invervention After the End of the 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 determine standard of care.

6.7. Treatment of Overdose

For this study, any dose of bermekimab greater than the highest dose at a single dosing visit within a 24-hour time period 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.
- Evaluate the participant to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- 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 eCRF.

6.8. Concomitant Therapy

Pre-study therapies administered up to 30 days before the screening visit should be continued. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

Every effort should be made to keep participants on stable concomitant medications. 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.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, or other specific categories of interest) different from the study intervention must be recorded in the eCRF. 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. Any questions regarding treatment with concomitant medication during the study, should be directed to the medical monitor.

6.8.1. 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.

6.8.2. 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.

6.8.3. Prohibited Therapies/Medications

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

- Topical corticosteroids, except for rescue therapy (see Section 6.8.4, Rescue Medication)
- Topical calcineurin inhibitors (eg, tacrolimus and pimecrolimus)

- Topical phosphodiesterase inhibitors 4 (eg, crisaborole)
- Leukotriene inhibitors
- Allergen immunotherapy
- Phototherapy (including psoralen and UV-A, UV-B, tanning beds, and excimer laser)
- Bleach baths
- Systemic corticosteroids (oral)
    - A single course of oral systemic corticosteroids per standard of care for conditions other than AD, for a maximum of 10 days, will be allowed. The use of intramuscular (IM) and IV corticosteroid formulations is prohibited, and will lead to participant discontinuation of study intervention.
    - 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, dupilumab)
- Topical and systemic janus kinase inhibitors
- Systemic immunosuppressant, cytotoxic, and immunomodulatory agents, including, but not limited to, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil. and immunomodulatory biologic therapies (eg, guselkumab, risankizumab, secukinumab, rituximab, alemtuzumab, abatacept, or visilizumab)
- Any prescription topical treatment for AD, including prescription moisturizer, unless the prescribed moisturizer can be obtained OTC and it doesn't require a prescription.
- Interlukin-1α inhibiting agents (eg, anakinra, rilonacept, canakinumab)
- Live vaccines, including BCG vaccine.

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

6.8.4. Rescue Medication

In the event that a participant experiences any unacceptable or worsening symptoms of AD, investigators should first attempt to control symptoms in participants 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. The rationale for rescue must be documented in source.

Hydrocortisone 2.5% ointment may be given to the participant for rescue treatment of any problem areas on the body unless otherwise contraindicated in that participant. In the event that hydrocortisone 2.5% ointment is not available for use in the locale of a study site, an alternate, equivalent potency topical corticosteroid may be supplied.

Participants should use rescue therapy only for as long as necessary to control problem areas, or for a maximum of 2 consecutive weeks. Participants using rescue by topical therapy will continue

to take investigational product and use of rescue therapy will be documented in the eCRF. 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.

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

For guidelines on management of IRR, refer to Section 2.3.1, Benefit-Risk Assessment for Study Participation.

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 (Food and Drug Administration [FDA] Guidance 2020). Therefore, upon initiation or discontinuation of bermekimab in participants 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)

Concomitant therapies (including any authorized for emergency use or fully approved, eg, COVID-19 or influenza vaccination) must be recorded throughout the study beginning with start of the first dose of study intervention to 4 weeks after the last dose of study intervention Concomitant therapies 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.

When considering use of locally-approved (including emergency use-authorized) COVID-19 vaccines in study patients, follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy. For study participants receiving a locally-approved (including emergency use-authorized) COVID-19 vaccine, 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 investigator believes that for safety reasons or tolerability reasons (eg, AE) it is in the best interest of the participant to discontinue study intervention
- Participants who experience a Grade ≥3 IRR should be discontinued from the study
- The participant has a serious adverse reaction that is related to an infusion of the study drug administration including a hypersensitivity reaction resulting 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 or systolic blood pressure <90 mm Hg (Sampson 2006). In general, discontinuation of study intervention administration must be considered for participants who develop a nonserious but severe infusion-related 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) occurring 1 to 14 days after an infusion 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 Section 10.5, Appendix 5: Contraceptive and Barrier 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 8.2.9, 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.
- Abnormal liver tests as outlined in Section 10.7, Appendix 7: Liver Safety: Suggested Actions and Follow-Up Assessments.
- Use of prohibited corticosteroids:
  - IM and IV formulations
  - Oral corticosteroids for more than 10 days.
- The participant has his/her treatment assignment unblinded by the investigator.
- Sponsor decision.

If a participant discontinues study intervention for any reason before the end of the double-blind phase,then the end-of-intervention assessments should be obtained and scheduled assessments off study intervention should be continued. Study intervention assigned to the participant who discontinued study intervention may not be assigned to another participant. Additional participants will not be entered.

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

Discontinuation of study intervention for abnormal liver tests is required by the investigator when a participant meets one of the conditions outlined in Section 10.7, Appendix 7: Liver Safety: Suggested Actions and Follow-Up Assessments 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.

When a participant withdraws before study completion, the reason for withdrawal is to be documented in the eCRF and in the source document. If the reason for withdrawal from the study is withdrawal of consent then no additional assessments are allowed.

Withdrawal of Consent

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 sample:

- The collected sample 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 sample, in which case the sample 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 sample has 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 sample 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 Section 10.3, Appendix 3, 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.
- Site personnel will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up.

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 SoA summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, pharmacogenomics and safety measurements applicable to this study. It is strongly recommended that the same investigator performs the efficacy assessment 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.

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 Section 10.9, Appendix 9: Study Conduct During a Natural Disaster.

Blood Sample Collection

The total blood volume to be collected from each participant will not exceed 500 mL over a 56-day period. This is considered to be an acceptable amount of blood to be collected over this time period from the population in this study based upon the standard of the American Red Cross. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples**.**

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF 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. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the Laboratory Manual.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Investigator's Brochure for bermekimab
- Protocol
- Site Investigational Product Binder
- Laboratory Manual
- Laboratory Kits
- IWRS Manual
- Sample eCRF
- eCRF Completion Guidelines
- ePRO equipment (tablet device questionnaires, completion instructions)
- Participant Diary
- Digital photographic equipment and instructions manual (at participating sites)
- Participant Study Participation Card
- Investigative Site File
- iPhone XR
- SWIFT Vision infrared camera iPhone add-on
- Scibase Nevisense Go device
- GPskin barrier device
- Recruitment materials, as needed.

8.1. Efficacy Assessments

Efficacy assessments (EASI, validated Investigator Global Assessment for Atopic Dermatitis [vIGA AD™], percent BSA involvement, SCORAD, and Hand Dermatitis IGA) and ePRO measures (DLQI, POEM, Patient Global Impression of Severity [PGIS], Patient Reported Outcomes Measurement Information System [PROMIS]-29, Eczema Skin Pain and Itch numeric rating scale [NRS], and Atopic Dermatitis Itch Scale [ADIS]) will be performed at visits according to the Schedules of Activities. Evaluation of EASI, SCORAD, and vIGA endpoints from digital photographs will be completed from a subgroup of participants who consent to these optional substudies at selected sites.

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/Ethics Review Committee submissions.
- The PRO and AE data will not be reconciled with one another.

8.1.1. Eczema Area and Severity Index (EASI)

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 (Section 1.3). See Section 10.10, Appendix 10: EASI for a representative example of the index.

8.1.2. Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD™)

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 (Section 1.3). See Section 10.11, Appendix 11: vIGA-AD for a representative example of the assessment.

8.1.3. Severity Scoring of Atopic Dermatitis (SCORAD)

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 BSA, 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 participant 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 will be extracted using SCORAD.

See Section 10.12, Appendix 12: SCORAD for a representative example of the assessment.

8.1.4. Hand Dermatitis Investigator Global Assessment (IGA)

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 Section 10.13, Appendix 13: Hand Dermatitis IGA for a representative example of the assessment.

8.1.5. Eczema Skin Pain and Itch Numeric Rating Scale (NRS)

The Eczema Skin Pain and Itch NRS is a 2-item PRO 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 Section 10.17, Appendix 17: Eczema Skin Pain and Itch NRS for a representative example of the scale.

8.1.6. Patient-Reported Dermatology Life Quality Index (DLQI)

The DLQI is a dermatology-specific QoL instrument designed to assess the impact of the disease on a participant's health-related quality of life (HRQoL; Finlay 1994). It is a 10-item questionnaire that assesses HRQoL over the past week and in addition to evaluating overall HRQoL, can be used to assess 6 different aspects that may affect QoL: 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 HRQoL. See Section 10.14, Appendix 14: DLQI for a representative example of the index.

8.1.7. Patient-Oriented Eczema Measure (POEM)

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.

8.1.8. Patient Global Impression of Severity (PGIS)

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". The PGIS questionnaire will be used as an anchor to establish a clinical response criterion of other participant or physician reported outcomes for future reference. The questionnaire will be administered at time points according to the SoA. See Section 10.15, Appendix 15: PGIS for a representative example of the questionnaire.

8.1.9. Patient-Reported Outcomes Measurement Information System-29 (PROMIS-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 Section 10.16, Appendix 16: PROMIS-29 for a representative example of the questionnaire.

8.1.10. Atopic Dermatitis Itch Scale (ADIS)

The ADIS will be used to assess pruritus (itching) among participants with AD, a condition commonly referred to as eczema. It will be evaluated by participants in 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 participant 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 Section 10.18, Appendix 18: ADIS for a representative example of the scale.

8.1.11. 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 77474462ADM2003, 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 Section 10.19, Appendix 19: Remote Endpoint Assessment Using Total Body Photography 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.

8.1.12. Skin Barrier Function Assessments

To explore the utility of digital health devices to measure skin barrier function before and after treatment, devices measuring transepidermal water loss (TEWL), Stratum Corneum Hydration (SCH) and electrical impedance of skin will be used. TEWL, SCH and Electrical Impedance Spectroscopy (EIS) will be measured at each visit (Weeks 0 through 16) from both lesional and non-lesional skin of participants. In addition, serial TEWL, SCH and EIS measurements will be acquired after every 5 tape strips at weeks 0, 4 and 16 on lesional skin. TEWL and SCH will be measured using the gpskin barrier device and EIS will be measured using the Scibase Nevisense GO device. The results of these analyses will be presented in a separate report.

8.2. Safety Assessments

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

Details regarding the internal and independent DRC are provided in Committees Structure in Section 10.3, Appendix 3, 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 Report and Section 10.4, Appendix 4: 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 eCRF.

The study will include the following evaluations of safety and tolerability according to the time points provided in the SoA (Section 1.3).

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

Temperature, pulse/heart rate, respiratory rate, blood pressure will be obtained prior to study intervention administration at visits specified in the schedule of activities.

In addition, all participants will have an extended in-clinic observation period of approximately 4 hours during the first 2 infusions. In this period, vital signs will be taken at the following time points: 0 hour (start of infusion), 30 minutes, 1 hour, 1 hour and 30 mins, 2 hours (end of infusion), 2 hours and 30 mins, 3 hours, 3 hours and 30 mins, and 4 hours (post-infusion). Beyond the first 2 infusions, all participants will have approximately a 1 hour infusion period and at least a 1 hour observation post infusion, as well as vital signs taken every 30 minutes.

Blood pressure and pulse/heart rate measurements should be preceded by approximately 5 minutes of rest in a quiet setting without distractions (eg, television, cell phones).

8.2.3. Electrocardiograms

Participants should rest in a supine position for approximately 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

A triplicate 12-lead ECG will be performed during screening to serve as a baseline reference for comparison, should a subsequent cardiovascular related safety event occur. A triplicate 12-lead ECG will also be performed at Week 0 (pre-dose, and post end of infusion [2 hours]), and at Week16. At each time point at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart. The full set of triplicates should be completed in approximately 5 minutes.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.2, Appendix 2: 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 AE section of the eCRF. 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 Section 10.2, Appendix 2: Clinical Laboratory Tests.

8.2.5. Pregnancy Testing

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.

Female participants of childbearing potential will undergo a serum pregnancy test at screening, and a urine pregnancy test before each study intervention administration, and at the Week 20 or early termination visit.

8.2.6. Concomitant Medication

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

8.2.7. Allergic Reactions

Before any IV infusion, 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 infusions are being administered.

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

Participants who experience reactions following an infusion 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 infusion 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.

8.2.8. Infusion-Related Reactions

In order to mitigate the risk of IRRs, the study drug will be infused over approximately 2 hours for the first 2 doses in the study followed by close monitoring for approximately 2 hours at the investigative site.

Availability of resuscitation equipment must be ensured.

Any participant who has experienced a Grade 2 IRR, will continue with the approximate 2-hour infusion regimen (and approximately a 2-hour post infusion observation) for the duration of the study.

Participants who experience a Grade ≥3 IRR should be discontinued from the study.

Pre-medication with antihistamines or corticosteroids is not recommended at this time as a lower risk of occurrence for IRR is expected with the approximately 2-hour infusion time. However, based on emerging clinical experience, the sponsor may implement a premedication regimen for all future participants **if** >1 incidents of IRR Grade 2 is observed in Part A, or ≥1 incidents of IRR

Grade 2 is observed in Parts B or C. Such a premedication regimen would be administered approximately 30 minutes before the infusion of the study drug and will consist of an oral non-sedating H1 histamine blocker (eg, loratadine 10 mg orally or equivalent) and oral paracetamol (eg, acetaminophen 650 mg orally or equivalent).

8.2.9. Tuberculosis Evaluations

8.2.9.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB (refer to Section 10.2, Appendix 2: Clinical Laboratory Tests 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 judgement, 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 participants. If no local country guidelines for immunocompromised participants 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.

8.2.9.2. 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 SoA [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 participants. If no local country guidelines for immunocompromised participants 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 SoA (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 AEs, serious AEs, 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, or surrogate) for the duration of the study.

Further details on AEs, SAEs, and PQC can be found in Section 10.4, Appendix 4: 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 AEs 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 SAEs, 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.

Information regarding serious adverse events will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the eCRF, 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 AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local at the infusion 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 AEs are all AEs 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 AE, SAE, 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 Section 10.4, Appendix 4: 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 AEs 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 AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events: No anticipated events have been identified for this study.

These anticipated events will be periodically analyzed in aggregate by the sponsor during study conduct. The sponsor will prepare a safety report in narrative format if the aggregate analysis indicates that the anticipated event occurs more frequently in the intervention group than in the control group and the sponsor concludes there is a reasonable possibility that the drug under investigation caused the anticipated event.

The plan for monitoring and analyzing the anticipated events is specified in a separate Anticipated Events Safety Monitoring Plan. The assessment of causality will be made by the sponsor's unblinded safety assessment committee.

The sponsor assumes responsibility for appropriate reporting of the listed anticipated events according to the requirements of the countries in which the studies are conducted.

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 SAEs and must be reported using the Serious Adverse Event 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 Section 10.4, Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting. 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

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 SoA (Section 1.3).

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, 1 for antibodies to bermekimab, and 1 back-up.

Serum samples will also be collected at the final visit from participants who terminate study participation/intervention early. Blood samples collected for serum bermekimab concentrations and/or antibodies to bermekimab may also be used for exploratory biomarker analyses.

A random venous blood sample for population PK analysis will be collected from the first 20 participants of the study on any day between Weeks 2 to 12, except on the days of the scheduled study visits. If possible, we would like to encourage obtaining this sample between Week 2 and Week 6, although if it is done after Week 6, it would not constitute a protocol deviation. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time

of study intervention administration. All the remaining participants (last 20 participants of Part B, and all 20 participants of Part C) may choose to also participate in the collection of this population PK sample as optional. 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 by or 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 pharmacogenomic whole blood sample will be collected to allow for pharmacogenomic research, as necessary (where local regulations permit). Participation in the pharmacogenomic research is optional.

Genotyping or sequencing techniques will be used to assess variation in the filaggrin 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.

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 bermekimab and aid in evaluating the intervention-clinical response relationship.

Biomarker assessment will include the evaluation of relevant markers in serum, blood, skin biopsies, and tape strips for all participants. 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 peripheral blood mononuclear cells (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, and 16, 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 biopsy samples will be collected from all participants of the study at time points specified in the SoA. At the baseline sampling time point (Week 0), biopsy samples will be collected from both lesional and adjacent non-lesional areas; at Week 6 or 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 vs nonresponders. At Week 6 or 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.

8.6.2. Serum Biomarkers

Serum samples will be collected from all participants at time points specified in the SoA (Section 1.3). 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 (Section 1.3), and 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 (Section 1.3). Total ribonucleic acid 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. Medical Resource Utilization and 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 is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

The hypothesis for this study is that at least 1 of the test doses/dosages IV bermekimab treatment is superior to placebo as assessed by the proportion of participants with an EASI-75 (≥75% improvement from baseline) at Week 16.

9.2. Sample Size Determination

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

The EASI-75 response rate in the bermekimab 400 mg qw group was approximately 70% at Week 7 from the open label study (2018-PT044 [NCT03496974]). The EASI-75 response rates in placebo group at Week 16 were 15% and 12%, in the 2 Phase 3 trials of dupilumab vs placebo in the treatment of adult participants with moderate-to-severe AD (Simpson 2016).

The EASI-75 response at Week 16 is assumed to be 15% for placebo, and 65% to 70% for the bermekimab treatment population (Table 3). Based on these assumptions, approximately 60 participants (10 in Part A, 30 in Part B, and 20 in Part C) are planned to be randomized. In each Part, participants will be randomized in a 4:1 ratio to bermekimab or placebo. Thus, there will be 8 participants in the bermekimab 800 mg group, 24 participants in the bermekimab 1200 mg group, 16 participants in the bermekimab C dose, and 12 participants total across the placebo groups.

These sample sizes provide the study with at least 80% power to detect a treatment difference between the each bermekimab treatment group and the pooled placebo treatment group in EASI-75 at Week 16 based on a Fisher's Exact test at a Type I error rate of 0.1 (2-sided).

Table 3: Power to detect a treatment difference in EASI-75 at Week 16*

Placebo	Bermekimab	Difference	Power
Bermekimab 1200 mg (n=24) vs placebo (n=12)			
15%	65%	50%	85%
15%	70%	55%	92%
12%	60%	48%	83%
12%	65%	53%	90%
12%	70%	58%	96%
Bermekimab dose C (n=16) vs placebo (n=12)			
15%	70%	55%	86%
15%	75%	60%	92%
12%	65%	53%	83%
12%	70%	58%	91%

EASI Eczema Area and Severity Index.
*Power is not calculated for Part A due to small sample size.

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 efficacy analyses.

Safety analyses will include all participants who received at least 1 dose 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 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

Efficacy and participant information analyses will include all randomized participants who received at least 1 dose of study intervention and will be analyzed based on the randomized treatment groups, regardless of the treatment they actually received.

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

In addition, treatment comparisons for binary endpoints will be performed using a Chi-Square test or Fisher's exact test in the case of rare events. For continuous efficacy endpoints, treatment comparisons will be performed using a mixed-effect model repeated measure (MMRM) model. The MMRM model includes treatment group, baseline value for the corresponding efficacy endpoint, visit, baseline value by visit, and treatment by visit interaction, if applicable. In addition, treatment differences and their associated 2-sided 90% confidence intervals (CIs) will be presented.

9.4.2. Primary Endpoint

The primary efficacy endpoint is the proportion of participants with EASI-75 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:** Binary response variable, where a responder is defined as a participant achieving an EASI-75 response at Week 16. A participant with an intercurrent event (ICE) in categories 1 to 3 defined below will be considered a non-responder.
- **Study intervention:**

  Bermekimab 800 mg, 1200 mg, dose C mg IV qw

  Placebo IV qw

- **Intercurrent Events:**

Table 4: Analysis Strategy for Addressing Intercurrent Events (ICEs)	
Intercurrent Events (ICEs)	**Analysis Strategy for Addressing Intercurrent Events (ICEs)**
1. Discontinuation of study intervention due to lack of efficacy, an AE of worsening of AD prior to Week 16 2. Initiation of a protocol-prohibited medication or therapy during the study that could improve AD prior to Week 16 3. Initiation of rescue medication for AD prior to Week 16	Composite Strategy: Participants with these intercurrent event are considered as EASI-75 non-responders after these events. The occurrence of these intercurrent event being captured in the variable definition.
4. Discontinuation of study intervention for reasons other than above defined reasons prior to Week 16	Treatment policy: Use observed data regardless of whether or not this intercurrent event had occurred

- **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 Fisher's exact test at an alpha level of 0.1 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 90% CI will be provided.

The study would be considered as positive if any of the comparisons for primary endpoint analysis (bermekimab 1200 mg vs placebo, and bermekimab C dose vs placebo) is less than or equal to p-value of 0.1. No formal statistical testing will be performed for the 800 mg vs placebo. For the analyses described above, participants with ICEs 1 through 3 before Week 16 will be considered as EASI-75 nonresponders at Week 16. For participants with ICE 4, observed data after this ICE will be utilized in the analysis. 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 data handling approaches; these analyses will be described in the SAP. To evaluate the consistency of the efficacy, subgroup analysis of the primary endpoint will be performed.

No adjustment for multiple comparisons will be made for primary endpoints.

Secondary Endpoints

The secondary analyses pertaining to efficacy 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.

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

9.4.3. Exploratory Endpoints

The exploratory endpoints are:

- The improvement from baseline in SCORAD at Week 16 will be compared between each bermekimab and the pooled placebo group.
- The change from baseline in DLQI at Week 16 will be compared between each bermekimab and the pooled placebo group.
- The improvement from baseline in POEM at Week 16 will be compared between each bermekimab and the pooled placebo group.
- The improvement from baseline in eczema-related itch NRS at Week 8 will be compared between each bermekimab and the pooled placebo group.
- The improvement from baseline in eczema-related pain NRS at Week 8 will be compared between each bermekimab and the pooled placebo group.
- The improvement from baseline in eczema-related pain NRS at Week 16 will be compared between each bermekimab and the pooled placebo group.
- The improvement from baseline in ADIS itch at Week 16 will be compared between each bermekimab and the pooled placebo group.
- The proportions of participants with a PGIS score of 1 (none) or 2 (mild) at Week 16 will be compared between each bermekimab and the pooled placebo group**.**
- The change from baseline in PROMIS-29 total score and sub-scores at Week 16 will be compared between each bermekimab and the pooled placebo group.
- Hand Dermatitis IGA at Week 16 will be compared between each bermekimab and the pooled placebo group.

9.4.4. Safety Analyses

All safety analyses will be made on the Safety Population, which include all participants who received at least 1 dose of study intervention. Safety data, including but not limited to, AEs, SAEs, infections, changes in laboratory assessments, and changes in vital signs will be summarized.

Treatment-emergent AEs will be summarized by treatment group and MedDRA system organ class and preferred terms. Details will be specified in the SAP.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA. Any AE occurring at or after the initial administration of study intervention is considered to be treatment emergent. All reported 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.

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.

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 infusion-related reactions.

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. Listings of participants with SAEs, severe AEs, anaphylactic reaction/serum sickness reactions, and AEs leading to discontinuation of study intervention will be provided.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for selected laboratory analyte and changes from baseline at each scheduled time point. A listing of participants with common toxicity criteria Grade 2 or higher laboratory results will also be provided.

Vital Signs

Vital signs including temperature, pulse/heart rate, respiratory rate, and blood pressure (systolic and diastolic) will be summarized over time, using descriptive statics.

9.4.5. 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.

Biomarkers 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 and skin 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.

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.

If applicable, 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.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum bermekimab concentration and efficacy (and/or biomarker levels) 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.

Pharmacogenomic Analyses

DNA samples will be used for research related to bermekimab or moderate-to-severe AD. They may also be used to develop tests/assays related to bermekimab and moderate-to-severe 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 moderate-to-severe AD clinical endpoints.

Results will be presented in a separate report.

9.5. Interim Analysis

An interim analysis will be conducted when the 10th participant of Part B reaches Week 6. The interim analysis will be used to inform the dose decision for Part C based on the safety, preliminary efficacy, PK and PD data accrued up to the interim analysis. Apart from the dose decision for Part C, no changes to the current study design 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. Sponsor representatives including but not limited to the individuals involved in the PK and PD analyses may be unblinded. An unblinding plan will be documented prior to the interim analysis. An additional Interim Analysis may also be considered.

9.6. Data Review Committee

An internal and independent DRC, whose members are not directly involved in the conduct of study 77474462ADM2003, 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 DRC will make recommendations to the study team regarding the conduct of the study. The DRC will consist of at least 1 clinical physician and one statistician, not involved in the conduct of the study. DRC responsibilities, authorities, and procedures will be documented in the DRC charter.

The DRC in Part A is planned to review unblinded safety data after the 7th participant has completed Week 4 dosing, and it will include the first 7 participants in Part A.

The DRC in Part B is planned to review unblinded safety data after the 8th participant has completed Week 4 dosing, and it will include the first 8 participants in Part B.

The DRC in Part C is planned to review unblinded safety data after the 8th participant has competed week 4 of dosing, and it will include the first 8 participants in Part C.

The DRC is also planned to review unblinded data from the IA.

Ad hoc DRC may also convene as requested by the clinical team.

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 transaminase
AUC	Area under the curve
BCG	Bacille Calmette-Guerin
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Confidence interval
COVID-19	Coronavirus Disease-19
CT	Computed tomography
CYP	Cytochrome
DBL	Database lock
DILI	Drug induced liver injury
DLQI	Dermatology Life Quality Index
DRC	Data Review Committee
EASI	Eczema Area and Severity Index
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EIS	Electrical Impedance Spectroscopy
EOS	End of Study
ET	Early termination
FAS	Full analysis set
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HRQoL	Health-Related Quality of life
HRT	Hormonal replacement therapy
HS	Hidradenitis suppurativa
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
IEC	Independent ethics committee
IGA	Investigator Global Assessment
IgG1κ	Recombinant human immunoglobulin g1 kappa
IL-1α	Human interleukin-1 alpha
IM	intramuscular
IND	Investigational New Drug
INR	International normalized ratio
IPPI	Investigational Product Preparation Instructions
IRB	Institutional review board
IRR	Infusion-related reaction
IWRS	Interactive web response system
K_D	Dissociation rate constant (K_D)
mAb	Monoclonal antibody

MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
NAbs	Neutralizing antibodies
NOAEL	No observed adverse effect level
NRS	Numeric Rating Scale
OTC	Over the counter
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic(s)
PFS	Preffilled syringe
PG	Pyoderma gangrenosum
PGIS	Patient Global Impression of Severity
PK	Pharmacokinetic(s)
POEM	Patient-oriented eczema measure
PPD	Purified protein derivative
PQC	Product quality complaint
PRO	Patient-reported outcome(s) (paper or electronic as appropriate for this study)
PROMIS	Patient-reported outcomes measurement information system
QoL	Quality of life
QTcF	QT corrected according to Fridericia's formula
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome Coronavirus-2
SC	subcutaneous(ly)
SCH	Stratum corneum hydration
SCORAD	Scoring of Atopic Dermatitis
SoA	Schedule of Activities
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TBP	Total body photography
TEAEs	Treatment-emergent adverse events
TEWL	Transepidermal water loss
TU	Tuberculin units
US	United States
UV	Ultraviolet
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis

Definitions of Terms

Electronic source system	Contains data traditionally maintained in a hospital or clinic record to document medical care or data recorded in a eCRF as determined by the protocol. Data in this system may be considered source documentation.
PRO	Reports directly from the patient without interpretation by clinician or anybody else.

10.2. Appendix 2: Clinical Laboratory Tests

The following tests will be performed according to the Schedule of Activities (Section 1.3) by the central laboratory:

Protocol-Required Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: MCV MCH	White Blood Cell count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils Bands
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate BUN Creatinine Glucose Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-pyruvic	Total bilirubin Indirect bilirubin Alkaline phosphatase Calcium Phosphate Albumin Total protein Lactic acid dehydrogenase (LDH)	
	Note: Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 10.7, Appendix 7: Liver Safety: Suggested Actions and Follow-Up Assessments		
Other Laboratory Tests	• Serum (or additional Urine) Pregnancy Testing for women of childbearing potential only • Lipid panel: HDL, LDL (calculated), Total cholesterol, triglycerides (Weeks 0 and 16) • Serology (HIV antibody, HBsAg, hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc], and hepatitis C virus antibody) • QuantiFERON-TB® test		

10.3. Appendix 3: Regulatory, Ethical, and Study Oversight Considerations

10.3.1. REGULATORY AND ETHICAL CONSIDERATIONS

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current International Council for Harmonisation (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 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) involves 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 eCRF 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 AEs 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.

10.3.2. 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.

10.3.3. 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.

Informed consent may be obtained remotely. Refer to Monitoring Guideline.

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 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.

10.3.4. 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.

10.3.5. 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 moderate-to-severe AD, to understand differential intervention responders, and to develop tests/assays related to bermekimab and moderate-to-severe AD. 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 in Future Research).

10.3.6. COMMITTEES STRUCTURE

Data Review Committee

An internal and independent DRC will be established to ensure the continuing safety of participants enrolled in this study. This committee will consist of at least one medical expert in the relevant therapeutic area and at least one statistician; committee membership responsibilities, authorities, and procedures will be documented in its charter. The committee will meet periodically to review interim data. After the review, the internal and independent DRC will make recommendations regarding the continuation of the study.

10.3.7. 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 EOS in order to ensure the statistical analyses are relevant.

10.3.8. 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 eCRF completion will be provided and reviewed with study site personnel before the start of the study.

10.3.9. 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 eCRF. All eCRF 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 eCRF 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 eCRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The eCRF 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 electronic data capture (eDC) tool. If corrections to an eCRF are needed after the initial entry into the eCRF, 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 studysite personnel.

10.3.10. 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 AEs and follow-up of AEs; 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.

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 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 eCRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the eCRF.

10.3.11. MONITORING

The sponsor will use a combination of monitoring techniques: central, remote, or on-site monitoring to monitor this study.

The sponsor will perform on-site monitoring visits as frequently as necessary. 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 regulations. 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); a sample may be reviewed. 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.

Central monitoring will take place for data identified by the sponsor as requiring central review.

10.3.12. 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.

10.3.13. RECORD RETENTION

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRF 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.

10.3.14. 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 intervention.

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

10.4. Appendix 4: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.4.1. 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 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 Event and Serious Adverse Event 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 judgement 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 AE 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.

10.4.2. 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.

10.4.3. 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 judgement in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.4.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention 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 participant 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 breastfeeding

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of a SAE should be recorded on the SAE page of the eCRF.

10.4.5. Procedures

All Adverse Events

All AEs, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the eCRF. 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 eCRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE 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 SAEs 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)

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during participation in the study must be reported as a SAE, 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 eCRF). 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 SAEs. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new SAE.

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 SAE.

Information regarding serious adverse events will be transmitted to the sponsor using a serious adverse event reporting form and safety report form of the eCRF, 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.

10.4.6. Product Quality Complaint Handling

Definition

A product quality complaint (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.

This definition includes any PQC related to a device constituent in a combination product, including those used in the administration of the study intervention or the comparator. A device deficiency is an inadequacy of a device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

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.

10.4.7. Contacting Sponsor Regarding 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.

10.5. Appendix 5: Contraceptive and Barrier 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 Section 10.4, Appendix 4: 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, and 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) *(Azoospermia 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.

10.6. Appendix 6: 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 TB. 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 participants, 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 participants** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised participants exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

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

References

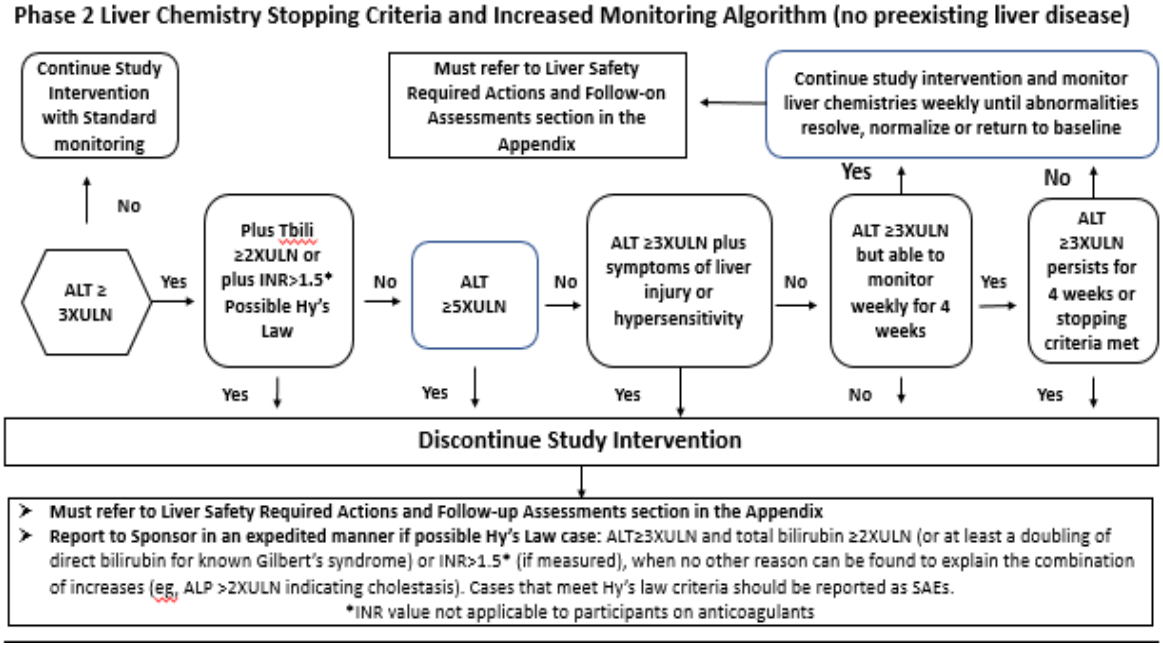
Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination;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

10.7. Appendix 7: Liver Safety: Suggested Actions and Follow-Up Assessments

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



Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase, INR=international normalized ratio; SAE=serious adverse event; ULN=upper limit of normal, Tbili=Total bilirubin.

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

Phase 2 Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT or AST-absolute	ALT or AST ³5×ULN
ALT or AST Increase	ALT or AST ³3×ULN persists for ³4 weeks
Bilirubin[1,2]	ALT or AST ³3×ULN **and** total bilirubin ³2×ULN
INR[2]	ALT or AST ³3×ULN **and** international normalized ratio (INR) >1.5
Cannot Monitor	ALT or AST ³3×ULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT or AST ³3×ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions, Monitoring, and Follow-up Assessments	
Actions	**Follow-Up Assessments**
Immediately discontinue study intervention • Report the event to the sponsor **within 24 hours** • Complete the liver event/expedited reporting form, and complete an SAE eCRF if the event also met the criteria for an SAE[2]	• Viral hepatitis serology[4] • Obtain blood sample for pharmacokinetic (PK) analysis after the most recent dose[5] • Obtain serum creatine phosphokinase, lactate dehydrogenase,

• 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 **MONITORING:** **<u>If ALT or AST ³3×ULN AND total bilirubin ³2×ULN or INR >1.5:</u>** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total 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 hepatology consultation is recommended • **If ALT or AST ³3×ULN AND total bilirubin <2×ULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline • **Do not restart/rechallenge** participant with study intervention unless allowed per protocol and sponsor approval is granted	gamma-glutamyltransferase, glutamate dehydrogenase, and serum albumin • Fractionate bilirubin, if total bilirubin ³2×ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the liver event/expedited reporting form • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF • Record alcohol use on the liver event alcohol intake form. • **<u>If ALT or AST ³3×ULN AND total bilirubin ³2×ULN or INR >1.5</u>** 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) to evaluate liver disease, complete liver imaging form • Liver biopsy may be considered and discussed with local specialist if available, for instance: • In participants when serology raises the possibility of autoimmune hepatitis • In participants when suspected drug induced liver injury (DILI) progresses or fails to resolve on withdrawal of study intervention • In participants with acute or chronic atypical presentation • If liver biopsy is conducted complete a liver biopsy form.

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 ≥3xULN **and** total bilirubin ≥2xULN (>35% direct bilirubin) or ALT or AST ≥3xULN **and** INR >1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. 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. PK sample may not be required for participants known to be receiving placebo or noncomparator 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 eCRF. 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 OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Reference Manual.

10.8. Appendix 8: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for 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):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Participants 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.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Participants 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 participant ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the participant ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the participant ***is NOT eligible*** for this study.

For participants 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.			

10.9. Appendix 9: Study Conduct During a Natural Disaster

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 eCRF.

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 participant 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 participants for study procedures eg, those related to safety monitoring / efficacy evaluation / study drug storage and administration (including training where pertinent)

  - 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 eCRF.
  - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in eCRFs 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).

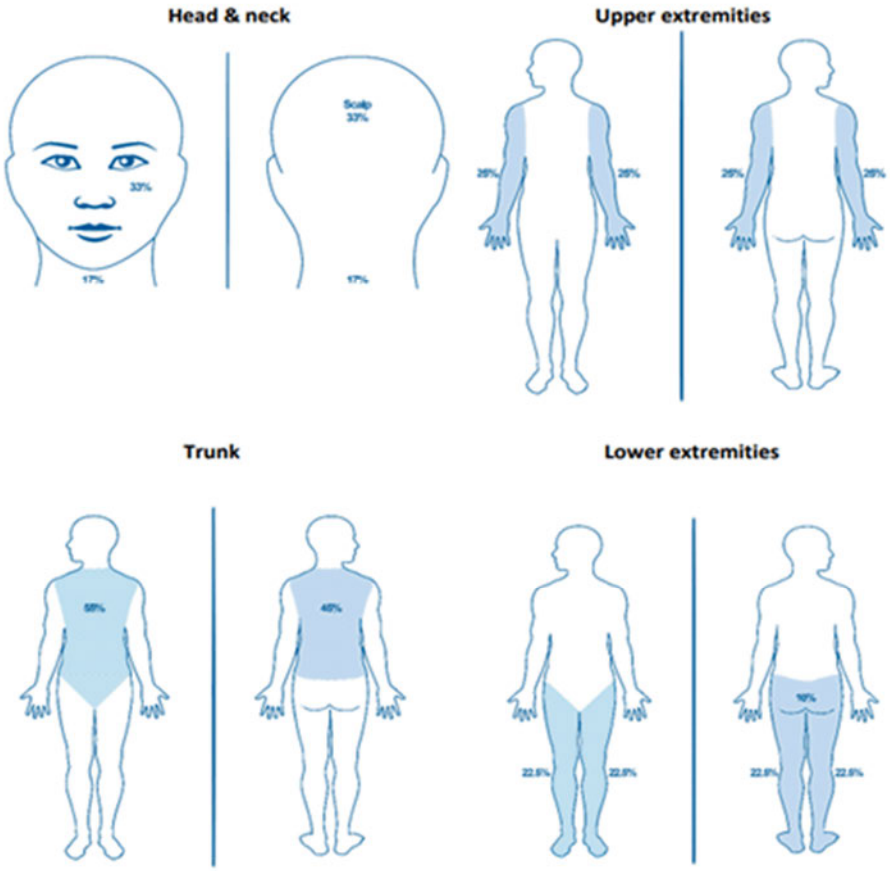
NOTES on COVID-related exclusion:

The field of COVID-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 (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.

10.10. Appendix 10: Eczema Area and Severity Index (EASI)

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 to 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). Below is a sample Score.



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%.

10.11. Appendix 11: Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD)

Below is a sample scale.

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.

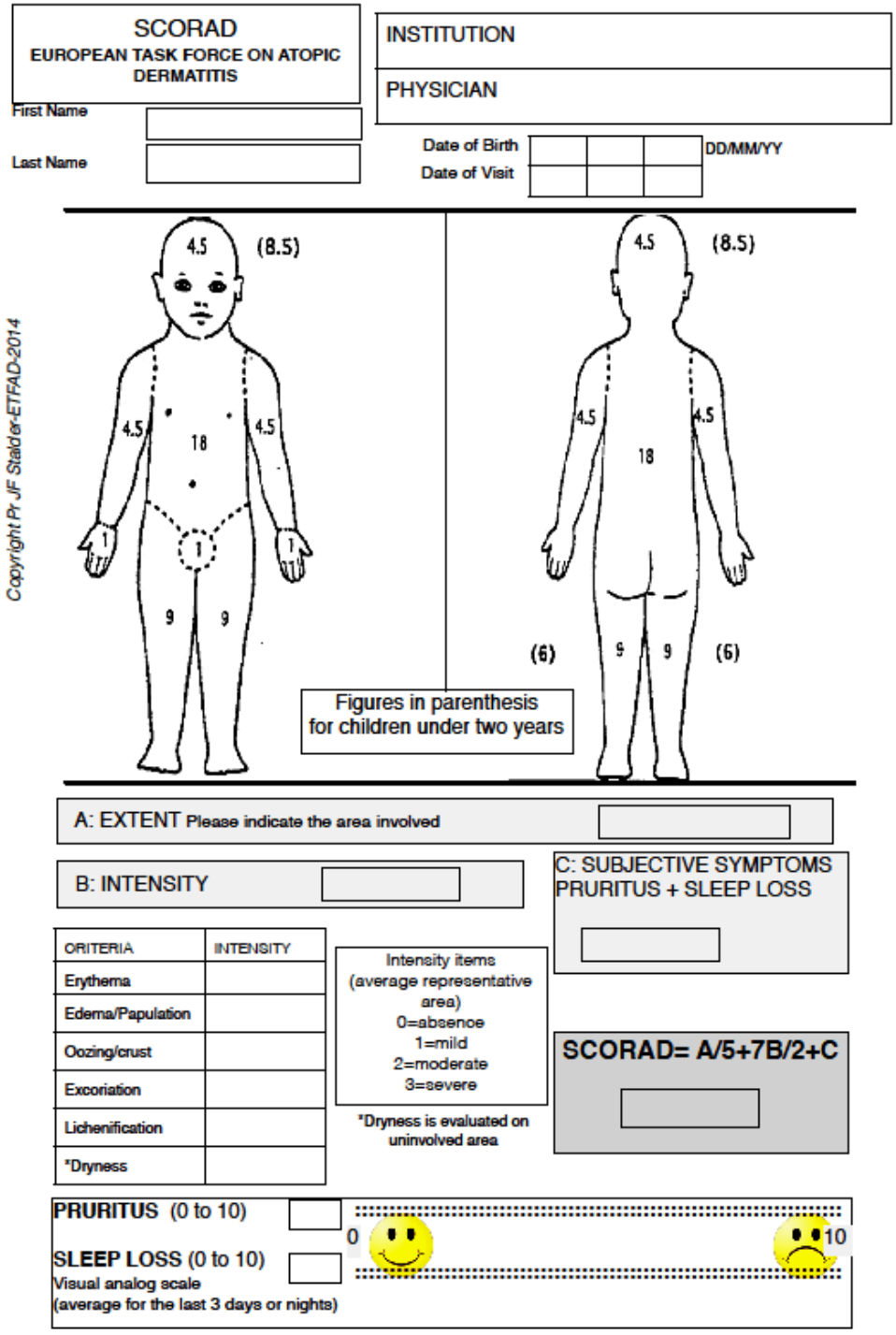
For example:

- *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.

10.12. Appendix 12: Severity Scoring of Atopic Dermatitis (SCORAD)

Below is a sample form.



10.13. Appendix 13: Hand Dermatitis Investigator Global Assessment (IGA)

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.

10.14. Appendix 14: Patient-Reported Dermatology Life Quality Index (DLQI)

Below is a sample questionnaire.

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.

10.15. Appendix 15: Patient Global Impression of Severity (PGIS)

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

10.16. Appendix 16: Patient-Reported Outcomes Measurement Information System (PROMIS)-29

Below is a sample questionnaire.

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	☐
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐
	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**
FI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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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

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10.17. Appendix 17: Eczema Skin Pain and Itch Numeric Rating Scale (NRS)

Below is a sample 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

10.18. Appendix 18: Atopic Dermatitis Itch Scale (ADIS)

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)

ϒ Yes
ϒ 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?

- ϒ No impact: itching did not affect sleep
- ϒ Mild impact: a little difficulty falling or staying asleep due to itching
- ϒ Moderate impact: a moderate amount of difficulty falling or staying asleep due to itching
- ϒ 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)

ϒ Yes
ϒ 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?

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

10.19. Appendix 19: Remote Endpoint Assessment Using Total Body Photography

A previous study (Hughes 2019) has described the capture of digital images of participants 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 AD, the well-established and validated scoring systems of the EASI (Section 10.10, Appendix 10: Eczema Area and Severity Index) and SCORAD (Section 10.12, Appendix 12: Severity Scoring of Atopic Dermatitis) 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 AD 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 0), Week 8, and Week 16 visits.

Participants will agree to have multiple series of total body photographs taken at specified visits. Instructions and photographic guides will be provided to the sites. Captured images will be transferred and stored in a secure manner. The site investigator (at some point after the Week 20 visit), will access the images for the participants at their site and will assess the participants' 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 site), and central reader assessment by images.

10.20. Appendix 20: Protocol Amendment History

This is an original protocol.

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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.

Signature

User	Date	Reason
PPD	23-Nov-2021 15:42:54 (GMT)	Document Approval