Janssen Research & Development

Statistical Analysis Plan

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

Protocol JNJ77474462ADM2002; Phase 2

JNJ77474462 (Bermekimab)

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Compliance: The study described in this report was performed according to the principles of Good Clinical Practice (GCP).

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
ALP	alkaline phosphate
ANCOVA	analysis of covariance
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic Class
AUC	area under the curve
BMI	body mass index
BSA	body surface area
CI	confidence interval
CL	total systemic clearance
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
EASI	Eczema Area and Severity Index Score
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
eCRF	electronic case report form
F (%)	absolute SC bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
GISS	Global Individual Signs Score
HADS	Hospital Anxiety Depression Scale
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment
IQ	interquartile
IL-6	Interleukin-6
LLOQ	lower limit of quantification
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimum required dilution
Nab	neutralizing antibodies
NRS	Numerical Rating Scale
PD	pharmacodynamic
PI	principal investigator
PK	pharmacokinetic(s)
POEM	Patient Oriented Eczema Measure
PP	per protocol
SCORAD	Severity Scoring of Atopic Dermatitis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SMQs	standardised MedDRA queries
TB	Tuberculosis
TEAE	treatment-emergent adverse event
US NCI	United States National Cancer Institute
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

Summary of Amendment 1

This amendment is to add additional statistical method of Fisher's Exact test for the binary efficacy endpoints in case of rare events. Originally, the planned analysis for treatment comparison in binary response endpoints is to use a Cochran-Mantel-Haenszel test.

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for the analysis of efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), Immunogenicity and health-related quality of life in the JNJ77474462ADM2002(PT-046) study.

1.1. Trial Objectives

Primary Objective

The primary objective of this study is to evaluate the initial efficacy, safety of different dose regimens of bermekimab in adult participants with moderate to severe Atopic Dermatitis (AD).

Secondary Objectives

The secondary objectives of this study are:

- To evaluate the effect of bermekimab on the dermatologic health-related quality of life in adult participants with moderate to severe AD.
- To evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of bermekimab therapy in adult participants with moderate to severe AD.

1.2. Trial Design

This is a phase II, randomized, double-blind, placebo-controlled study to further establish the efficacy, safety, PK, and explore dose effects for bermekimab monotherapy in adults with moderate to severe Atopic Dermatitis (AD). The participant population will comprise men and women who have had chronic atopic dermatitis present for at least 3 years. The study is approximately 40 weeks (30 day screening period, 32-week treatment period and a 4-week follow-up period) for all subjects.

A diagram of the study design (Figure 1) is provided below, approximately 90 patients who meet the eligibility criteria at screening will be randomized in a 1:1:1 ratio to one of two active treatment arms or placebo:

- Arm 1: 400 mg loading dose of bermekimab (2mL SC injection containing 400 mg of bermekimab and one 2mL SC injection of placebo) at Week 0 followed by weekly (qw) subcutaneous (SC) injections of 400 mg bermekimab through Week 31
- Arm 2: 800 mg loading dose of bermekimab (2 x 400 mg SC injections) at Week 0 followed by subcutaneous (SC) injections of 400 mg bermekimab every other week (q2w) alternating with matching placebo q2w through Week 31.

- Arm 3: 4mL loading dose of placebo (2 x 2mL SC injections) at Week 0 followed by weekly placebo injections from Week 1 through Week 15. Patients in Arm 3 will begin to receive weekly (qw) blinded subcutaneous (SC) injections of 400 mg bermekimab beginning at Week 16 through Week 31.

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

Efficacy assessments include Eczema Area and Severity Index Score (EASI) score, Itch Numerical Rating Scale (NRS), Pain NRS, Severity Scoring of Atopic Dermatitis (SCORAD), Patient Oriented Eczema Measure (POEM), Global Individual Signs Score (GISS), Dermatology Life Quality Index (DLQI), Hospital Anxiety Depression Scale (HADS), Body Surface Area (BSA) and Investigator's Global Assessment (IGA) will be performed according to the Study Calendars (Section 5.2 of the protocol).

Blood samples will be collected for laboratory testing including chemistry, hematology, inflammation markers, bermekimab concentration (PK), PD marker(s), and anti-drug antibody (ADA).

Figure 1: Study Flow Diagram of JNJ77474462ADM2002

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

After completion of the 36-week study period, data will be locked and analysed for safety and efficacy. In addition to the analyses that will be performed following the formal Week 36 database lock at the end of the study, an additional database lock will be performed at Week 16 and the unblinded efficacy data analyses will be conducted to help plan potential future development activities.

1.3. Statistical Hypotheses for Trial Objectives

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

1.4. Sample Size Justification

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

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

1.5. Randomization and Blinding

1.5.1. Procedures for Randomization and Stratification

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

1.5.2. Maintenance of Blind

The study blind will be maintained for the duration of the study, until after the Final (Week 36) DBL.

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

The investigator will not be provided with randomization codes. The codes will be maintained within the Electronic Data Capture (EDC) system, 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-bermekimab antibodies, and intervention allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question

from view by the investigators, clinical team, or others as appropriate until the time of DBL and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. However, a number of prospectively identified Sponsor individuals will be unblinded at the Week 16 DBL. Identification of sponsor personnel who will have access to the unblinded data at subject-level and who will have access to the unblinded data at group-level will be documented prior to unblinding at the Week 16 DBL. All site personnel and participants will remain blinded to the treatment assignments until the last participant completes Week 36 evaluations and the database has been locked.

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

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

The investigator may, in an emergency, determine the identity of the intervention through the EDC system. 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 unblinding must be documented in the appropriate section of the eCRF, and in the source document.

Participants who have had their intervention assignment unblinded by the investigator will not be eligible to receive further study intervention but should continue to complete evaluations specified in the Study Calendars (Section 5.2 of the protocol).

2. GENERAL ANALYSIS DEFINITIONS

This analysis plan provides the general analysis definitions and describes the planned subject information, efficacy, safety, pharmacokinetics, and antibody analyses for the two planned DBLs.

2.1. Imputation Rules for Partial or Missing AE Dates

Partial AE onset dates will be imputed as follows:

- If the onset date of an adverse event is missing day only, it will be set to:
  - First day of the month that the AE occurred, if month/year of the onset of AE is different than the month/year of the study agent start
  - The day of study agent start, if the month/year of the onset of AE is the same as month/year of the study agent start date and month/year of the AE resolution date is different
  - The day of study agent start or day of AE resolution date, whichever is the earliest, if month/year of the onset of AE and month/year of the study agent start date and month/year of the AE resolution date are same
- If the onset date of an adverse event is missing both day and month, it will be set to the earliest of:
  - January 1 of the year of onset, as long as this date is on or after the study agent start date
  - Month and day of the study agent start date, if this date is in the same year that the AE occurred
  - Last day of the year if the year of the AE onset is prior to the year of the study agent start date,
  - The AE resolution date.
- Completely missing onset dates will not be imputed.

Partial AE resolution dates not marked as ongoing will be imputed as follows:

- If the resolution date of an adverse event is missing day only, it will be set to the earliest of the last day of the month of occurrence of resolution or the date of death, if the death occurred in that month.
- If the resolution date of an adverse event is missing both day and month, it will be set to the earliest of December 31 of the year or the day and month of the date of death, if the death occurred in that year.
- Completely missing resolution dates will not be imputed.

2.2. Visit Windows

Nominal visits will be used for all by-visit analyses in the study. The study visits scheduled post randomization should occur at the times delineated in the Schedule of Activities. The study visits through Week 36 should occur within ± 3 days of the scheduled visit. The sponsor must be contacted for any significant deviation in the scheduling of a visit outside the appropriate window and determine how the subject should resume his/her normal dosing schedule relative to the baseline visit (Week 0).

2.3. Pooling Algorithm for Analysis Centers

Unless otherwise specified, data from all investigational centers/sites will be pooled for analyses.

2.4. Analysis Sets

There will be two database locks at Weeks 16 and 36 respectively.

Week 16 database lock

Week 16 database lock will include selected efficacy, safety, and PK data through Week 16 for all randomized and treated participants. The data will be primarily used in planning for future bermekimab clinical development in AD. The selected efficacy and safety data include but are not limited to the following:

1. Eczema Area and Severity Index (EASI)
2. Investigators Global Assessment (IGA) score
3. Itch Numeric Rating Scale (NRS) score
4. Pain Numeric Rating Scale (NRS) score
5. Baseline Disease Characteristics for 1-4 above
6. Demography
7. AE
8. PK

Week 36 database lock

Week 36 DBL would include all data through Week 36 for all randomized and treated participants.

2.4.1. Efficacy Analysis Set(s)

2.4.1.1. Full Analysis Set

The full analysis set (FAS) population includes all randomized participants who received at least 1 dose of study agent. This analysis set will be used for the efficacy analyses of the endpoints through Week 36, ***unless otherwise specified***.

In the efficacy analyses, participants will be analyzed according to the randomized treatment groups they were assigned to, regardless of the treatments they actually received.

2.4.1.2. Per Protocol Analysis Set

The primary endpoint will also be analyzed using the per-protocol population, which includes participants who are generally compliant with the protocol.

Specifically, the per protocol population includes participants in FAS except those

- who did not meet the inclusion criteria in the protocol as listed below:
  - EASI score ≥16 at screening and baseline visits.
  - IGA score ≥3 at screening and baseline visits.
  - ≥10% body surface area (BSA) of AD involvement at screening and baseline visits.

  - NRS Weekly Average of worst daily Skin Itch Scores at least 3 at screening

- who did not receive all scheduled study agent administrations prior to Week 16.

However, for those who discontinued the study agent prior to Week 16 will be included in the per protocol analysis and the data handling rule specified in section 5.2.2 will apply.

2.4.2. Safety Analysis Set

The safety analysis set includes all randomized participants who received at least 1 dose of study agent, i.e., the treated population.

2.4.3. Pharmacokinetics Analysis Set

The pharmacokinetic (PK) analysis set includes all participants who received at least 1 dose of bermekimab and had at least 1 valid blood sample drawn for PK analysis after their first dose of bermekimab.

2.4.4. Pharmacodynamics Analysis Set

The Pharmacodynamics (PD) analysis set includes all participants who received at least 1 dose of bermekimab and had at least 1 valid blood sample drawn for PD analysis after their first dose of bermekimab.

2.4.5. Immunogenicity Analysis Set

The immunogenicity analysis set includes all participants who received at least 1 dose of bermekimab and who have at least 1 sample obtained after their first dose of bermekimab for the detection of antibodies to bermekimab.

2.5. Definition of Subgroups

To evaluate the consistency in the primary efficacy endpoint (proportion of participants who achieve EASI-75 at Week 16) over demographics, baseline disease characteristics, and prior and baseline medication use, subgroup analyses will be performed when sample sizes are permitted. The subgroups include, but are not limited to, the following:

Baseline demographics:

- Sex (male, female)
- Race
- Baseline Age (<40 years, 40 to <65 years, ≥65 years)
- Baseline weight (≤80 kg, >80 kg)
- BMI (Normal [<25], Overweight [25 -<30], Obese [≥ 30])

Baseline disease characteristics and AD medication:

- Age at diagnosis (years) (< median, ≥ median)
- AD disease duration (years) (< median, ≥ median)
- Baseline EASI severity (less severe [EASI <28] or more severe [EASI ≥28])
- Baseline IGA (3, 4)
- Baseline C-reactive protein (CRP) (< median, ≥ median)
- Baseline Erythrocyte Sedimentation Rate (ESR) (< median, ≥ median)
- Prior biologic therapy (Yes/No)

2.6. Study Day and Relative Day

Study day is defined as the number of days from the study reference date to the event/visit date. It will be calculated as follows:

- If the event/assessment occurs on or after the reference date, then study day = event/assessment date – reference date + 1.
- If the event/assessment occurs before the reference date, then study day = event/assessment date – reference date.

Hence, the day of reference date is Study Day 1; the previous day is Study Day -1.

2.7. Baseline and Endpoint

In general, the baseline measurement is defined as the closest measurement taken prior to or at the time of the first study agent administration date unless otherwise specified.

3. INTERIM ANALYSIS AND DATA MONITORING COMMITTEE REVIEW

No interim analysis or data monitoring committee review is planned for this study.

4. SUBJECT INFORMATION

Unless specified otherwise, FAS will be used for the subject information analyses and participants will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received. The number of participants in each analysis set will be summarized by treatment group and overall.

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables will be used to summarize most data and no formal hypothesis testing for treatment comparisons will be performed. In addition, subject listings will also be used to present the data.

4.1. Demographics and Baseline Characteristics

The FAS will be used for all tabulations. Participants' demographic data and baseline disease characteristics will be summarized by treatment group. If imbalances are found at baseline, then additional analyses may be performed adjusting for baseline differences.

4.1.1. Demographic

Table 1 presents a list of the demographic variables that will be summarized by treatment group, and overall for the FAS.

Table 1: Demographic Variables

Continuous Variables:	**Summary Type**
Age (years)	Descriptive statistics (N, mean, standard deviation [SD], median and range [minimum and maximum], and IQ range).
Weight (kg)	
Height (cm)	
Categorical Variables:	
Age (<40 years, 40 to <65 years, and ≥65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female)	
Weight (kg) (<= 80 kg, > 80 kg)	
Race (American Indian or Alaska Native, Asian, Black or African American, White, Other)	
Ethnicity (Hispanic or Latino, Not Hispanic or Latino)	
BMI (Normal [<25], Overweight [25 -<30], Obese [≥30])	

4.1.2. Baseline Disease Characteristics

Baseline disease characteristics (e.g., duration of AD disease, EASI score, GISS, POEM, SCORAD score, BSA, baseline IGA, NRS pain, NRS Itch, HADS, DLQI) will be summarized by treatment group.

4.1.3. Medical History

Summaries of participants' alcohol intake, and smoking status will be provided by treatment group. In addition, the distribution of participants by prior biologic use (yes/no) and type of biologic therapy will also be provided.

Medical history will be listed including body systems and condition/non-drug allergy as captured on the eCRF.

4.2. Disposition Information

The number of participants in the following disposition categories will be summarized by treatment group and overall:

- Participants screened: met the inclusion criteria regarding the target indication and signed the informed consent
- Participants randomized
- Participants randomized and received at least 1 study agent
- Participants who completed the study through Week 16 and Week 36
- Participants who discontinued study and the reasons for discontinuation through Week 16 and Week 36

Listings of participants will be provided for the following categories:

- Participants who discontinued study
- Participants who were unblinded during the study period

4.3. Treatment Compliance

Study agent compliance will be summarized descriptively through Week 16 and through the end of the study (Week 36) for the FAS. Number of the participants receiving each scheduled treatment will be summarized. In addition, treatment compliance will also be assessed by protocol deviations related to study agent administration (i.e., incorrect study agent or dose received).

4.4. Extent of Exposure

The exposure data will be summarized through Week 16 and Week 36. The number and percentage of participants who receive study agent will be summarized by treatment group for the safety analysis set. Descriptive statistics will be presented for the following parameters:

- Number of administrations
- Cumulative total dose

In addition, the average exposure (number of administrations) and average duration of follow-up (weeks) will also be summarized by treatment group in the safety tables through different study time periods.

4.5. Protocol Deviations

In general, the following list of major protocol deviations may have the potential to impact participants' rights, safety or well-being, or the integrity and/or result of the clinical trial. Participants with major protocol deviations will be identified prior to database lock and will be summarized by category by treatment group through Week 16 and Week 36 for the FAS.

- Entered study and did not satisfy entry criteria
- Received wrong treatment or incorrect dose
- Received excluded concomitant or non-drug therapy
- Out of window visit
- Out of window procedure
- Other

A listing of participants with major protocol deviations and a listing of patients who missed scheduled study agent administration will also be provided by randomized treatment group. In addition, analyses of COVID-19 related protocol deviations will be provided.

4.6. Concomitant Medications

Concomitant medications for atopic dermatitis will be summarized by treatment group for the FAS. Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study agent. Concomitant medications are defined as any therapy used on or after the same day as the first dose of study agent, including those that started before and continued after the first dose of study agent.

A list of participants who received a concomitant treatment that could improve AD will be provided.

5. EFFICACY

5.1. General Method of Analysis

Unless specified otherwise, efficacy data summaries will be provided by treatment group for the FAS. Statistical comparisons will be made between each of the bermekimab treatment groups (qw, q2w) and the placebo treatment group.

In general, for response efficacy endpoints, treatment comparisons will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by the baseline EASI severity (less severe EASI<28, more severe EASI ≥28) or the Fisher's Exact test in case of rare events. For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) with treatment group, visit, baseline EASI severity (less severe, more severe) and baseline value for the efficacy endpoint as explanatory factors. The MMRM model will also include treatment group by visit interaction, baseline EASI severity by visit and baseline

value by visit interaction as additional explanatory factors. In addition, treatment differences and their associated 95% confidence intervals will be presented.

Descriptive statistics, such as mean, median, standard deviation, minimum and maximum, interquartile range for continuous variables, and counts and percentages for categorical variables will be used to summarize the data. Graphical data displays and subject listings may also be used to summarize the data.

5.2. Analysis Specifications

5.2.1. Level of Significance

Unless otherwise specified, all statistical testing procedures will be performed at a 2-sided significance level of 0.05. Multiplicity adjustment was planned for the primary endpoint as specified in protocol Section 10.5.3 to maintain an overall Type I error of 0.05 or less for the primary endpoint analysis.

However, since this is a Phase 2 trial and stricter multiplicity adjustment for the primary endpoint at an overall alpha level of 0.05 is not required; a less stringent type I error control will be implemented instead. The study would be considered as positive if any of the comparisons for primary endpoint analysis (weekly injection group vs placebo, and every other week injection group vs placebo) is less than or equal to 0.05. Therefore, an overall Type I error rate will be maintained at 0.1 or less for the primary endpoint analysis. Nominal p-values will be reported for secondary analyses.

5.2.2. Data Handling Rules

No imputation will be performed for missing baseline values.

For the main analysis of primary endpoint of EASI-75 response at Week 16, a subject who discontinued treatment will be considered as a non-responder from that point onward. The remaining missing data will be imputed as non-responder. Supplementary analyses will be performed and include (1) using observed data regardless of whether the subject discontinued treatment or have missing data, and (2) data after treatment discontinuation will be considered as missing, missing response will be imputed by multiple imputation methods under the assumption of missing at random. Similar data handling rules (i.e., main analysis with non-responder imputation and 2 supplementary analyses) will also be applied for EASI-75 response over time through Week 16. The following data handling rules will be applied for other endpoints:

Binary secondary endpoints:

- Analyses will be similar to the main analysis of the primary endpoint. A subject who discontinued treatment will be considered as a non-responder from that point onward. The remaining missing data will be imputed as non-responder. Supplementary analyses will be performed for selected endpoint (i.e IGA responses) in the same manner as the primary endpoint.

Continuous secondary endpoints:

- If a subject discontinued treatment, zero will be assigned to improvement or percent improvement. Remaining missing data will not be imputed. A MMRM model will adjust for missing post baseline data and all available data from the 3 treatment groups through Week 16 or from Week 16 through Week 36 will be included. Under the assumption of missing at random (MAR), the missing data will be accounted for through correlation of repeated measures in the model. Supplementary analyses will be performed for selected endpoints (i.e. EASI total score, NRS itch score) and include (1) using observed data regardless of whether the subject discontinued treatment or have missing data, and (2) data after treatment discontinuation will be considered as missing, missing data will be addressed by MMRM model.

5.2.3. Treatment Groups

In the efficacy analyses, FAS will be used and the participants will be analyzed according to the randomized treatment groups they were assigned to, regardless of the treatments they actually received. Unless otherwise specified, efficacy analyses during each of study periods below are in general displayed as follows:

- Analysis through Week 16
  - Efficacy analyses for placebo comparison at Week 16 or through Week 16 will be summarized by randomized treatment group:
    - **Placebo**: Participants randomized to placebo group.
    - **Bermekimab 400 mg q2w**: Participants randomized to bermekimab 400 mg every other week injection group.
    - **Bermekimab 400 mg qw**: Participants randomized to bermekimab 400 mg weekly injection group.
    - **Combined Column**: Combined column which combines the data from the randomized and treated participants who are assigned to bermekimab 400 mg q2w or qw treatment groups.
- Analysis from Week 16 through Week 36
  - Efficacy data from Week 16 through Week 36 will be summarized by the following treatment groups:
    - **Placebo → Bermekimab 400 mg qw**: efficacy in participants randomized to placebo group.
      - Only placebo participants crossover to bermekimab 400 mg qw and received bermekimab at Week 16 will be included in the summary for the visits after Week 16.
    - **Bermekimab 400 mg q2w**: Participants randomized to bermekimab 400 mg every other week injection group.

- **Bermekimab 400 mg qw**: Participants randomized to bermekimab 400 mg weekly injection group.
- **Combined Column**: Combined column which combines the data from the randomized and treated participants who are assigned to bermekimab q2w or qw treatment groups at baseline.

These presentations allow assessment of efficacy over time between treatment groups.

5.3. Primary Efficacy Endpoint(s)

5.3.1. Definition

The primary efficacy endpoint is the proportion of patients achieving an EASI-75 response at Week 16. The EASI is a validated measure used in clinical practice and clinical trials to assess the severity and extent of AD. Four AD disease characteristics will be assessed for severity by the investigator or designee on a scale of "0" (absent) through "3" (severe). In addition, the area of AD involvement will be assessed as a percentage by body area of head, trunk, arms, and legs and converted to a score of 0 to 6.

For each region, severity score is the sum of intensity for each of four signs.

- Severity score = Erythema + Edema/Papulation + Excoriation + lichenification intensity

For each region, multiple the severity score by the region score and by a multiplier. The multiplier is different for each body site.

- Head and neck: severity score x region score x 0.1
- Trunk: severity score x region score x 0.3
- Upper extremities: severity score x region score x 0.2
- Lower extremities: severity score x region score x 0.4

Add up the total scores for each region to determine the final EASI score. The minimum EASI score is 0 and the maximum EASI score is 72.

EASI-75 responder is defined as at least a 75% improvement from baseline in EASI total score.

5.3.2. Estimands

Primary Estimand:

The **Composite Estimand** will be targeted for the primary endpoint. The Composite Estimand for the primary endpoint is defined by the following 5 attributes:

- Treatment:
  - Bermekimab 400mg q2w
  - Bermekimab 400mg qw

- Placebo

Note: treatment regimen includes protocol specified rescue therapy as needed.

- Population: Adult participants with chronic moderate to severe atopic dermatitis present for at least 3 years.
- Variable (Endpoint): EASI-75 binary responder variable at Week 16, where a subject who discontinues treatment is considered as non-responder after discontinuation.
- Intercurrent event: The intercurrent event of treatment discontinuation is addressed by the composite strategy, as reflected in the variable definition.
- Population-level summary: Difference in the proportions of subjects achieving EASI-75 response at Week 16 between the bermekimab and placebo treatment groups.

Supplementary Estimands for primary endpoint:

Supplementary Estimand 1

Same components as the primary estimand, except for the strategy used for treatment discontinuation.

Hypothetical strategy: assess the treatment effect as if the participants would not have discontinued treatment.

Note: Under this hypothetical strategy, EASI data collected after treatment discontinuation will not be used and will be set to missing in analysis.

Supplementary Estimand 2

Same components as the primary estimand, except for the strategy used for treatment discontinuation.

Treatment policy strategy: assess the treatment effect regardless of treatment discontinuation.

Note: Under the treatment policy strategy, EASI data collected after treatment discontinuation will also be used in analysis.

5.3.3. Data Handling

Participants who discontinued treatment prior to Week 16 will be considered EASI-75 non-responder at Week 16. In addition, participants with missing EASI evaluation at Week 16 will be considered as non-responders at Week 16.

5.3.4. Analysis Methods

The primary endpoint will be compared between the each bermekimab group and the placebo group. The primary endpoint will be analyzed at Week 16 based on the composite estimand (Section 5.3.2) and the data from all participants in FAS (Section 2.4.1.1) will be analyzed according to randomized treatment group regardless of the treatment actually received.

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

5.3.5. Analysis for Supplementary Estimands

Supplementary Analysis 1 (Hypothetical Estimand)

Under this estimand, for subjects who do not return for evaluation or discontinued study treatment for any reason, EASI score will be considered missing after discontinuation and missing data will be imputed using multiple imputations (MI)[1] by fully conditional specification (FCS).

More specifically, the missing EASI-75 response will be imputed with FCS logistic regression including treatment group, baseline EASI, and EASI-75 response status through Week 16 in the model with seed = 789 and 500 imputations. The proportion difference of EASI-75 response at Week 16 adjusted for baseline EASI severity using Mantel-Haenszel weight between the bermekimab groups and the placebo group and its 95% CI combining multiple datasets will also be provided. In addition, the p-value for testing the treatment difference will be obtained from SAS PROC MIANALYZE based on these combined Mantel-Haenszel estimates from the multiple imputation datasets.

Supplementary Analysis 2 (Treatment Policy Estimand)

The primary endpoint will be analyzed utilizing the treatment policy estimand. For participants who do not return for evaluation or skipped visit at Week 16, the analysis will be performed using observed data regardless of treatment discontinuation. The EASI-75 values collected after treatment discontinuation will be used in analysis and missing data will not be imputed.

5.3.6. Subgroup Analysis

For each of the subgroups defined in Section 2.5, the difference between each of the bermekimab treatment group and placebo group in the proportion of participants achieving EASI-75 at Week 16 and its 95% confidence interval (when the number of participants permits) will be calculated. Subgroup analyses will not be stratified by baseline EASI severity.

In addition, the proportion of participants achieving EASI-75 at Week 16 by investigator site will be summarized. The same data handling rules specified in Section 5.2.2 will apply for subgroup analysis.

5.3.7. Per-protocol Analysis

The primary estimand will also be performed on per-protocol analysis set (Section 2.4.1.2). The same data handling rules specified in Section 5.3.3 will apply.

5.4. Secondary Efficacy Endpoints

This section outlines the definition and analyses of these secondary endpoints related to NRS, EASI, IGA, DLQI, HADS, POEM, SCORAD, and GISS. Data from all participants in FAS will be included and analyzed according to the randomized treatment groups. For participants randomized to placebo, only participants who crossed over to receive bermekimab at Week 16 will be included in the efficacy summaries for the visits after Week 16. All statistical testing will be performed at the 2-sided 0.05 significance level. Nominal p-values will be presented.

Secondary efficacy endpoints will be summarized using descriptive statistics for continuous variables (n, mean, standard deviation, median, minimum and maximum value) and number and percentage for categorical variables. Continuous endpoints will be analyzed using a MMRM model to test the difference between treatment groups and adjust for missing data. The MMRM will includes treatment, visit, baseline EASI severity, baseline score, baseline score by visit interaction, baseline EASI severity by visit interaction and the treatment-by-visit interaction, if applicable. The Least Square mean (LSmean) estimates and their corresponding 95% confidence interval (CI) will be provided at each time points. In addition, the estimates of LSmean difference and 95% CIs between treatment groups will be provided over time through Week 16 and p-values will be calculated at Week 16.

For the MMRM model, an unstructured covariance matrix for repeated measure within a participant will be used. In case that convergence cannot be achieved, autoregressive (1) covariance structure will be used.

For binary response endpoints, treatment comparisons will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline EASI severity with missing data imputed with Non-Responder Imputation (NRI) defined in Section 5.2.2. In case of rare events, the Fisher's Exact test will be used for treatment comparisons in binary response endpoints.

Graphical data displays may also be used to summarize the over time data if applicable.

5.4.1. Data Handling

Unless otherwise specified, data handling rules specified in Sections 5.2.2 will be applied to the secondary analyses.

5.4.2. EASI

5.4.2.1. Definition

Refer to Section 5.3.1 for the definition of EASI score.

EASI-100 responder is defined as a 100% improvement from baseline in EASI total score (EASI score=0).

EASI-90 responder is defined as at least a 90% improvement from baseline in EASI total score.

EASI-75 responder is defined as at least a 75% improvement from baseline in EASI total score.

EASI-50 responder is defined as at least a 50% improvement from baseline in EASI total score.

5.4.2.2. Analyses Related to EASI

- The proportion of participants who achieve EASI-50, EASI-90, EASI-100 at Week 16 will be compared between each of the bermekimab group and the placebo group.

- The improvement from baseline in EASI total score at Week 16 will be compared between each bermekimab group and placebo group using a MMRM model including treatment group, visit, treatment group by visit interaction as factors, baseline EASI score, and baseline EASI score by visit interaction as covariates.

- The proportion of participants who achieve EASI-50, EASI-75, EASI-90, and EASI-100 will be summarized by treatment group over time. In addition, for participants who discontinued study treatment or have missing data, the proportion of participants who achieve EASI-75 through Week 16 will be analyzed utilizing the hypothetical estimand (i.e. MI method) and treatment policy estimand (i.e. observed data).

- The proportion of participants who achieve EASI-75 by baseline EASI severity will be summarized by treatment group over time through Week 16. In addition, a line plot displaying the proportions and 95% CIs for EASI-75 response through Week 16 by treatment group will be provided.

- The improvement from baseline and percent improvement from baseline in EASI total score will be summarized by treatment group over time.

- The proportion of subjects who achieve 100% improvement, ≥90%, ≥75%, or ≥50% improvement from baseline in EASI component (Edema/Papulation, erythema, and Excoriation) and region component (heck/neck, trunk, upper extremities, and lower extremities) will be summarized over time by treatment group.

In addition, two supplementary analyses (a) improvement from baseline in EASI total score at Week 16, and (b) improvement from baseline and percent improvement from baseline in EASI total score over time will be performed with the following data handling rules:

- Data is considered as missing after the discontinuation of study intervention, missing data is handled through the MMRM model.

- Data will be analyzed based on observed data regardless of whether the subject discontinued treatment or have missing data.

5.4.3. Numerical Rating Scale (NRS) for Itch & Pain

5.4.3.1. Definition

Patients will be given a diary to complete each night before bed. Patients will be asked to report "average pain", and "worst moment pain" as well as "average itch" and "worst moment itch" on a 0-10 numeric rating scale. Patient diaries will be collected weekly. A higher score indicates more severe disease (0 indicate no itch or no pain). The baseline is defined as the average score of last 7 days prior to Week 0 study agent administration. If there are more than 3 days missing data, then baseline is set as missing. Missing baseline will not be imputed.

Seven daily NRS scores are averaged into a weekly score (ie 7 days [from day -7 to -1] prior to a visit). Four days out of 7 days (either consecutive or nonconsecutive) are necessary to derive a weekly score; otherwise data are considered missing for that week.

5.4.3.2. Analyses Related to NRS

- The improvement (reduction) from baseline in NRS score (weekly average overall pain, weekly average worst daily pain, weekly average overall Itch, weekly average worst daily Itch) at Week 16 will be compared between each bermekimab group and placebo group using a MMRM model.

- The proportion of participants who achieve ≥4-point improvement (reduction) in NRS score (weekly average overall pain, weekly average worst daily pain, weekly average overall Itch, weekly average worst daily Itch) from baseline at Week 16 will be compared between each bermekimab group and placebo group using a CMH test stratified by baseline EASI severity in patients with baseline score ≥4.

- The improvement (reduction) from baseline in NRS score (weekly average overall pain, weekly average worst daily pain, weekly average overall Itch, weekly average worst daily Itch) will be summarized by treatment group over time.

- The proportion of participants who achieve ≥4-point improvement (reduction) in NRS score (weekly average overall pain, weekly average worst daily pain, weekly average overall Itch, weekly average worst daily Itch) from baseline will be summarized by treatment group over time in patients with baseline score ≥4.

In addition, two supplementary analyses (a) improvement from baseline in NRS itch score at Week 16, and (b) improvement from baseline in NRS itch score over time will be performed with the following data handling rules:

- Data is considered as missing after the discontinuation of study intervention, missing data is handled through the MMRM model.

- Data will be analyzed based on observed data regardless of whether the subject discontinued treatment or have missing data.

5.4.4. Investigators Global Assessment (IGA)

5.4.4.1. Definition

The Investigator's Global Assessment (IGA) documents the investigator's assessment of severity of AD and clinical response to treatment based on a 5-point scale clear (0), almost clear (1), mild (2), moderate (3), or severe (4). A higher score indicates more severe disease

5.4.4.2. Analyses Related to IGA

- The proportion of subjects achieve an IGA score of clear (0), IGA score of clear (0) or almost clear (1), and IGA score of mild or better (≤2) and at least 2 grade improvement from baseline at Week 16 will be compared between each of the bermekimab groups and the placebo group.

- The proportions of subjects who achieve an IGA score of clear (0) response, IGA score of clear (0) or almost clear (1) response, and IGA score of mild or better (≤2) and at least 2 grade improvement from baseline response over time will be summarized by treatment group. In addition, supplementary analyses for the proportion of participants who achieve IGA responses through Week 16 will be performed utilizing the hypothetical estimand (i.e. MI method where appropriate using the similar method as for EASI-75) and treatment policy estimand (i.e. observed data).

- Line plots will be provided displaying the proportions and 95% CIs of subjects achieve an IGA score of clear (0); and an IGA score of clear (0) or almost clear (1) through Week 16 by treatment group.

5.4.5. DLQI

5.4.5.1. Definition

The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of AD disease on a subject's quality of life. It is a simple response (0 to 3 where 0 is "not at all" and 3 is "very much") to 10-item questionnaire that, in addition to evaluating overall quality of life, can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The DLQI is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. A higher score indicates more severe disease. A score of ≤1 indicates no effect at all of disease on subject's health related quality of life, and a reduction of 5 points or more in total DLQI score is considered clinically meaningful improvement.

For a partially answered questionnaire (eg, not all 10 answers in the DLQI questionnaire were available):

- If one question's answer is not available, this question will be scored 0. The total score will then be calculated.

- If two or more questions' answers are unavailable, the questionnaire is not scored. Hence, the total score and each of the 6 component scores will be set to missing.

If one question from one of the 6 component scores is missing, the affected component score will be set to be missing.

5.4.5.2. Analyses Related to DLQI

- The change from baseline in DLQI at Week 16 will be compared between each bermekimab group and placebo group using a MMRM model to test the difference between treatment groups.

- The proportions of participants with DLQI score of 0 and 1 at Week 16 for the participants with baseline DLQI score >1 and the proportion of participants with a reduction of 5 or more points in DLQI score for the participants with baseline DLQI score ≥ 5 at Week 16 will be compared between each of the bermekimab groups and the placebo group.

- The change from baseline in DLQI total score will be summarized over time by treatment group.

- The proportions of participants with DLQI score of 0 and 1 for the participants with baseline DLQI score >1 and the proportion of participants with a reduction of 5 or more points in DLQI score for the participants with baseline DLQI score ≥ 5 will be summarized by treatment group over time.

- The change from baseline in each DLQI component score will be summarized by treatment at Week 16.

5.4.6. Hospital Anxiety Depression Scale (HADS)

5.4.6.1. Definition

The HADS is an instrument for screening anxiety and depression in non-psychiatric populations; repeated administration also provides information about changes to a patient's emotional state. The HADS consists of 14 items, 7 each for anxiety and depression symptoms; Each item on the questionnaire is scored from 0-3 resulting in a score between 0 and 21 for either anxiety or depression. The following cut-off scores are recommended for both subscales: 7 to 8 for possible presence, 10 to 11 for probable presence, and 14 to 15 for severe anxiety or depression. The HADS is provided in the study reference manual.

If one or more of the items within each domain are left unanswered, that HADS component score will be considered missing.

5.4.6.2. Analyses Related to HADS

- The improvement from baseline in Hospital Anxiety and Depression scale at Week 16 will be compared between each of the bermekimab groups and placebo group using a MMRM model.

- The proportion of participants with hospital anxiety scale <8 and depression scale <8 at Week 16 will be compared between each of the bermekimab groups and placebo groups among participants with a baseline hospital anxiety scale and depression scale >=8.

- Hospital anxiety scale and depression scale shift from baseline to Week 16 with respect to the hospital anxiety and depression scale category (<8, >=8) will be summarized.

- The improvement from baseline in Hospital Anxiety and Depression Scale will be summarized by treatment group over time.

5.4.7. Patient Oriented Eczema Measure (POEM)

5.4.7.1. Definition

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

5.4.7.2. Analysis Methods

- The change from baseline in POEM total score at Week 16 will be compared between each of the bermekimab groups and placebo group using a MMRM model.

- The change from baseline in POEM total score will be summarized by treatment group over time.

- The change from baseline in each POEM component score will be summarized by treatment group at Week 16.

5.4.8. SCORing Atopic Dermatitis (SCORAD)

5.4.8.1. Definition

The SCORAD is a validated tool used in clinical research and clinical practice that was developed to standardize the evaluation of the extent and severity of AD. There are 3 components to the assessment: A = extent or affected body surface area, B = severity, and C = subjective symptoms. The extent of AD is assessed as a percentage of each defined body area, and reported as the sum

of all areas, with a maximum score of 100% (assigned as "A" in the overall SCORAD calculation). The severity of 6 specific symptoms of AD (redness, swelling, oozing/crusting, excoriation, skin thickening/ lichenification, dryness) is assessed using the following scale: none (0), mild (1), moderate (2), or severe (3) (for a maximum of 18 total points, assigned as "B" in the overall SCORAD calculation). Subjective assessment of itch and sleeplessness is recorded for each symptom by the patient or relative on a VAS, where 0 is no itch (or sleeplessness) and 10 is the worst imaginable itch (or sleeplessness), with a maximum possible score of 20. This parameter is assigned as "C" in the overall SCORAD calculation. The SCORAD is calculated as: A/5 + 7B/2 + C where the maximum is 103. A higher score indicates more severe disease.

Body surface area (BSA) 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.

5.4.8.2. Analysis Methods

- The improvement from baseline in SCORAD total score at Week 16 will be compared between each of the bermekimab groups and the placebo group using a MMRM.
- The improvement from baseline in BSA total score at Week 16 will be compared between each of the bermekimab groups and the placebo group using a MMRM.
- The improvement from baseline in SCORAD total scores will be summarized by treatment group over time.
- The improvement from baseline in SCORAD component scores (extent, severity, and subjective symptoms) will be summarized by treatment group at Week 16.
- The improvement from baseline in BSA will be summarized by treatment group over time.

5.4.9. Global Individual Signs Score (GISS)

5.4.9.1. Definition

Individual components of the AD lesions (erythema, infiltration/papulation, excoriations, and lichenification) are rated globally (ie, each assessed for the whole body, not by anatomical region) on a 4-point scale (from 0=none to 3=severe) using the EASI severity grading criteria. The cumulative score, which ranges from 0 to 12, is the sum of the four components. A higher score indicates more severe disease.

5.4.9.2. Analysis Methods

- The improvement from baseline in GISS total score at Week 16 will be compared between each of the bermekimab groups and the placebo group using a MMRM.

- The improvement from baseline in GISS total score will be summarized by treatment group over time.

- The improvement from baseline in GISS component score (erythema, infiltration/papulation, excoriations, and lichenification) will be summarized by treatment group at Week 16.

6. SAFETY

Safety will be assessed by summarizing the incidence and type of AEs and examining changes in laboratory parameters (hematology and chemistry), and vital signs data.

In all the safety analysis, randomized participants who received at least 1 (partial or complete) dose of study agent administration will be included. For safety analyses, participants will be analyzed according to the randomized treatment groups they were assigned to, regardless of the treatments they actually received. No formal statistical comparison is planned.

Depending on the safety data categories, the cumulative safety data will be analyzed through different study periods through Week 16 and Week 36. Unless otherwise specified, tabular summaries of safety events for key study periods are in general presented as following:

Summaries through Week 16 (placebo controlled):

Safety data through Week 16 will be summarized by treatment groups

1. Placebo
2. Bermekimab q2w
3. Bermekimab qw
4. Combined Bermekimab

This allows between-group comparisons of safety between the bermekimab regimens and the placebo group based on similar follow-up period in each group.

Summaries through Week 36

Safety data through Week 36 will be summarized by treatment groups including

1. Placebo → bermekimab qw
2. Bermekimab q2w
3. Bermekimab qw
4. Combined Bermekimab

This allows safety comparisons between each bermekimab regimen through Week 36 based on the similar follow-up time in each group.

The list of actual treatment groups for safety analyses and inclusions of participants and safety events/measurements in each group are defined as follows:

1. **Placebo:** all participants who were randomized to placebo and received treatment with placebo only or received treatment with placebo prior to receiving treatment with bermekimab. For participants who started treatment with placebo but later received bermekimab, the safety events/measurements on and after the first dose of bermekimab will be excluded from this group. Only the safety events/measurements that occurred while the participants had been receiving placebo only will be included in this group.

2. **Placebo → bermekimab 400 mg qw:** all participants who were randomized to placebo started treatment with placebo only and later received treatment with bermekimab qw. Only the safety events/measurements from these participants that occurred on and after their first administration of bermekimab will be included in this group.

3. **Bermekimab 400 mg qw:** all participants who were randomized to bermekimab qw and received bermekimab qw. All the safety events/measurements from these participants that occurred on and after their first administration of bermekimab will be included in this group.

4. **Bermekimab 400 mg q2w:** all participants who were randomized to bermekimab q2w and received bermekimab q2w. All the safety events/measurements from these participants that occurred on and after their first administration of bermekimab will be included in this group.

6.1. Adverse Events

The verbatim terms used in the CRF by investigators to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Any AE starting at or after the initial administration of study agent through the end of the trial is considered as treatment emergent. If the event occurs on the day of the initial administration of study agent, and either event time or time of administration are missing, then the event will be assumed to be treatment emergent. If the event date is recorded as partial or completely missing, then the event will be considered as treatment emergent unless it is known to be prior to the first administration of study agent based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis.

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.
- AEs of severe intensity
- AEs leading to discontinuation of study
- The incidence and type of reasonably related AEs.

These summary tables will provide the count and percentage of participants with 1 or more of the specified AEs by treatment group. In addition to the summary tables, listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation of study
- Had AEs of severe or life threating, or fatal based on CTCAE (grade>=3) intensity
- Had anaphylactic or serum sickness-like reactions.

Since safety should be assessed relative to exposure and follow-up, most AE summary tables will include average weeks of follow-up and average number of study agent administrations, and injections for each treatment group.

In addition, a participant who had injection site reaction(s) in 30 minutes (+/- 10) post injection at Weeks 0, 1, and 2 were recorded in eCRF. The incidence of injection-site reaction during this time frame will be summarized.

6.2. Clinical Laboratory Tests

All clinical laboratory reports will be displayed for the participants included in the safety analysis set. The clinical laboratory parameters to be evaluated by the central laboratory include but are not limited to:

- **Hematology**: Basophils, Eosinophils, Hemoglobin, Lymphocytes, Monocytes, Neutrophils, Platelets and WBC.
- **Chemistry**: Albumin, Alkaline Phosphatase, Bicarbonate (CO2), Calcium, Chloride, Creatinine, GGT, Glucose, Potassium, SGOT, SGPT, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen.

Box plots of laboratory measurements and change from baseline will be provided for the selected laboratory measurement.

Applicable laboratory results will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE version 5.0). The worst NCI-CTCAE will be summarized by treatment group.

A listing of participants with 1 or more NCI-CTCAE toxicity grade ≥2 in hematology and clinical chemistry laboratory measurements will be provided.

6.3. Vital Signs and Physical Examination Findings

Vital signs including pulse, blood pressure (systolic and diastolic), body temperature, peripheral blood oxygen saturation (SpO2) and respiratory rate will be measured at visits (pre-injection and post-injection) as per the schedule of activities in the protocol. Descriptive statistics of the observed value and change from baseline of the vital signs will be summarized by treatment group over time.

Physical exam findings will not be analyzed. When physical exam findings are captured as AEs, those will be included in the analyses of AEs.

7. PHARMACOKINETICS/PHARMACODYNAMICS

Blood was drawn into three 6 ml collection tubes at each specified time point. These samples will be used for PK, immunogenicity, PD, biomarker, and general research analyses.

7.1. Pharmacokinetics

All PK analyses will be based on the PK analysis set (Section 2.4.3). Participants will be analyzed according to the randomized treatment groups they were assigned to, regardless of the treatments they actually received. Unless otherwise specified, tabular summaries of PK for key study periods are in general presented as following:

Summaries through Week 16:

PK data through Week 16 will be summarized by treatment groups

- Bermekimab 400 mg q2w
- Bermekimab 400 mg qw

Summaries through Week 36:

PK data through Week 36 will be summarized by treatment groups including

- Placebo → Bermekimab 400 mg qw
- Bermekimab 400 mg q2w
- Bermekimab 400 mg qw

7.1.1. Bermekimab Concentrations

Bermekimab concentrations will be summarized using descriptive statistics, including n, arithmetic mean, SD, coefficient of variation (%CV), median, interquartile range, range (minimum and maximum), by treatment group at each PK sampling time where appropriate. PK data may be displayed graphically. The following analyses will be performed as appropriate:

- Summary of bermekimab concentrations at each visit by treatment group

- Proportion of participants without detectable bermekimab concentration (below the lower limit of quantification) at each visit by treatment group
- Summary of bermekimab concentrations at each visit by treatment group and baseline body weight (quartiles). Other covariates may also be applied.
- Summary of bermekimab concentrations at each visit by treatment group and baseline EASI severity.
- Plot of mean (SD) bermekimab concentrations over time by treatment group
- Plot of median (IQ) bermekimab concentrations over time by treatment group

7.1.1.1. Data Handling Rules

Unless otherwise specified, the following data handling rules will apply to PK analyses:

- Participants will be analyzed according to the treatment groups that they actually received.
- All concentration summaries for a particular timepoint will include data obtained from treated participants at the timepoint of interest without imputing any missing data.
- A concentration not quantifiable (below the lower limit of quantification) will be treated as 0 in the summary statistics and shown as the lower limit of quantification (< LLOQ) in the data listings.
- The data from a subject who meets 1 of the following dosing deviation criteria (if applicable) will be excluded from the by-visit data analyses from that point onwards:
- Discontinue bermekimab administrations.
- Skipped a bermekimab administration.
- Received an incomplete/ incorrect dose (if applicable).
- Received an incorrect study agent (if applicable).
- Received an additional bermekimab dose.

In addition, if a subject has an administration outside of dosing windows (Table 2), the concentration data collected at and after that visit will be excluded from the by-visit data analyses. Additional exclusions for incongruous PK data to be implemented based on Janssen SOP-07948. All participants and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Table 2: Dosing Window

Visit	Window
Week 0 through Week 32	± 3 days from scheduled visit day
Final Safety and Efficacy Follow-up visits Week 36	± 7 days from scheduled visit day

7.1.2. PK vs Efficacy

The relationship between bermekimab concentrations and efficacy endpoints may be explored, e.g.:

- The relationship between bermekimab concentrations (quartiles) and proportion of participants achieving EASI-75

7.1.3. Population PK Analysis

When appropriate, population PK analysis may be performed using bermekimab concentration-time data with the nonlinear mixed-effects modeling (NONMEM) approach. Details will be provided in a separate technical report.

7.2. Immunogenicity

Immunogenicity analyses will be based on the Immunogenicity Analysis Set (Section 2.4.5). Participants will be analyzed according to the randomized treatment groups they were assigned to, regardless of the treatments they actually received. No imputation for missing concentration data will be performed.

Immunogenicity data through Week 36 will be summarized by treatment groups including

- Placebo → Bermekimab 400 mg qw
- Bermekimab 400 mg q2w
- Bermekimab 400 mg qw
- Combined Bermekimab

7.2.1. Antibodies to Bermekimab

Blood samples will be collected to examine the formation of anti-drug antibody (ADA) to bermekimab at the specified visits as shown in the schedule of activities in the protocol. Samples will also be collected at the final visit from participants who terminate study participation early.

The antibodies to bermekimab status (positive/negative) and titers will be summarized by treatment group for participants who receive at least one dose of bermekimab and have appropriate samples for detection of antibodies to bermekimab. The maximum titers of antibodies to bermekimab will be provided for participants who are positive for antibodies to bermekimab.

A listing of participants who are positive for antibodies to bermekimab will be provided. This listing will provide information regarding dose administered, bermekimab concentration, and antibody status for all visits.

7.2.2. Antibody vs PK/Efficacy/Safety

To explore the relationship between antibodies to bermekimab status and bermekimab concentrations, efficacy and safety, the following analysis may be performed if sufficient numbers of participants are positive for antibodies:

- Summary of bermekimab concentrations by antibodies to bermekimab status
- Plots of mean (SD) trough bermekimab concentrations over time by antibodies to bermekimab status
- Summary of clinical response status (e.g., proportion of participants achieving EASI-75) by antibodies to bermekimab status
- Summary of injection-site reactions by antibodies to bermekimab status (if applicable)
- List of antibodies to bermekimab status in participants who discontinued study early

7.3. Biomarkers

Biomarker assessments will include the evaluation of relevant markers in serum for all participants. The samples will be used to better understand the biology of AD in some or all of the following ways: to provide mechanistic assessment of the pharmacodynamic response of participants to treatment with bermekimab, to analyze differences between responders and nonresponders, and to determine if the markers might be used to classify participants as potential responders prior to treatment.

Serum samples will be analyzed for circulating factors such as cytokines and other inflammatory markers, and other categories of biomarkers potentially associated with the development and progression of AD or related to the bermekimab mechanism of action. These analyses are considered exploratory and will be summarized in a separate biomarker technical report.

REFERENCES

1. Rubin DB, Multiple Imputations for Nonresponse in Surveys. New York: John Wiley & Sons. 1987.