Janssen Research & Development

Statistical Analysis Plan
Amendment 1

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

Protocol 77474462ADM2001; Phase 2b

JNJ-77474462 (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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VERSION HISTORY

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
Final	28 September 2021	Not Applicable	Initial release
Amendment 1	02 March 2022	Updates were made to the primary estimand with respect to the strategy to handle COVID related (not infection) discontinuation and COVID-related missing data for the primary and key secondary endpoints. In addition, analyses for some exploratory endpoints were removed.	The IA futility criterion was met and the decision was made to terminate the study on 02 February 2022. The SAP has been updated with reduced efficacy and PK analyses. Since COVID-19 can no longer be viewed as a temporary problem, all COVID-19 related reasons will be treated similarly to "Discontinuations of study intervention due to reasons other than lack of efficacy or worsening of AD" for which treatment policy strategy was used in the past. In addition, there is no or minimal occurrence of treatment discontinuation due to COVID related reason (not infection).

1. INTRODUCTION

This statistical analysis plan (SAP) contains definitions of analysis sets, derived variables, and statistical methods for all planned analyses of efficacy, safety, pharmacokinetics (PK), and immunogenicity of bermekimab. This SAP incorporates all analyses through the Week 36 final database lock (DBL) for the study 77474462ADM2001.

1.1. Objectives and Endpoints

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

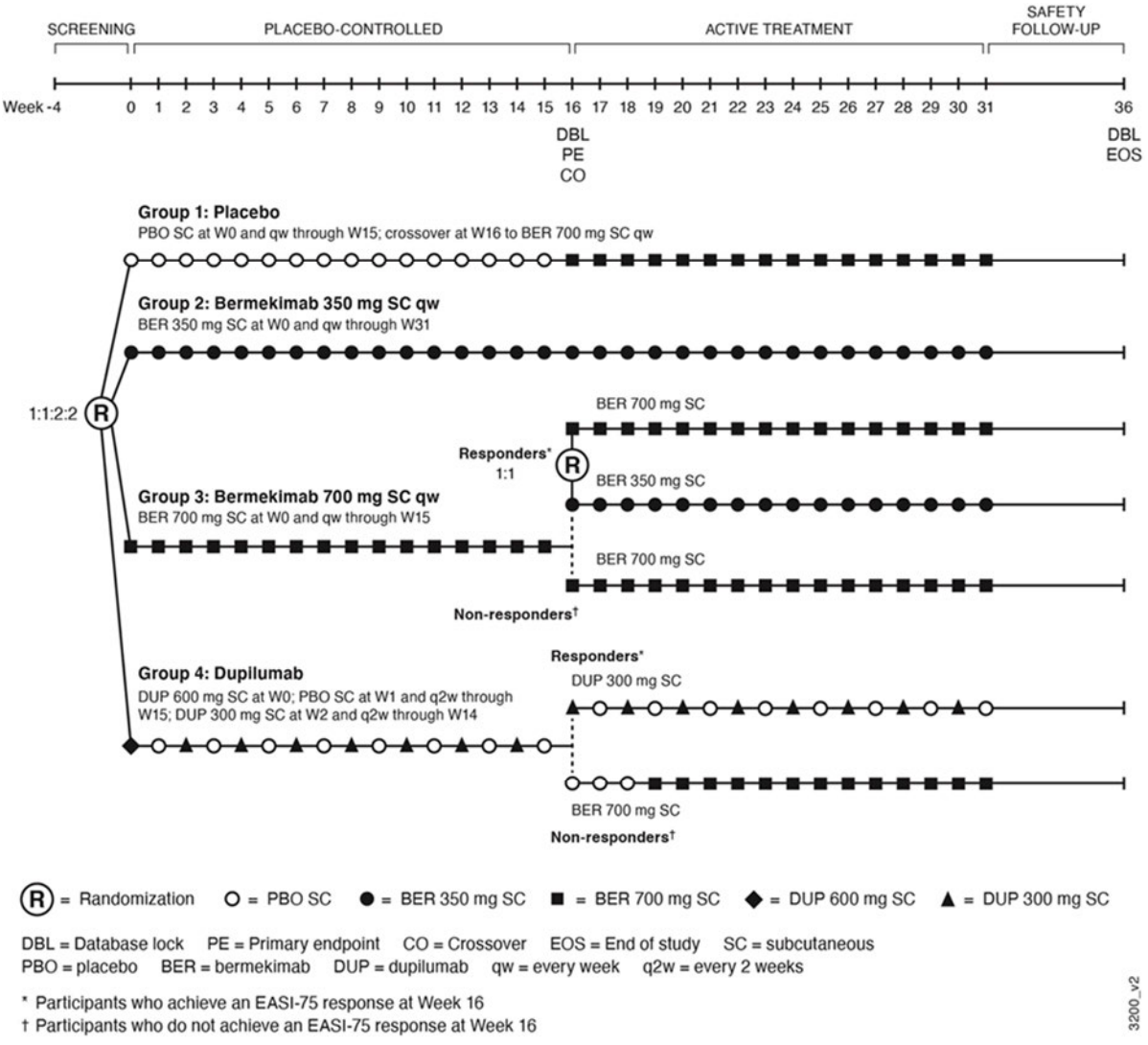
Objectives	Endpoints
	• Number/proportion of participants with treatment-emergent serious adverse events (SAEs)
• To evaluate the pharmacokinetics (PK) and immunogenicity of bermekimab in adult participants with moderate to severe AD	• Bermekimab concentration over time • The incidence of antibodies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

1.2. Study Design

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

A diagram of the study design is provided in Figure 1.

Figure 1: Schematic Overview of the Study



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

Group 1: Placebo

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

Group 2: Bermekimab 350 mg SC qw

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

Group 3: Bermekimab 700 mg SC qw

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

Group 4: Comparator/Reference Arm (Dupilumab)

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

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

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

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

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

photographs will be completed from a subgroup of participants who consent to these optional substudies at selected sites.

An interim analysis of data through Week 16 is planned for this study when approximately 50% of participants have completed the Week 16 visit. An independent, internal committee will review the results of the interim analysis. In addition, an independent, external DMC will review unblinded safety data to ensure the safety of the participants enrolled in this study.

2. STATISTICAL HYPOTHESES

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

The null hypothesis to be tested to address the primary objective of this study is that there is no difference between any of the bermekimab doses (350 mg or 700 mg) and placebo treatment based on the primary efficacy endpoint.

3. SAMPLE SIZE DETERMINATION

Approximately 270 participants are planned to be screened with 200 participants randomized in order to have sufficient power to detect a difference between the bermekimab groups and the placebo group for the primary endpoint of the proportion of participants achieving EASI-75 at Week 16. The sample size was also chosen to have adequate confidence level for the treatment difference between the bermekimab 700 mg group and the dupilumab group for the primary endpoint.

The EASI-75 response rate in the bermekimab 400 mg qw group was 35% at Week 16 and 70% at Week 7 from the placebo-controlled study (77474462ADM2002) and the open label study (2018-PT044), respectively. The EASI-75 response rates at Week 16 were 15% and 12% with placebo and 51% and 44% with dupilumab, respectively, in the two Phase 3 trials of dupilumab versus placebo in the treatment of adult participants with moderate to severe AD (Simpson 2016).

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

Table 1: Power to detect a treatment difference in EASI-75 at Week 16			
Placebo	**Intervention group**	**Difference**	**Power**
bermekimab 700 mg (n=67) vs placebo (n=33)			
15%	50%	35%	95%
15%	60%	45%	>99%
15%	70%	55%	>99%
12%	50%	38%	98%
12%	60%	48%	>99%
12%	70%	58%	>99%
bermekimab 350 mg (n=33) vs placebo (n=33)			
15%	50%	35%	88%
15%	55%	40%	94%
12%	50%	38%	93%
12%	55%	43%	97%
dupilumab (n=67) vs placebo (n=33)			
15%	45%	30%	88%
15%	50%	35%	95%
15%	55%	40%	99%
12%	45%	33%	94%
12%	50%	38%	98%
12%	55%	43%	>99%

Note: The power calculation is based on two-sample Z-test (pooled variance) .

In addition, a sample size of 67 participants in each of the bermekimab 700 mg and dupilumab groups produce a two-sided 80% confidence interval for the difference in two groups with a width of 22.9% when the observed EASI-75 response is 60% and 50% in the bermekimab 700 mg and the dupilumab group, respectively. With an observed EASI-75 response rate of 50% in both the bermekimab 350 mg and dupilumab groups, a sample size of 33 participants in the 350 mg group and 67 participants in the dupilumab group would provide a two-sided 80% confidence interval of difference with a width of 27.3% (Table).

Table 2: Confidence interval for the treatment difference in EASI-75 at Week 16					
EASI-75 Response (P1)	**EASI-75 Response (P2)**	**Difference (P1 − P2)**	**Width**	**Confidence Limit**	**Confidence Level**
bermekimab 700 mg (n=67; P1) vs dupilumab (n=67; P2)					
60%	50%	10%	22.9%	(−1%, 21%)	80%
65%	50%	15%	21.6%	(4%, 26%)	80%
70%	50%	20%	21.2%	(9%, 31%)	80%
bermekimab 350 mg (n=33; P1) vs dupilumab (n=67; P2)					
50%	50%	0%	27.3%	(−14%, 14%)	80%
55%	50%	5%	27.2%	(−9%, 19%)	80%
60%	50%	10%	26.9%	(−3%, 23%)	80%

bermekimab 700 mg (n=67; P1) vs bermekimab 350 mg (n=33; P2)					
60%	50%	10%	27.1%	(−4%, 24%	80%
65%	50%	15%	26.8%	(2%, 28%)	80%
70%	50%	20%	26.5%	(7%, 33%)	80%

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The populations for analysis are defined in Table 3 below.

Table 3 Description of analysis sets used to analyze the data in the study

Analysis Sets	Description
Enrolled	All participants who sign the ICF
Randomized Analysis Set	The randomized analysis set includes all participants who were randomized at Week 0 in the study.
Re-randomized Analysis Set	The re-randomized analysis set includes all participants who were randomized at Week 16 in the study.
Full Analysis Set (FAS)	The full analysis set (FAS) includes all participants who were randomized at Week 0 and received at least 1 dose of study intervention.
Modified Full Analysis Set (mFAS)	The mFAS includes all FAS participants who could have reached a visit by the time of the decision was made to terminate the study on 02 February 2022. projected visit (weeks) = (decision date of study termination – first dose date +1) /7 Participants will be excluded in the analysis after projected visit.
Safety	The safety analysis set includes all participants who received at least 1 dose of study intervention.
Pharmacokinetics Analysis Set	The PK analysis set is defined as participants who received at least 1 dose of bermekimab and have at least 1 valid blood sample drawn for PK analysis.
Immunogenicity Analysis Set	The immunogenicity analysis set is defined as 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.

5. STATISTICAL ANALYSES

5.1. General Considerations

The statistical analyses will include all analyses from Week 0 through Week 16 and through Week 36 (the final safety follow-up).

In general, baseline is defined as the last observation prior to or at the time of the first study agent administration, unless otherwise specified.

5.1.1. 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 should occur within ± 3 days of the scheduled visit throughout the study.

5.1.2. Reference Date, Study Day and Relative Day

The Reference Date is the date of the first study agent administration. If the date of the first study agent administration is missing or the first study agent administration is not done, then the

Reference Date equals the corresponding visit date (eg, Week 0 visit date). If the corresponding visit date is also missing, then the Reference Date equals the randomization date. 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.

5.2. Participant Dispositions

The number of screened participants will be summarized overall.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall based on the randomized analysis set:

- Participants randomized
- Participants who received study intervention
- Participants who completed the study
- Participants who discontinued study intervention
  - Reasons for discontinuation of study intervention
- Participants who terminated study prematurely
  - Reasons for termination of study

The above categories will include summaries over the placebo-controlled period (through Week 16) and the entire study (through Week 36).

Listings of participants will be provided for the following categories:

- Participants who discontinued study intervention
- Participants who terminated study prematurely
- Participants who were unblinded during the study period
- Participants who were randomized but did not receive study intervention. Participants who were randomized with incorrect stratum.

5.3. Primary Endpoint Analysis

5.3.1. Definition of Endpoint(s)

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 body region, the total severity score is multiplied by the body area score for the same region, and then applied a multiplier that represents the proportion of the total body surface area contained in the body region assessed.

- 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-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.

5.3.2. Estimand

Primary Trial Objective: to evaluate the efficacy of bermekimab in participants with moderate to severe AD.

Estimand Scientific Question of interest: What is the proportion of participants considered to have benefited from bermekimab versus placebo assessed by the EASI-75 at Week 16, administered together with the protocol allowed background standard-of-care medication?

5.3.2.1. Primary Estimand (Estimand 1)

The primary estimand (i.e. a precise definition of the primary targeted treatment effect) is defined by the following 5 attributes:

Study intervention:

- Bermekimab 350 mg, 700 mg SC qw through Week 15
- Dupilumab 300 mg SC q2w through Week 14 with dupilumab 600 mg at Week 0
- Placebo SC qw through Week 15

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 in categories 1-3 defined below will be considered as a non-responder.

Intercurrent Events (ICEs) and their corresponding strategies.

ICEs	Analysis Strategy for Addressing Intercurrent Events
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. The occurrence of these intercurrent event being captured in the variable definition.
4. Discontinuation of study intervention or missed 4 or more administrations due to COVID-19 related reasons (excluding COVID-19 infection) prior to Week 16	**Treatment Policy** Observed data will be used regardless of the intercurrent event.
5. Discontinuation of study intervention for reasons other than ICEs 1 and 4 including COVID-19 infection prior to Week 16	**Treatment Policy:** Observed data will be used regardless of the intercurrent event.

Note: For participants experiencing multiple ICEs, ICEs in categories 2-3 will override ICEs 4 and 5.

Population level summary: Difference in the proportions of participants achieving an EASI-75 response at Week 16 between the bermekimab group and placebo group.

For ICEs 2 and 3, the protocol-prohibited medications/therapies and rescue medications include:

Topical Therapies:

Any topical therapies (such as corticosteroid, calcineurin inhibitors) used for atopic dermatitis (except for topical moisturizers).

Phototherapy or Systemic Therapies:

Any systemic corticosteroid used for an indication of "Atopic Dermatitis".

Any other systemic or biologic therapy for atopic dermatitis.

Phototherapy of UVB/ PUVA or tanning beds, excimer laser, bleach baths.

5.3.2.2. Treatment Policy Estimand (Estimand 2):

This supplementary estimand has the same components as the primary estimand, except for the strategies used for ICEs 1-3.

Treatment policy strategy: assess the treatment effect regardless of whether or not intercurrent events had occurred. Under the treatment policy strategy, observed EASI data collected after ICEs will be used in analysis.

5.3.3. Analysis Methods for Primary Estimand

The primary endpoint will be analyzed at Week 16 based on the primary estimand (Section 5.3.2.1) and the data from all participants in mFAS (Section 4) will be analyzed according to randomized intervention group regardless of the treatment actually received. Participants whose projected Week 16 visits occur after study termination will be excluded in the primary analysis. Participants with ICEs 1-3 before Week 16 will be considered as EASI-75 non-responders at Week 16. Participants with ICE 4-5, observed data after these ICEs will be utilized in the analysis. A listing of participants with intercurrent events will be provided.

After accounting for the ICEs for the primary estimand, a participant with missing data will be considered as a non-responder.

In this primary analysis, the proportion of participants who achieve an EASI-75 at Week 16 will be summarized for each intervention group. To address the primary objective, a CMH chi-square test stratified by baseline EASI severity (less severe [EASI score<28] or more severe [EASI score≥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. In case of rare events, the Fisher's Exact test will be used for treatment comparisons in primary endpoint.

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

In addition, the proportion of participants achieving EASI-75 at Week 16 by investigator site will be summarized.

5.3.4. Analysis for Supplementary Estimand

The primary endpoint will be analyzed utilizing the treatment policy estimand in mFAS. The analysis will be performed using observed data regardless of intercurrent event. The EASI-75 values collected after intercurrent event will be used in analysis and missing data will not be imputed. A CMH test stratified by baseline EASI severity will be used to analyze the data.

5.4. Secondary Endpoints Analysis

5.4.1. Multiplicity Adjustment for Testing Procedures

No multiplicity adjustments will be made for the secondary endpoints. All statistical testing will be performed at the 2-sided 0.05 significance level. Nominal p-values will be presented.

5.4.2. Key Secondary Endpoint(s)

Objective: to characterize additional assessments of efficacy for bermekimab relative to placebo in participants with moderate to severe AD.

The key secondary endpoints to address the objective are the following:

- Proportion of participants with both vIGA-AD 0 or 1 and a reduction from baseline of ≥2 points at Week 16
- The proportion of participants with improvement of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4
- Proportion of participants with EASI-90 at Week 16

Objective: to evaluate the efficacy for bermekimab relative to dupilumab in participants with moderate to severe AD.

The key secondary endpoints to address the objective are the following:

- Proportion of participants with EASI-75 at Week 16
- Proportion of participants with EASI-90 at Week 16
- Proportion of participants with both vIGA-AD 0 or 1 and a reduction from baseline of ≥2 points at Week 16
- The proportion of participants with improvement of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4

5.4.2.1. Definition of Endpoints

5.4.2.1.1. Eczema Area and Severity Index

Details refer to section 5.3.1.

5.4.2.1.2. Validated Investigator Global Assessment for Atopic Dermatitis

The vIGA-AD™ developed by Eli Lilly and Company is an assessment instrument used in clinical studies to rate the severity of AD, based on a 5-point scale ranging from 0 (clear) to 4 (severe). 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 key secondary endpoint is the proportion of participants with vIGA-AD 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16.

5.4.2.1.3. Eczema Skin Pain and Itch Numeric Rating Scale

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

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

Each item is on a 0 to 10 NRS ranging from 0 “none” to 10 “worst possible” and will be scored separately. Participants will complete the rating scale daily from the screening visit through the last study visit as detailed in the protocol SoA.

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.

5.4.2.2. Estimands for Key Secondary Endpoints

5.4.2.2.1. Estimands 3-5

The following describes the attributes of the estimands for the key secondary endpoints (Estimands 3-5)

Study intervention:

- Bermekimab 350 mg, 700 mg SC qw through Week 15

- Dupilumab 300 mg SC q2w through Week 14 with dupilumab 600 mg at Week 0
- Placebo SC qw through Week 15

Population: adult participants with moderate to severe AD

Variable: variables (for estimands 4-6) are listed below

Estimand	Variable (Endpoint)
3	Binary response variable, where a responder is defined as a participant achieving vIGA-AD 0 or 1 and a reduction from baseline of ≥2 points at Week 16 who does not have ICEs 1-3 (definition of ICEs in 5.3.2.1)
4	Binary response variable, where a responder is defined as a participant with improvement of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 who does not have ICEs 1-3
5	Binary response variable, where a responder is defined as a participant with EASI-90 response at Week 16 who does not have ICEs 1-3

Summary measure (population-level summary): Difference in proportions of responses between each bermekimab group and placebo.

Intercurrent events and their corresponding strategies: The intercurrent events for all key secondary endpoints at Week 16 are the same as those used in the primary estimand specified in section 5.3.2.1.

5.4.2.2.2. Estimands 6-9

The following describes the attributes of the estimands for the key secondary endpoints (Estimands 6-9)

Study intervention:

- Bermekimab 350 mg, 700 mg SC qw through Week 15
- Dupilumab 300 mg SC q2w through Week 14 with dupilumab 600 mg at Week 0
- Placebo SC qw through Week 15

Population: adult participants with moderate to severe AD

Variable: variables (for estimands 6-9) are listed below

Estimand	Variable (Endpoint)

6	Binary response variable, where a responder is defined as participants with EASI-75 response at Week 16 who does not have ICEs 1-3
7	Binary response variable, where a responder is defined as participants with EASI-90 response at Week 16 who does not have ICEs 1-3
8	Binary response variable, where a responder is defined as participant achieving vIGA-AD 0 or 1 and a reduction from baseline of ≥2 points at Week 16 who does not have ICEs 1-3
9	Binary response variable, where a responder is defined as participants with improvement of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 who does not have ICEs 1-3

Summary measure (population-level summary): Difference in proportions of responders between each bermekimab group and dupilumab group.

Intercurrent events and their corresponding strategies: The intercurrent events for all key secondary endpoints at Week 16 are the same as those used in the primary estimand specified in section 5.3.2.1.

5.4.2.3. Analysis Methods

The key secondary efficacy analyses of data will be based on the mFAS. The key secondary analyses are:

Comparison between bermekimab and placebo

- 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 group and the placebo group.
- The proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 will be compared between each of the bermekimab group and the placebo group.
- The proportion of participants who achieve EASI-90 at Week 16 will be compared between each of the bermekimab group and the placebo group.

Estimation of treatment effect between bermekimab and dupilumab

- The difference in the EASI-75 response rate between each of the bermekimab groups and the dupilumab group and the corresponding 80% CIs will be provided at Week 16.
- The difference in the EASI-90 response rate between each of the bermekimab groups and the dupilumab group and the corresponding 80% CIs will be provided at Week 16.

- The difference and 2-sided 80% CIs in the proportion of participants with both vIGA-AD 0 or 1 (on a 5-point scale) and a reduction from baseline of ≥2 points at Week 16 between each of the bermekimab groups and the dupilumab group will be provided.

- The difference and 2-sided 80% CIs in the proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline to Week 16 among participants with a baseline itch value ≥4 between each of the bermekimab groups and the dupilumab group will be provided.

The proportions of participants for the above key secondary efficacy endpoints will be summarized for each intervention group. A CMH chi-square test stratified by baseline EASI severity (less severe [EASI score<28] or more severe [EASI score≥28]) at an alpha level of 0.05 will be used for comparison. In case of rare events, the Fisher's Exact test will be used for treatment comparisons in binary response endpoints. The proportion differences between active intervention groups and placebo and their 2-sided CIs will be provided based on normal approximation with Mantel-Haenszel weights adjusting for baseline EASI severity.

The key secondary endpoints will be analyzed using the estimands described in sections 5.4.2.2. The analysis strategy for ICEs and missing data will be handled in the same manner as the primary estimand for the primary endpoint.

5.5. Exploratory Efficacy Analyses

5.5.1. Definition of Endpoints

5.5.1.1. Eczema Area and Severity Index

The definition of EASI score is described in section 5.3.1.

5.5.1.2. Eczema Skin Pain and Itch Numeric Rating Scale

The definition of NRS score is described in section 5.4.2.1.3

5.5.1.3. Validated Investigator Global Assessment for Atopic Dermatitis

The definition of vIGA-AD is described in section 5.4.2.1.2.

5.5.2. Analysis Methods

Unless otherwise specified, the exploratory efficacy analyses for mFAS outlined in the following sections in general will be carried out for 2 periods:

Analyses through Week 16

The efficacy analyses at Week 16 and through Week 16 will be summarized by randomized intervention group at Week 0.

- Placebo

- bermekimab 350 mg
- bermekimab 700 mg
- dupilumab

Analyses from Week 16 through Week 36

The efficacy analyses from Week 16 through Week 36 will be summarized by following intervention group based on mFAS.

Placebo → bermekimab 700 mg: include participants randomized to placebo at Week 0 and crossed over to receive bermekimab 700 mg at or after Week 16.

Bermekimab 350 mg: include participants randomized to bermekimab 350 mg at Week 0 and continued to receive bermekimab 350 mg at or after Week 16.

Bermekimab 700 mg (non-responders): include participants who were randomized to bermekimab 700 mg at Week 0, were EASI-75 non-responder at week 16 and continued to receive bermekimab 700 mg at or after Week 16.

Bermekimab 700 mg (responders): include participants who were randomized to bermekimab 700 mg at Week 0, were EASI-75 responders at week 16 and were re-randomized to:

- **Bermekimab 700 mg:** participants received bermekimab 700 mg at or after Week 16
- **Bermekimab 350 mg:** participants received bermekimab 350 mg at or after Week 16

Dupilumab: include participants who were randomized to dupilumab at Week 0, were EASI-75 responders at week 16 and continued to receive dupilumab at or after Week 16.

Dupilumab → bermekimab 700 mg include participants who were randomized to dupilumab at Week 0, were EASI-75 non-responders at week 16, and crossed over to receive bermekimab 700 mg at or after Week 16.

5.5.2.1. Analyses for Binary and Continuous Endpoints

This section outlines the definition and analyses of exploratory endpoints. All statistical testing will be performed at the 2-sided 0.05 significance level. Nominal p-values will be presented.

Exploratory efficacy endpoints will be summarized using 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 participant listings may also be used to summarize the data.

Binary Endpoints

For binary response endpoints, treatment comparisons will be performed using 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. The proportion difference between each active 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. Additionally, the proportion difference between each bermekimab group and dupilumab group and corresponding 2-sided 80% CI will be provided.

Unless otherwise specified, the analyses for binary endpoints through Week 16, and from Week 16 through Week 36 will be based on the following strategies to handle ICEs.

> ICEs in categories 1-3 (definitions in Section 5.3.2) will be handled with the composite strategy. Participants experiencing ICEs 1-3 will be considered not to have achieved the binary endpoints.
>
> ICE 4-5 (definitions in Section 5.3.2) will be handled with the treatment policy strategy, which targets the treatment effect regardless of the occurrence of this ICE. For participants experiencing ICEs 4-5, their observed clinical response status will be used.

Participants with any missing data for an endpoint after application of ICE categories 1-5 will be imputed as not achieving the associated binary endpoints.

Continuous Endpoints

For continuous endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model under the assumption of missing at random (MAR) with intervention group, visit, baseline EASI severity (less severe, more severe), baseline value for the efficacy endpoint, treatment by visit, baseline EASI severity by visit and baseline value by visit interaction as explanatory factors, if appropriate. An unrestricted (UN) variance-covariance matrix for repeated measures within a participant will be used unless there are issues related to convergence, where an autoregressive matrix structure will be used instead. In addition, LSmean estimate of treatment differences and their associated 95% confidence intervals will be presented for the analyses through Week 16.

Unless otherwise specified, the analyses for continuous endpoints through Week 16, and from Week 16 through Week 36 will be based on the following strategies to handle ICEs.

> ICEs in categories 1 - 3 (definitions in Section 5.3.2) will be handled with the composite strategy. Participants experiencing ICEs 1-3 will have a zero change (or zero improvement) from baseline assigned from that point onward.
>
> ICE 4-5 (definitions in Section 5.3.2) will be handled with the treatment policy strategy, which targets the treatment effect regardless of the occurrence of this ICE. For participants experiencing ICEs 4-5, their observed clinical response status will be used.

To account for the missing data for continuous endpoints of change (or percent change) from baseline measured at more than one post-baseline visit, a MMRM will be used. In MMRM, missing data will not be imputed, but rather missing data will be accounted for through correlation of repeated measures in the model. For the analyses from W16 through W36, MMRM model will be used only for the treatment comparison between 700 mg and 350 mg among participants who were randomized in 700 mg group at Week 0, were EASI-75 responder at Week 16, and were re-randomized at Week 16. The analyses from Week 16 through Week 36 for other study intervention groups will be based on observed data.

5.5.2.1.1. Analyses Related to EASI

- The improvement from baseline in EASI total score at Week 16 will be compared between each of the active groups and placebo group.

- The percent improvement from baseline in EASI total score at Week 16 will be compared between each of the active groups and placebo group.

- The proportion of participants who achieve EASI-50, EASI-75, EASI-90, and EASI-100 will be summarized over time by intervention group.

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

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

- The proportion of participants who achieve EASI-75 will be summarized by baseline EASI severity and intervention group over time through Week 16.

- The proportion of participants 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 through Week 16 by intervention group.

5.5.2.1.2. Analyses Related to NRS

- The proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline among participants with a baseline itch NRS value ≥4 will be summarized over time by intervention group.

- The proportion of participants with improvement (reduction) of eczema-related pain NRS ≥4 from baseline over time among participants with a baseline pain NRS value ≥4 will be summarized over time by intervention group.

- The improvement from baseline in eczema-related itch NRS will be summarized over time by intervention group.

- The improvement from baseline in eczema-related pain NRS will be summarized over time by intervention group.

5.5.2.1.3. Analyses Related to vIGA-AD

- The proportion of participants who achieve a vIGA-AD score of 0, vIGA-AD score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16, vIGA-AD score of mild or better (≤2) and a reduction from baseline of ≥2 points will be summarized through Week 16 by intervention group.

- The proportion of participants who achieve a vIGA-AD score of 0, vIGA-AD score of 0 or 1 and a reduction from baseline of ≥2 points at Week 16, vIGA-AD score of mild or better (≤2) and a reduction from baseline of ≥2 points will be summarized from Week 16 through Week 36 by intervention group.

5.6. Safety Analyses

All safety analyses will be performed using safety analysis set based on actual intervention received. No formal statistical comparison is planned.

For all continuous safety variables, descriptive statistics by intervention group will include the N, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by intervention group using frequency counts and percentages.

Depending on the safety data, the cumulative safety data will be analyzed through different study periods which include but are not limited to from Week 0 through Week 16, and from Week 0 through Week 36 as appropriate. Unless otherwise specified, tabular summaries of safety events are in general presented as following:

Summaries through Week 16 (placebo controlled)

Safety data through Week 16 will be summarized by following intervention group:

- Placebo
- bermekimab 350 mg
- bermekimab 700 mg
- dupilumab

Summaries through Week 36

Safety data through Week 36 will be summarized by following intervention groups.

- Placebo
- Placebo → Bermekimab 700 mg

- Bermekimab 350 mg
- Bermekimab 700 mg
- Bermekimab 700 mg → Bermekimab 350 mg
- Dupilumab
- Dupilumab → Bermekimab 700 mg

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention (placebo, bermekimab 350 mg, bermekimab 700 mg, and dupilumab) will be summarized. The number and percentage of participants will also be summarized by visit.

Descriptive statistics will be presented by intervention group for the following parameters:

- Number of administrations
- Cumulative total dose
- Duration of study intervention (weeks)

Study intervention duration is defined as (date of last dose of study intervention – date of first dose of study intervention +1)/7.

5.6.2. 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 occurring at or after the initial administration of study intervention is considered to be treatment emergent. If the event occurs on the day of the initial administration of study intervention, 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 to be treatment emergent unless it is known to be prior to the first administration of study intervention based on partial onset date or resolution date. All reported treatment-emergent adverse events will be included in the analysis. For each adverse event, the number and percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group.

Summary tables will be provided for treatment-emergent adverse events:

- AEs
- Serious AEs (SAEs)
- AEs of infections

- AEs leading to discontinuation of study intervention
- AEs of severe intensity
- AEs reasonably related to study intervention
- AEs of injection site reaction

In addition to the summary table, listings will be provided for participants who:

- Had SAEs
- Had AEs leading to discontinuation of study intervention
- Had AEs of severe 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 for each intervention group.

A listing of participants who died will be provided.

5.6.3. Additional Safety Assessments

5.6.3.1. Clinical Laboratory Tests

Clinical laboratory tests will be displayed for the participants included in the safety analysis set.

Descriptive statistics of change from baseline through Week 16 and through Week 36 will be presented for selected chemistry and hematology laboratory tests at scheduled time points.

- **Hematology** will include but are not limited to the following: Basophils, Eosinophils, Hemoglobin, Lymphocytes, Monocytes, Neutrophils, Platelets, WBC, CRP and ESR.
- **Chemistry** will include but are not limited to the following: ALT, AST, Albumin, Alkaline Phosphatase, Calcium, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen.

Applicable laboratory results will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE). The proportion of participants with post-baseline values by maximum toxicity grade for clinical laboratory tests will be summarized by study intervention group. Participants with toxicity grades ≥2 will be listed.

5.6.3.2. Vital Signs

Continuous vital sign parameters including temperature, pulse, blood pressure (systolic and diastolic) and respiratory rate will be summarized. Change from baseline will be summarized through Week 16 and Week 36. Descriptive statistics (mean, standard deviation, median, minimum and maximum) will be presented.

Incidence of treatment-emergent abnormal vital signs during intervention, as defined in Table 4, will be summarized for participants who had a baseline assessment and at least 1 postbaseline assessment for that vital sign.

Table 4: Clinically Important/Markedly Abnormal Vital Signs

Vital Sign	Criteria
Pulse	>[120] bpm and with >[30] bpm increase from baseline
	<[50] bpm and with >[20] bpm decrease from baseline
Systolic blood pressure	>[180] mm Hg and with >[40] mm Hg increase from baseline
	<[90] mm Hg and with >[30] mm Hg decrease from baseline
Diastolic blood pressure	>[105] mm Hg and with >[30] mm Hg increase from baseline
	<[50] mm Hg and with >[20] mm Hg decrease from baseline
Respiratory rate	>[20] breaths per minute

5.6.3.3. Electrocardiogram

The overall interpretation (i.e., normal, abnormal, not evaluable) of the ECGs as determined by investigator will be summarized by the number and percentage of participants at Week 0 and Week 16.

A listing of participants with abnormal ECG interpretation will be provided.

5.7. Other Analyses

5.7.1. Pharmacokinetics

Blood samples will be collected for the measurement of serum bermekimab concentrations and antibodies to bermekimab at the timepoints presented in the Schedules of Activities. Blood samples should also be collected at the final visit or at the Early Termination Visit from participants who are discontinued from intervention or withdrawn from the study. A random venous blood sample for population PK analysis will be collected from all participants on any day between Weeks 2 to 12, except on the days of the scheduled study visits. Additionally, this blood sample

must be collected at least 24 hours prior to or after the actual time of study intervention administration.

PK analyses will be performed on the PK analysis set, defined as participants who have received at least 1 complete dose of bermekimab and have at least 1 valid blood sample drawn for PK analysis. Subjects will be analyzed according to the treatment groups that they actually receive. No imputation for missing concentration data will be performed.

Descriptive statistics (N, mean, SD, median, range, CV (%) and IQ range) will be used to summarize serum bermekimab concentrations at each sampling time point. PK data may be displayed graphically. The following analyses will be performed by treatment group as appropriate:

- Summary of serum bermekimab concentrations at each visit by treatment group
- Proportion of subjects without detectable serum bermekimab concentration at each visit by treatment group
- Summary of serum bermekimab concentrations at each visit by treatment group and baseline body weight (>=median or < median)
- Summary of serum bermekimab concentrations at each visit by treatment group and baseline EASI score categories (EASI <28 or EASI ≥28)
- Plot of median (IQ) serum bermekimab concentrations over time by treatment group
- Plot of median (IQ) serum bermekimab concentrations over time by baseline body weight and treatment group

For summary statistics of serum bermekimab concentrations, concentration values below the lower limit of quantification will be treated as zero. Once a subject meets one of the following dosing deviation criteria, the subject's data will be excluded from the by-visit data analyses from that point onwards.

Dosing deviation criteria:

- Discontinue SC bermekimab administrations.
- Skipped an SC bermekimab administration.
- Received an incomplete/ incorrect SC dose.
- Received an incorrect SC study agent.
- Received an additional SC bermekimab dose.

In addition, if a subject has an administration outside of visit windows (Section 5.1.1), 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.

If sufficient data are available, then population PK analysis using serum bermekimab concentration-time data will be performed using nonlinear mixed-effects modeling. Details will be given in a population PK analysis plan and the results of the analysis will be presented in a separate report.

PK analyses will be summarized through the end of study (Week 36). For the analyses, a subject is included in one and only one treatment group on the basis of the treatment regimen followed. The description of treatment groups are as follows:

- Placebo → Bermekimab 700 mg qw
- Bermekimab 350 mg qw
- Bermekimab 700 mg qw → Bermekimab 350 mg qw (EASI-75 responders)
- Bermekimab 700 mg qw → Bermekimab 700 mg qw (EASI-75 responders)
- Bermekimab 700 mg qw → Bermekimab 700 mg qw (EASI-75 non-responders)
- Combined bermekimab 700 mg qw

5.7.2. Immunogenicity (Antibodies to Bermekimab)

Blood samples will be collected to examine the formation of antibodies 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.

Participants evaluable for immunogenicity are defined as having at least 1 dose (complete or partial) of bermekimab and have at least 1 valid blood sample drawn for antibody detection. The antibodies to bermekimab summary and analysis will be based on the observed data; therefore no imputation of missing data will be performed.

The following analysis of antibodies to bermekimab will be performed by treatment group:

- Summary of incidence of antibody to bermekimab status
- List of subjects positive for antibodies to bermekimab

In addition, to explore the relationship between antibodies to bermekimab status and serum bermekimab concentrations, and safety, the following analysis may be performed as appropriate:

- Summary of injection-site reactions by antibody to bermekimab status

- Summary of serum bermekimab concentrations by antibody to bermekimab status
- Plots of median (IQ) serum bermekimab concentrations over time by antibody to bermekimab status

Immunogenicity analyses will be summarized through the following time periods:

- Through Week 16
- Through End of Study (Week 36)

For the analyses, a subject is included in one treatment group (or combined group) on the basis of the treatment regimen followed. The description of treatment groups are as follows:

- Through Week 16
    1. Bermekimab 350 mg qw
    2. Bermekimab 700 mg qw
    3. Combined (Groups 1/2)
- Through End of Study (Week 36)
    1. Placebo → Bermekimab 700 mg qw
    2. Bermekimab 350 mg qw
    3. Bermekimab 700 mg qw → Bermekimab 350 mg qw (EASI-75 responders)
    4. Bermekimab 700 mg qw → Bermekimab 700 mg qw (EASI-75 responders)
    5. Bermekimab 700 mg qw → Bermekimab 700 mg qw (EASI-75 non-responders)
    6. Bermekimab 700 mg qw combined (Groups 3/4/5)
    7. All Bermekimab combined (Groups 1/2/3/4/5)

5.7.3. Biomarkers

Biomarker analyses will be provided in a separate document.

5.7.4. Definition of Subgroups

To evaluate the consistency of the primary efficacy endpoint EASI-75 at Week 16, subgroup analyses may be performed when the number of participants in the subset permits. The subgroups for subgroup analysis may include, but are not limited to the following:

Table 5 Demographic subgroups

Subgroup	Variant	Definition
Region	1	Define based on UN guidance as per the M49 standard • Asian Pacific • North America • Latin America • Europe
Sex	1	• male • female
Race	1	• American Indian or Alaska Native • Asian • Black or African American • Native Hawaiian or other Pacific Islander • White • Other
Age Group	1	• <40 • 40-64 • >=65
BMI	1	• <25 kg/m^2 • 25-<30 kg/m^2 • >=30 kg/m^2
Body Weight Group	1	• <80 kg • >=80 kg

Table 6 Baseline disease characteristics and AD medication

Subgroup	Variant	Definition
Age at diagnosis (years)	1	• <18 yrs • ≥18 yrs
AD disease duration (years)	1	• < median • ≥ median
Baseline EASI severity	1	• less severe [EASI <28] • more severe [EASI ≥28]
Baseline IGA	1	• 3 • 4
Systemic Corticosteroids		• Never used • Ever used

The primary estimand will be used for these subgroup analyses and missing data rule (Section 5.3.3) used for primary estimand will be applied.

5.8. Interim Analyses

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

5.9. Data Monitoring Committee (DMC) or Other Review Board

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

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AD	Atopic dermatitis
ADIS	Atopic Dermatitis Itch Scale
AE	adverse event
ALT/SGPT	alanine aminotransferase
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
Cmax	maximum concentration
CRF	case report form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DMC	Data Monitoring Committee
DPS	Data Presentation Specifications
eCRF	electronic case report form
FAS	full analysis set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
IQ	interquartile
IWRS	interactive web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
MRD	minimum required dilution
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
POEM	Patient-oriented eczema measure
PP	per protocol
PROMIS	Patient-reported outcomes measurement information system
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TEAE	treatment-emergent adverse event
Tmax	time to maximum concentration
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

N/A

6.3. Appendix 3 Demographics and Baseline Characteristics

The number of participants in each analysis set will be summarized and listed by intervention group, combined active intervention group, and overall. In addition, the distribution of participants by region, country, and site ID will be presented unless otherwise noted.

Table 7 presents a list of the demographic variables that will be summarized by intervention group, combined active intervention group, and overall for the FAS analysis set.

Table 7: 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)	
Body Mass Index (BMI) (kg/m2)	
Body Surface Area (BSA) (m2)	
Categorical Variables	
Age (<40 years, 40-64 years, and >=65 years)	Frequency distribution with the number and percentage of participants in each category.
Sex (male, female)	
Weight (<80 kg, >=80 kg)	
Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White, Multiple)	
Ethnicity (Hispanic or Latino, not Hispanic or Latino)	
BMI ([normal <25 kg/m2, overweight 25-<30 kg/m2, obese >=30 kg/m2])	

[a]If multiple race categories are indicated, the Race is recorded as 'Multiple'

Baseline disease characteristics (e.g., duration of AD disease, EASI score, vIGA-AD, hand dermatitis IGA, GISS, POEM, ADIS, SCORAD score, BSA, NRS pain, NRS Itch, DLQI, PROMIS-29, PGIS) will be summarized by intervention group.

6.4. Appendix 4 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 study. Participants with major protocol deviations will be identified prior to database lock and the participants with major protocol deviations will be summarized by category through Week 16 and through the end of study.

- Developed withdrawal criteria but not withdrawn
- Entered but did not satisfy criteria
- Received a disallowed concomitant treatment
- Received wrong treatment or incorrect dose
- Other

6.5. Appendix 5 Prior and Concomitant Medications

Prior medications are defined as any therapy used before the day of first dose (partial or complete) of study intervention. Previous atopic dermatitis medications/therapy will be summarized by intervention group.

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD). Concomitant medications are defined as any therapy used on or after the same day as the first dose of study intervention, including those that started before and continue on after the first dose of study intervention.

Summaries of concomitant medications will be presented by anatomic and therapeutic class (ATC) term, and intervention group. The proportion of participants who receive each concomitant medication will be summarized as well as the proportion of participants who receive at least 1 concomitant medication.

6.6. Appendix 6 Medical History

Summaries of participants' alcohol intake, and smoking status will be provided by intervention 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 summarized by intervention groups.

6.7. Appendix 7 Intervention Compliance

Compliance to randomized intervention versus actual intervention will be presented in a summary table.

In addition, a listing of participants with missed study intervention administration will be provided.

6.8. Appendix 8 Adverse Events of Special Interest

Not applicable.

6.9. Appendix 9 Medications of Special Interest

Not applicable.

6.10. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE 5.0)'.

If a laboratory value falls within the grading as specified below but also within the local laboratory normal limits, the value is considered to be normal and will be reset to grade 0.

Pre-baseline measurements will use the same grading ranges as applied to baseline measurements. In case a test has two sets of ranges – one for baseline normal and one for baseline abnormal, the one for baseline normal will be applied for all measurements taken pre-baseline and on baseline.

Text in gray italic in the table is present in the grading scale, but is not applied by Janssen when grading lab data.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Blood and lymphatic system disorders					
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hemoglobin (Hgb) <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hemoglobin (Hgb) <8.0 g/dL; <4.9 mmol/L; <80 g/L; *transfusion indicated*	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Leukocytosis	-	-	>100,000/mm3; >100 x 10e9 /L	*Clinical manifestations of leucostasis; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading; Added ranges in SI unit (x 10e9 /L)
Investigations					
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; *bleeding*	-	Clinical signs and symptoms are not taken into consideration for grading.
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal;	>1.5 - 3.0 x ULN if baseline was normal;	>3.0 - 10.0 x ULN if baseline was normal;	>10.0 x ULN if baseline was normal;	Ranges defined for "abnormal baseline" are

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
	> 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x baseline if baseline was abnormal	applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	
Creatinine increased	Creatine Kinase >ULN - 1.5 x ULN	Creatine Kinase >1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	Creatine Kinase >3.0 x baseline; >3.0 - 6.0 x ULN	Creatine Kinase >6.0 x ULN	
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	Ranges defined for "abnormal" are applied only on values < LLN. Grade 0 will be assigned to values > ULN.
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	Ranges defined for "abnormal baseline" are applied only if baseline > ULN. If baseline < LLN, then ranges for "normal baseline" are applied.
Haptoglobin decreased	<LLN	-	-	-	
Hemoglobin increased	Increase in >0 - 2 g/dL; Increase in >0 - 20 g/L	Increase in >2 - 4 g/dL; Increase in >20 - 40 g/L	Increase in >4 g/dL; Increase in >40 g/L	-	The increase indicates the level of increase above normal (above ULN). Applied as, e.g. grade 1 (g/dL): >ULN – ULN+2 g/dL; Added ranges in SI unit (g/L).
INR increased	>1.2 - 1.5; *>1 - 1.5 x baseline if on anticoagulation; monitoring only indicated*	>1.5 - 2.5; *>1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated*	>2.5; *>2.5 x baseline if on anticoagulation; bleeding*	-	Concomitant therapy or clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN with signs or symptoms; *>5.0 x ULN and asymptomatic*	>5.0 x ULN and with signs or symptoms	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3; >4 - 20 x 10e9 /L	>20,000/mm3; >20 x 10e9 /L	-	Added ranges in SI unit (x 10e9 /L).
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	Both Neutrophils and segmented neutrophils are graded using these criteria.
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; *>2.0 - 5.0 x ULN and asymptomatic*	>2.0 - 5.0 x ULN *with signs or symptoms; >5.0 x ULN and asymptomatic*	>5.0 x ULN *and with signs or symptoms*	"Asymptomatic" ranges are not taken into consideration for grading, i.e. worst case grading is applied.
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	
Metabolism and nutrition disorders					
Acidosis	pH <normal, but >=7.3	-	pH <7.3	*Life-threatening consequences*	pH <normal is implemented as pH <LLN. Clinical signs and symptoms are not taken into consideration for grading.
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	*Life-threatening consequences*	pH >normal is implemented as pH >ULN. Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; *symptomatic*	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; *hospitalization indicated*	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyperkalemia	Potassium >ULN - 5.5 mmol/L	Potassium >5.5 - 6.0 mmol/L; *intervention initiated*	Potassium >6.0 - 7.0 mmol/L; *hospitalization indicated*	Potassium >7.0 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypermagnesemia	Magnesium >ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	Magnesium >3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	Magnesium >8.0 mg/dL; >3.30 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypernatremia	Sodium >ULN - 150 mmol/L	Sodium >150 - 155 mmol/L; *intervention initiated*	Sodium >155 - 160 mmol/L; *hospitalization indicated*	Sodium >160 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypertriglyceridemia	Triglycerides 150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	Triglycerides >300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	Triglycerides >500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	Triglycerides >1000 mg/dL; >11.4 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hypoalbuminemia	Albumin <LLN - 3 g/dL; <LLN - 30 g/L	Albumin <3 - 2 g/dL; <30 - 20 g/L	Albumin <2 g/dL; <20 g/L	*Life-threatening consequences; urgent intervention indicated*	Clinical signs and symptoms are not taken into consideration for grading.
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L;	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L;	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L;	Clinical signs and symptoms are not taken into consideration for grading.

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
		symptomatic	*hospitalization indicated*	*life-threatening consequences*	
Hypoglycemia	Glucose <LLN - 55 mg/dL; <LLN - 3.0 mmol/L	Glucose <55 - 40 mg/dL; <3.0 - 2.2 mmol/L	Glucose <40 - 30 mg/dL; <2.2 - 1.7 mmol/L	Glucose <30 mg/dL; <1.7 mmol/L; *life-threatening consequences; seizures*	Clinical signs and symptoms are not taken into consideration for grading. Urine glucose is not graded.
Hypokalemia	*Potassium <LLN - 3.0 mmol/L*	*Symptomatic with* Potassium <LLN - 3.0 mmol/L; intervention indicated	Potassium <3.0 - 2.5 mmol/L; *hospitalization indicated*	Potassium <2.5 mmol/L; *life-threatening consequences*	"Symptomatic" ranges are applied for grade 2, grade 1 not assigned, i.e. worst case applied. Clinical signs and symptoms are not taken into consideration for grading of grade 3 and 4.
Hypomagnesemia	Magnesium <LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	Magnesium <1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	Magnesium <0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	Magnesium <0.7 mg/dL; <0.3 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading.
Hyponatremia	Sodium <LLN - 130 mmol/L	*Sodium 125-129 mmol/L and asymptomatic*	*Sodium 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms* Sodium <130-120 mmol/L	Sodium <120 mmol/L; *life-threatening consequences*	Clinical signs and symptoms are not taken into consideration for grading. Worst case ("<130-120 mmol/L" for grade 3 added by Janssen) is applied across grade 2/3 ranges: 120-129 mol/L assigned to grade 3, grade 2 not used.
Renal and urinary disorders					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs; urinary protein ≥ULN - <1000 mg/day	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs;	**Adult:** 4+ proteinuria; urinary protein >=3.5 g/24 hrs;	-	In case both 24-h urine collection and dipstick are collected, then worst case is taken, as opposed to having 24-h urine

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Janssen implementation notes
		urinary protein 1000 - <3500 mg/day **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9; Urine P/C (Protein/Creatinine) 56.5 – 214.7 g/mol	urinary protein >=3500 mg/day; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9; Urine P/C (Protein/Creatinine) >214.7 g/mol		collection take precedence over dipstick. Added ranges in SI unit for urinary protein (mg/day) and for urine P/C (g/mol). Pediatric grading is applied to age range [0-18]. Adult grading is applied for ages [>18].

* Grade 0 is assigned to a lab assessment when the lab test is described in the table, but the lab value is not assigned a grade 1 or higher.

7. REFERENCES

Simpson EL, Bieber T, Guttman-Yassky E, et al. Two Phase 3 trials of dupilumab versus placebo in atopic dermatitis. N Engl J Med. 2016;375(24):2335-2348.