Janssen Research & Development

Statistical Analysis Plan

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

Protocol 77474462ADM2003; Phase 2a

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		Not Applicable	Initial release

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 20 final database lock (DBL) for the study 77474462ADM2003. Due to early termination of the study by the sponsor with only a small number of participants enrolled, listings will be provided for efficacy and safety data. No formal analyses will be performed.

1.1. Objectives and Endpoints

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

Objectives	Endpoints
	• Proportion of participants with both vIGA-AD of 0 or 1 and a reduction from baseline of ≥2 points • Proportion of participants with improvement (reduction) of eczema-related itch NRS ≥4 from baseline among participants with a baseline itch value ≥4 • Proportion of participants with EASI-90
Exploratory	
To further characterize efficacy of 16 weeks of multiple IV doses of bermekimab, compared with placebo, in participants with moderate-to-severe AD.	• Improvement from baseline to Week 16 in SCORAD • Change from baseline to Week 16 in DLQI • Improvement from baseline to Week 16 in POEM • Improvement from baseline to Week 8 in eczema-related itch NRS • Improvement from baseline to Week 8 in eczema-related pain NRS • Improvement from baseline to Week 16 in eczema-related pain NRS • Improvement from baseline to Week 16 in itch as measured by the ADIS • Proportions of participants with a PGIS score of 1 (none) or 2 (mild) at Week 16 • Change from baseline to Week 16 in PROMIS-29 total score and sub-scores • Improvement in Hand Dermatitis IGA from baseline to Week 16.
To assess the impact of treatment with 16 weeks of multiple IV doses of bermekimab, compared with placebo, on selected biomarkers.	Analyses of the following at all applicable visits from Week 0 through Week 16: • Changes in cellular and molecular PD biomarkers levels in skin and blood from baseline compared with placebo. • Changes in skin barrier function from baseline compared with placebo.

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

1.2. Study Design

This is a Phase 2, double-blind, randomized, placebo-controlled, multicenter, interventional study designed to assess the efficacy, safety, pharmacokinetics (PK), pharmacodynamics (PD), biomarkers, and immunogenicity of multiple doses of bermekimab administered via IV infusion for the treatment of moderate-to-severe AD in adult participants. The participant population will be comprised of men and women ≥18 years of age, with moderate-to-severe AD, that has been present for at least 1 year before the first administration of study intervention, as determined by the investigator through participant interview and/or review of the medical history. Participants must also have a history of inadequate response to treatment for AD with topical medications or for whom topical treatments are otherwise medically inadvisable, an EASI score ≥16, an IGA score ≥3, and an involved percent body surface area (BSA) ≥10% at both screening and at baseline. Participants must agree to apply moisturizers at least once daily for at least 7 days before randomization and continue the treatment throughout the study.

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

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

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

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

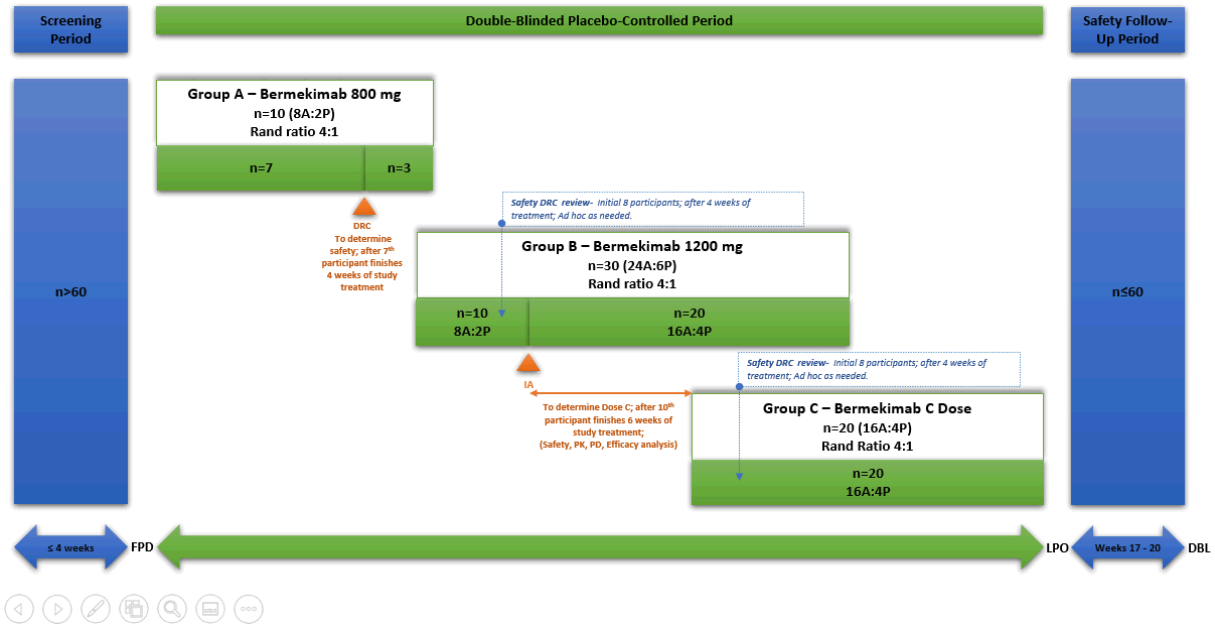
An internal and independent DRC will be commissioned for this study to ensure the safety of the participants enrolled in this study. In addition, an interim analysis will be conducted when the 10th

participant of Part B reaches Week 6. The interim analysis will be used to inform the dose decision for Part C based on the safety, preliminary efficacy, PK and PD data accrued up to the interim analysis.

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

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

Figure 1: Schematic Overview of the Study



2. STATISTICAL HYPOTHESES

The hypothesis for this study is that intravenous (IV) bermekimab treatment is superior to treatment with 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 (800 mg, 1200 mg, or Dose C) and placebo treatment based on the primary efficacy endpoint.

3. SAMPLE SIZE DETERMINATION

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

The EASI-75 response rate in the bermekimab 400 mg qw group was approximately 70% at Week 7 from the open label study (2018-PT044 [NCT03496974]). The EASI-75 response rates

in placebo group at Week 16 were 15% and 12%, in the 2 Phase 3 trials of dupilumab vs placebo in the treatment of adult participants with moderate-to-severe AD (Simpson 2016).

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

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

Table 1: Power to detect a treatment difference in EASI-75 at Week 16*

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

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

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The populations for analysis are defined in Table 2 below.

Table 2: 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.
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.
Safety	The safety analysis set includes all participants who received at least 1 dose of study intervention.

5. STATISTICAL ANALYSES

5.1. General Considerations

The statistical analyses will include all analyses from Week 0 through Week 20 (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 through Week 20 should occur within ± 3 days of the scheduled visit.

5.1.2. Polling Algorithm for Analysis Centers

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

5.1.3. 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

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 yet did not receive study intervention.

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 (erythema, thickness [induration, papulation, edema], [excoriation], and lichenification) 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. In each body region, the area is expressed as 0, 1 (1% to 9%), 2 (10% to 29%), 3 (30% to 49%), 4 (50% to 69%), 5 (70% to 89%), or 6 (90% to 100%).

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-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. Analysis Methods for Primary Endpoint

Due to the early termination of the study, the primary endpoint of EASI-75 response at Week 16 will be listed. No formal analyses will be performed.

5.4. Secondary Endpoints Analysis

5.4.1. Definition of Secondary Endpoints

5.4.1.1. Eczema Area and Severity Index

Details refer to section 5.3.1.

5.4.1.2. 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.

5.4.1.3. 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. Analysis Methods

The following secondary efficacy endpoints will be listed.

- The 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 (reduction) of eczema-related itch NRS ≥4 from baseline to Week 16.
- The proportion of participants with EASI-90 response at Week 16.

5.5. Exploratory Endpoints 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 5.4.1.3

5.5.1.3. Validated Investigator Global Assessment for Atopic Dermatitis

The definition of vIGA-AD is defined in section 5.4.1.2.

5.5.2. Analysis Methods

The following efficacy data from all participants in FAS will be included and listed by study intervention groups from Week 0 through Week 20.

- EASI
- vIGA-AD
- eczema-related NRS

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.

5.6.1. Extent of Exposure

A list of study intervention administration through Week 15 will be provided.

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.

Listings will be provided for treatment-emergent adverse events.

5.6.3. Clinical Laboratory Tests

The clinical laboratory parameters to be evaluated by the central laboratory include but are not limited to:

- **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, Bicarbonate (CO2), Calcium, Chloride, Creatinine, GGT, Glucose, Potassium, SGOT, SGPT, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen.

Participants in the safety analysis set with toxicity grades ≥2 will be listed.

5.6.4. Vital Signs

Participants with markedly abnormal vital signs will be listed.

Table 3: 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
Temperature	>[38]ºC and with >=[1]ºC increase from baseline
Respiratory rate	>[20] breaths per minute

5.7. Other Analyses

5.7.1. Pharmacokinetics and Immunogenicity (Antibodies to Bermekimab)

Due to early termination of the study by the sponsor with a small number of participants enrolled, pharmacokinetics and immunogenicity analyses will not be performed.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1 List of Abbreviations

AD	Atopic dermatitis
ADIS	Atopic Dermatitis Itch Scale
AE	Adverse event
ALT	alanine aminotransferase
AST	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
DRC	Data Review Committee
DPS	Data Presentation Specifications
EASI	Eczema Area and Severity Index
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	interbermekimab web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NRS	Numeric Rating Scale
PD	pharmacodynamic(s)
PGIS	Patient Global Impression of Severity
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
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

Due to early termination of the study with a small number of participants enrolled, only data listings will be provided. No formal analyses will be performed.

6.3. Appendix 3 Demographics and Baseline Characteristics

The demographic (age, weigh, height, BMI, race, sex, and ethnicity) and baseline disease characteristics (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 listed.

6.4. Appendix 4 Protocol Deviations

Major protocol deviations will be listed by following category.

- 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 listed 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.

A listing of concomitant medications will be provided.

6.6. Appendix 6 Medical History

Medical history will be listed by intervention groups.

6.7. Appendix 7 Intervention Compliance

A listing of 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)'.

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.

Participants with toxicity grades ≥2 will be listed.

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.