Janssen Research & Development

Statistical Analysis Plan

A Phase 2b, Multicenter, Randomized, Placebo and Active Comparator-controlled, Double-Blind, Dose-ranging Study to Evaluate the Safety and Efficacy of Bermekimab (JNJ-77474462) for the Treatment of Subjects with Moderate to Severe Hidradenitis Suppurativa.

Protocol JNJ-77474462HDS2001; 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		Not Applicable	Initial release

1. INTRODUCTION

The protocol JNJ-77474462HDS2001 is comprised of 2 parts, Phase 2a (Part 1) and Phase 2b (Part 2). An interim analysis (IA) was performed when 50% participants in Part 1 have completed Week 16 visit. The IA futility criterion was met and the decision was made to terminate the study on October 14, 2022. 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 for Part 1.

1.1. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the clinical efficacy of bermekimab in participants with moderate to severe HS.	• Proportion of participants achieving HiSCR50 at Week 16 in Part 1. • Proportion of participants achieving HiSCR50 at Week 12 in Part 2.
Secondary	
• To evaluate the clinical efficacy of bermekimab in participants with moderate to severe HS.	• Proportion of participants achieving HiSCR75 and HiSCR90 at Week 16 in Part 1, and at Week 12 in Part 2. • Change from baseline in the abscess and inflammatory nodule (AN) count at Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants achieving at least 50%, 75%, 90%, and 100% reduction in total AN count at Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants achieving an AN count of 0/1 and 0/1/2 at Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants achieving complete elimination of abscesses at Week 16 in Part 1, and at Week 12 in Part 2 among those participants with abscesses at baseline. • Change in the number of abscesses from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants achieving complete elimination of draining fistulas at Week 16 in Part 1, and at Week 12 in Part 2 among those participants with draining fistulas at baseline. • Change in number of draining fistulas from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants achieving complete elimination of inflammatory nodules at Week 16 in Part 1, and at Week 12 in Part 2 among those participants with inflammatory nodules at baseline.

Objectives	Endpoints
	• Change in number of inflammatory nodules from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Change of International Hidradenitis Suppurativa Severity Score System (IHS4) score from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants with HS-Investigator's Global Assessment (HS-IGA) score of inactive (0), almost inactive (1), or mild (2) and with at least 2-grade improvement relative to baseline at Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants with HS-IGA score of inactive (0) or almost inactive (1) at Week 16 in Part 1, and at Week 12 in Part 2 among participants with HS-IGA score of moderate (3) or severe (4) at baseline.
• To characterize additional patient-reported outcome efficacy measures of bermekimab in participants with moderate to severe HS.	• Change in Dermatology Life Quality Index (DLQI) score from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Change in Hidradenitis Suppurativa Symptom Diary (HSSD-24h) score from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Change in pain scale score of HSSD-24h from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Change in itch scale score of HSSD-24h from baseline to Week 16 in Part 1, and at Week 12 in Part 2.
• To assess the safety and tolerability of bermekimab in participants with moderate to severe HS.	• Number/proportion of participants with treatment-emergent adverse events (TEAEs). • Number/proportion of participants with treatment-emergent serious adverse events (SAEs). • Number/proportion of participants with abnormal safety laboratory values.
• To evaluate the pharmacokinetics (PK) and immunogenicity of bermekimab in participants with moderate to severe HS.	• Bermekimab concentration will be summarized for treated participants over time. • The incidence of antibodies to bermekimab will be summarized.
Exploratory	
• To evaluate the clinical efficacy of bermekimab in participants with moderate to severe HS.	• Change of Hidradenitis Suppurativa Area and Severity Index (HASI) score from baseline to Week 16 in Part 1, and at Week 12 in Part 2. • Proportion of participants achieving HiSCR50, HiSCR75, and HiSCR90 over time.

Objectives	Endpoints
	• Change from baseline in AN count over time. • Proportion of participants achieving at least 50%, 75%, 90%, and 100% reduction in total AN count over time. • Change in the number of abscesses, draining fistulas, and inflammatory nodules from baseline over time. • Change of HASI score from baseline over time. • Change of IHS4 score from baseline over time. • Proportion of participants with HS-IGA score of inactive (0), almost inactive (1), or mild (2) and with at least 2-grade improvement relative to baseline over time. • Proportion of participants with HS-IGA score of inactive (0) or almost inactive (1) over time among participants with HS-IGA score of moderate (3) or severe (4) at baseline. • Change in high-sensitivity C-reactive protein (hs-CRP) from baseline to Week 16 in Part 1 and from baseline to Week 12 in Part 2.
• To characterize additional patient-reported outcome efficacy measures of bermekimab in participants with moderate to severe HS.	• Change in DLQI score from baseline over time. • Change in Hidradenitis Suppurativa Symptom Diary (HSSD-24h) score from baseline over time. • Change in pain scale score of HSSD-24h from baseline over time. • Change in itch scale score of HSSD-24h from baseline over time. • The distribution of the Patient Global Impression of Change (PGIC) of HS at Week 16 in Part 1, and at Week 12 in Part 2. • The distribution of the Patient Global Impression of Severity (PGIS) of HS at Week 16 in Part 1, and at Week 12 in Part 2. • Change in PROMIS 29 total score and sub-scores from baseline to Week 16 in Part 1, and at Week 12 in Part 2 and over time. • Change in Hidradenitis Suppurativa Symptom Diary (HSSD-7d) score from baseline over time.
• 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, Phase 2a/2b, multicenter study to assess the efficacy, safety, PK, and immunogenicity of subcutaneous (SC) administered bermekimab for the treatment of moderate to severe HS in adult participants. The participant population will comprise men and women who have had moderate to severe HS for at least 1 year and are Hurley Stage II or Hurley Stage III as determined by the investigator.

This study employs a Phase 2a/2b design, in which the decision to proceed to the Phase 2b portion of the study will depend on the results of the interim analyses.

Enrollment of this Phase 2a/Phase 2b design study will be divided in 2 parts. Part 1 will enroll approximately 150 participants, and Part 2 will enroll approximately 100 or 150 additional participants, depending on the number of dose regimens to be studied. Enrollment of Part 2 of the study will only begin after a positive benefit risk assessment is confirmed either at Interim Analysis 1 or Interim Analysis 2. Therefore, a total number of approximately 250 or 300 participants will be enrolled in the study.

Part 1 of this study contains 4 study periods: Screening (Period 1), 16-week placebo-controlled period (Period 2), 16-week cross over period (Period 3), and 4-week safety follow up (Period 4). Part 2 of this study also contains 4 study periods: Screening (Period 1), 12-week placebo-controlled period (Period 2), 20-week cross over period (Period 3), and 4-week safety follow up (Period 4).

During Study Period 3 (Weeks 16 to 32 in Part 1 and Weeks 12 to 32 in Part 2), the participants receiving placebo will crossover to receive bermekimab 1050 mg at Week 16 in Part 1 and Week 12 in Part 2 and weekly thereafter through Week 31. Participants receiving bermekimab will continue to receive their assigned treatment through Week 31.

All participants who complete Week 31 of the study will enter safety follow-up (Week 31 through Week 36). The total duration of study participation will be approximately 42 weeks.

During Part 1 of the study, 150 participants will be randomized to receive bermekimab 1050 mg, adalimumab, or placebo in a 1:1:1 ratio. Two interim analyses are planned. The first interim analysis will occur after approximately 50% of participants complete 16 weeks of treatment. The second interim analysis will occur when 100% (n=150) of the participants complete 16 weeks of treatment. The goal of the interim analyses is to assess efficacy and safety of bermekimab at the dose evaluated prior to enrollment of Part 2 of this study.

An internal Interim Analysis Committee (IAC) composed of members that are not involved with the study conduct will be established to review the interim data and recommend actions to the study team in accordance with the objectives of the interim analyses.

If a positive benefit-risk is observed in either the first or the second planned interim analysis based on data in Part 1, screening and randomization of participants will resume as planned in Part 2 of the study, with additional participants being randomized to receive placebo, bermekimab 1050 mg qw, bermekimab 1050 mg qw through Week 11 and from Week 12, bermekimab 1050 mg q2w

(bermekimab 1050 mg qw→q2w) or bermekimab 700 mg qw through Week 11 and from Week 12, bermekimab 700 mg q2w (bermekimab 700 mg qw→q2w), in a 1:1:2:2 ratio (approximately 25 participants randomized to receive bermekimab 1050 mg qw and placebo, respectively, and approximately 50 participants randomized to receive bermekimab 1050 mg qw→q2w and bermekimab 700 mg qw→q2w, respectively). Based on the interim analysis result, the bermekimab 700 mg qw→q2w arm may not be included in Part 2. Thus, Part 2 will enroll approximately 100 or 150 participants, depending on the number of dose regimens to be studied.

If the results from interim analysis 1 meet the futility criteria, the totality of the data including other efficacy analyses provided for the first interim analysis will be reviewed before the decision is made on whether to terminate the trial for futility. If futility criteria are met following the Interim Analysis 2, enrollment will remain paused while the sponsor considers whether to terminate the study at that point for insufficient efficacy, to resume enrollment as planned, or to resume the study with modification.

In addition to the 2 interim analyses described above (database lock [DBL] is planned at the Interim Analysis 2 for Part 1), 2 planned DBLs will occur at Week 12 and at Week 36.

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

Efficacy assessments (Hidradenitis Suppurativa Investigator's Global Assessment [HS-IGA], lesion counts, Hurley Staging, Hidradenitis Suppurativa Symptom Diary [HSSD], Dermatological Life Quality Index [DLQI], Patient Global Impression of Change [PGIC] of Hidradenitis Suppurativa Severity, Hidradenitis Suppurativa Area and Severity Index (HASI), and Patient Global Impression of Severity [PGIS]) and Patient-Reported Outcomes Measurement Information System-29 [PROMIS-29] will be performed at visits according to the SoA. Serum samples for PK, immunogenicity and biomarker analyses will be collected at the timepoints in the SoA of the protocol.

An external independent Data Monitoring Committee (iDMC), whose members are not directly involved in the conduct of Study 77474462HDS2001, will review unblinded safety data to ensure the safety of the participants enrolled in this study. A prespecified look at safety will be implemented after a minimum of 12 participants have received 4 weekly doses. Furthermore, the iDMC will review the unblinded safety data at the time of the interim analysis and will be kept informed of any IA results impacting the benefit-risk considerations for the study.

INTERVENTION GROUPS AND DURATION

Part 1:

Group 1: Placebo

Participants will receive 4 placebo SC injections at Week 0. Participants will receive 3 placebo SC injections at Week 1 and every week thereafter through Week 15.

At Week 16, participants will cross over to receive 3 bermekimab 350 mg SC injections weekly through Week 31.

Group 2: Adalimumab

Participants will receive 4 adalimumab 40 mg SC injections at Week 0. Participants will receive 3 placebo SC injections at Week 1. Participants will receive 2 adalimumab 40 mg SC injections and 1 placebo SC injection at Week 2. Participants will receive 3 placebo SC injections at Week 3. Participants will receive 1 adalimumab 40 mg SC injection and 2 placebo SC injections at Week 4 and every week thereafter through Week 31.

Group 3: Bermekimab 1050 mg SC qw

Participants will receive 3 bermekimab 350 mg SC injections and 1 placebo SC injection at Week 0. Participants will receive 3 bermekimab 350 mg SC injections at Week 1 and every week thereafter through Week 31.

Part 2:

Group 1: Placebo

Participants will receive 3 placebo SC injections from Week 0 through Week 11. At Week 12, participants will cross over to receive 3 bermekimab 350 mg SC injections weekly through Week 31.

Group 2: Bermekimab 1050 mg SC qw

Participants will receive 3 bermekimab 350 mg SC injections at Week 0 and every week thereafter through Week 31.

Group 3: Bermekimab 1050 mg SC qw→q2w

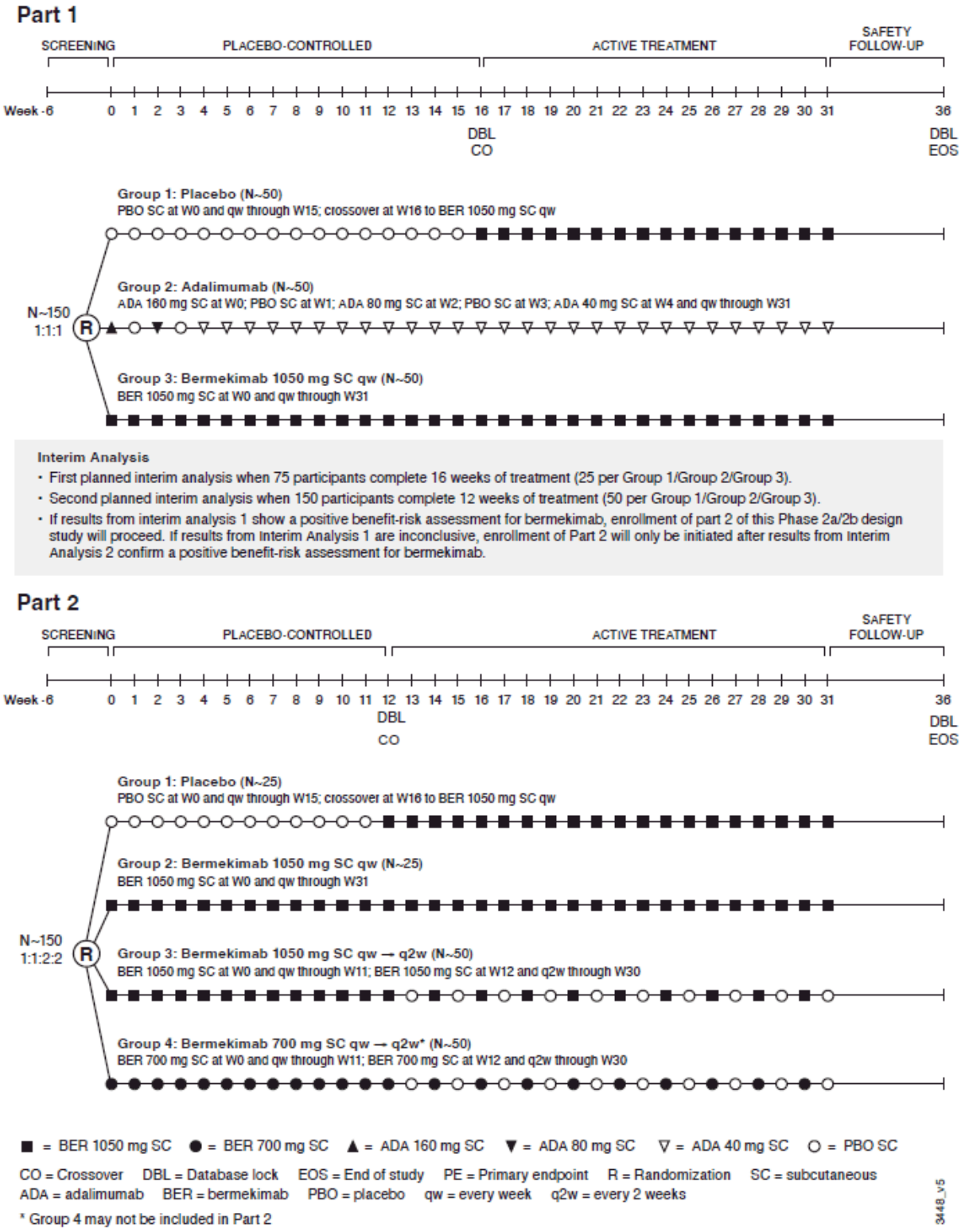
Participants will receive 3 bermekimab 350 mg SC injections at Week 0 and every week thereafter through Week 11. From Week 12, participants will receive 3 bermekimab 350 mg SC injections every other week thereafter through Week 30. During weeks in which bermekimab is not administered, participants will receive 3 placebo SC injections through Week 31.

Group 4: Bermekimab 700 mg SC qw→q2w

Participants will receive 2 bermekimab 350 mg SC injections and 1 placebo SC injection at Week 0 and every week thereafter through Week 11. From Week 12, participants will receive 2 bermekimab 350 mg SC and 1 placebo SC injection every other week thereafter through Week 30. During weeks in which bermekimab is not administered, participants will receive 3 placebo SC injections through Week 31.

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

Figure 1: Schematic Overview of the Study



2. STATISTICAL HYPOTHESES

The primary hypothesis of this study is that bermekimab is superior to placebo as assessed by the proportion of participants achieving Hidradenitis Suppurativa Clinical Response (HiSCR50) at Week 16 in Part 1 subjects with moderately to severely Hidradenitis Suppurativa disease.

- HiSCR50 is defined as at least 50% reduction in total abscess and inflammatory nodule counts (AN count) with no increase in abscess count and no increase in draining fistula count relative to baseline.

The null hypothesis to be tested is that there is no difference between the bermekimab and the placebo in proportion of participants achieving HiSCR50 at Week 16 in Part 1 subjects with moderately to severely Hidradenitis Suppurativa disease.

3. SAMPLE SIZE DETERMINATION

This study is designed to enroll approximately 250 or 300 participants, in order to provide sufficient data to have adequate power for the primary endpoint.

The sample size of 250 or 300 participants was also chosen 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 HiSCR50 at Week 16 between the bermekimab treatment group and the placebo group in Part 1 and at Week 12 between bermekimab treatment groups and placebo group combining Part 1 and Part 2.
- Have an adequate confidence level for the treatment difference between the bermekimab high dose group and the adalimumab group in HiSCR50 at Week 16 in Part 1.
- Provide greater precision for the interim analysis efficacy analysis with more participants in the bermekimab 1050 mg, adalimumab, and placebo groups.

The assumptions for the sample size and power calculations specified below were mainly based on the clinical data from the 77474462HDS2002 (PT-047) Phase 2 clinical study and from 2 adalimumab (Humira) Phase 3 clinical studies M11-313 (PIONEER I) and M11-810 (PIONEER II) that evaluated the safety and efficacy of adalimumab in the treatment of adult participants with moderate to severe HS.

The response rates observed in the 77474462HDS2002 (PT-047) study for HiSCR50 at Week 12/Week 16 were 55%/57% (bermekimab qw group), 44%/52% (bermekimab q2w group), and 44%/44% (placebo group), respectively. In addition, the HiSCR50 response rates in the adalimumab Phase 3 Studies M11-313 and M11-810 at Week 12 were 42% vs 26% and 59% vs 28% in the adalimumab weekly and placebo groups, respectively.

Comparisons between treatment groups at Week 16 with Part 1 data (all comparisons are at a 2-sided type 1 error rate of 0.10; Table 1 and Table 2)

- For comparison between bermekimab with placebo using data from Part 1 only for the primary endpoint at Week 16, the study sample size provides 83% power to detect a 25% treatment difference (50% vs 25%) with 50 participants per arm.
- Greater than 99% power to detect a 40% (75% vs 35%) difference between the bermekimab 1050 mg treatment group (n=50) and the placebo group (n=50).
- From comparison between adalimumab with placebo using data from part 1 only for the primary endpoint, the study sample size provides 83% power to detect a 25% (50% vs 25%) treatment difference with 50 participants per arm.

No formal comparisons will be performed between the bermekimab 1050 mg qw group and the adalimumab group from Part 1, however the treatment difference and its 2-sided 80% CI for the primary endpoint at Week 16 between these 2 groups will be provided. A sample size of 50 participants in each of the treatment groups will produce a 2-sided 80% CI for the treatment difference with a width of approximately 29%.

Comparisons between treatment groups at Week 12 with combining Part 1 and Part 2 data

Assuming HiSCR50 response rates at Week 12 are 25% to 35% for placebo and 50% to 75% for the bermekimab groups, respectively; based on these assumptions, approximately 250 participants across Part 1 and Part 2 are planned to be randomized to the placebo (n=75), bermekimab 700 mg qw to q2w (n=50), bermekimab 1050 mg qw to q2w (n=50), and bermekimab 1050 mg qw (n=75) treatment groups. Comparisons between the bermekimab groups and the placebo groups will be based on data combining Part 1 and Part 2.

For comparisons between bermekimab groups with placebo combining Part 1 and Part 2 for the primary endpoint, bermekimab 1050 mg qw and 1050 mg qw → q2w groups will be grouped together as bermekimab 1050 mg group (n=125) and 700 mg qw → q2w group will be denoted as bermekimab 700 mg group, the study sample size provides:

- At least 87% power to detect a 25% treatment difference between the bermekimab 700 mg treatment group (n=50) and the placebo group (n=75).
- 97% power to detect a 25% (50% vs 25%) treatment difference between the bermekimab 1050 mg treatment group (n=125) and the placebo group (n=75).
- Greater than 99% power to detect a 40% (75% vs 35%) difference between the bermekimab 1050 mg treatment group (n=125) and the placebo group (n=75) or between 700 mg treatment group (n=50) and the placebo group (n=75).

in HiSCR50 at Week 12 combining Part 1 and Part 2 based on a 2-sample Z-test at a Type I error rate of 0.10 (2-sided; Table 3).

Table 1: Power to detect a treatment difference in HiSCR50 at Week 16 in Part 1

Placebo	Treatment Group	Difference	Power
Bermekimab 1050 mg (n=50)/Adalimumab (n=50) vs placebo (n=50)			
25%	50%	25%	83%
25%	55%	30%	93%
25%	60%	35%	97%
25%	65%	40%	99%
25%	70%	45%	>99%
25%	75%	50%	>99%
30%	55%	25%	81%
30%	60%	30%	92%
30%	65%	35%	97%
30%	70%	40%	99%
30%	75%	45%	>99%
35%	60%	25%	81%
35%	65%	30%	92%
35%	70%	35%	97%
35%	75%	40%	99%

Table 2: Confidence interval for the treatment difference in HiSCR at Week 16 in Part 1

HiSCR (P1)	HiSCR (P2)	Difference (P1 − P2)	Width	Confidence Limit	Confidence Level
Bermekimab 1050 mg qw dose regimen (n=50; P1) vs adalimumab (n=50; P2)					
60%	50%	10%	29.3%	(-4.7%,24.6%)	80%
65%	50%	15%	29.0%	(0.5%,29.5%)	80%
70%	50%	20%	28.6%	(5.7%,34.3%)	80%
75%	50%	25%	27.9%	(11.0%, 38.9%)	80%

Table 3: Power to detect a treatment difference in HiSCR50 at Week 12 Combining Part 1 and Part 2

Placebo	Treatment Group	Difference	Power
Bermekimab 1050 mg (n=125) vs placebo (n=75)			
25%	50%	25%	97%
25%	55%	30%	>99%
25%	60%	35%	>99%
25%	65%	40%	>99%
25%	70%	45%	>99%
25%	75%	50%	>99%
30%	55%	25%	97%
30%	60%	30%	99%
30%	65%	35%	>99%
30%	70%	40%	>99%
30%	75%	45%	>99%
35%	60%	25%	96%
35%	65%	30%	99%
35%	70%	35%	>99%
35%	75%	40%	>99%
Bermekimab 700 mg (n=50) vs placebo (n=75)			
25%	50%	25%	89%
25%	55%	30%	96%
25%	60%	35%	99%
25%	65%	40%	>99%
25%	70%	45%	>99%
25%	75%	50%	>99%
30%	55%	25%	87%
30%	60%	30%	95%
30%	65%	35%	99%
30%	70%	40%	>99%
30%	75%	45%	>99%
35%	60%	25%	87%
35%	65%	30%	95%
35%	70%	35%	99%
35%	75%	40%	>99%

4. POPULATIONS (ANALYSIS SETS) FOR ANALYSIS

The populations for analysis are defined in Table 4 below.

Table 4 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.
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 14 October 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 data available through the end of the study. Unless otherwise specified, data from all investigational centers/sites will be pooled for analysis.

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 32 should occur within ± 3 days of the scheduled visit.

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 participants screened, and the number of participants screen failed will be summarized for all enrolled participants.

The number of participants in the following disposition categories will be summarized throughout the study by intervention group and overall based on Full 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 yet 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 participants achieve a HiSCR50 at Week 16 in Part 1. HiSCR50 is defined as a ≥ 50% reduction in inflammatory lesion AN count (sum of

abscesses and inflammatory nodules), and no increase in abscesses and draining fistulas in HS compared with the lesions counted at baseline.

5.3.2. Estimand

An estimand is a precise definition of the primary targeted treatment effect defined by the following 5 attributes: Study Intervention, population, variable (endpoint), intercurrent events (ICEs) and corresponding strategies, and population-level summary.

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

Estimand Scientific Question of interest: What is the proportion of participants considered to have benefited from bermekimab versus placebo assessed by the HiSCR50 at Week 16 in Part 1, administered together with the protocol allowed background standard-of-care medication.

5.3.2.1. Primary Estimand (Composite Estimand)

- **Study intervention:**
  - Bermekimab 1050 mg
  - Placebo
- **Population:** adult participants with moderate to severe HS
- **Variable/endpoint:** Response binary variable, where a responder is defined as a participant achieving an HiSCR50 response at Week 16 in Part 1 without experiencing any of the ICEs in categories 1-2 as outlined below prior to the Week 16 visit.

Intercurrent Events (ICEs)	Analysis Strategy for Intercurrent Events
1. Discontinuation of study intervention due to lack of efficacy, an AE of worsening of HS 2. Initiation of a protocol-prohibited medication or therapy during the study that could improve H S	**Composite Strategy:** Participants with these intercurrent event are considered as HiSCR50 non-responders after these events, and prior to Week 16, as reflected in variable definition.
3. Discontinuation of study intervention for reasons other than ICE 1	**Treatment Policy:** observed data will be used regardless of whether or not this intercurrent event had occurred.

Note: For participants experiencing multiple ICEs, ICE 2 will override ICE 3.

The composite strategy assesses the treatment effects not only based on the variable measurements, but also based on ICEs. This estimand acknowledges that having an ICE in categories 1-2 is an unfavorable outcome. For participants experiencing an ICE in category 3, the treatment policy

strategy considers the occurrence of ICE 3 irrelevant in defining the treatment effect, and any data observed after the associated ICE event will be used for the analysis.

Population level summary: Difference in the proportions of participants achieving an HiSCR50 response at Week 16 between the bermekimab 1050 mg and placebo intervention groups.

5.3.2.2. Supplementary Estimand (Treatment Policy Estimand):

The supplementary estimand has the same components as the primary estimand, except for the strategy used below 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 data collected after ICEs will be used in analysis.

5.3.3. Analysis Methods for the Primary Estimand

The primary endpoints will be analyzed based on the composite estimand (Section 5.3.2.1) and the data from all participants in mFAS (Section 4.4) will be analyzed according to randomized treatment 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 1-2 before Week 16 will be considered as HiSCR50 non-responders at Week 16. Participants with ICE 3, observed lesion data after this ICE will be utilized in the analysis. For participants experiencing multiple ICEs, an ICE 2 will override an ICE 3. After accounting for the ICEs for the primary estimand, the remaining missing data of the primary endpoint at Week 16 will be considered as a non-responder.

In this primary analysis, the proportion of participants who achieve a HiSCR50 at Week 16 will be summarized for each treatment group. To address the primary objective, a CMH chi-squared statistic stratified by baseline Hurley stage status (II, III) at an alpha level of 0.1 will be used for each of the comparisons between bermekimab treatment groups and placebo group. The comparison between adalimumab and placebo for the primary endpoints will also be performed. Difference in response rates between each of the active groups and the placebo group adjusted for baseline Hurley stage status (II, III) using Mantel-Haenszel weight and the corresponding 90% CI will be presented.

In addition, the proportion of participants achieving a HiSCR50 response at Week 16 by investigator regions and site will be summarized.

5.3.4. Analysis for Supplementary Estimand (Treatment Policy Estimand)

To examine the robustness of the primary endpoint analysis, the primary endpoint will be analyzed utilizing the treatment policy estimand. For participants who experience an intercurrent event, the analysis will be performed using observed data regardless of intercurrent events. The HiSCR50 values collected after intercurrent event will be used in analysis and missing data will not be imputed.

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 0.1 significance level. Nominal p-values will be presented.

5.4.2. Definition of Secondary Endpoints

5.4.2.1. Hidradenitis Suppurativa Clinical Response (HiSCR)

- HiSCR75 is defined as a ≥ 75% reduction in inflammatory lesion AN count (sum of abscesses and inflammatory nodules) from baseline and no increase in abscesses or draining fistulas in HS compared with the lesions counted at baseline.
- HiSCR90 is defined as a ≥ 90% reduction in inflammatory lesion AN count (sum of abscesses and inflammatory nodules) from baseline and no increase in abscesses or draining fistulas in HS compared with the lesions counted at baseline.

Please also refer to Section **Error! Reference source not found.** for the definition of the HiSCR50 responder status.

5.4.2.2. Lesion Count

Lesion counts are defined as the number of abscesses, inflammatory nodules, non-inflammatory nodules, draining fistulas, and non-draining fistulas respectively. Lesions will be counted during each visit. AN count is defined as total abscess and inflammatory nodule count.

5.4.2.3. International Hidradenitis Suppurativa Severity Score System (IHS4)

IHS4 is a dynamic severity assessment of HS. IHS4 score is arrived at by the number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4-10 signifies moderate and 11 or higher signifies severe disease.

5.4.2.4. Hidradenitis Suppurativa Investigator's Global Assessment

The HS-IGA documents the investigator's assessment of the participant's HS at a given timepoint. The anatomic region with the most severe HS activity at the baseline visit should be evaluated for erythema, drainage, and pain and/or tenderness to palpation for each participant. For each participant, the same anatomic site selected for evaluation at the baseline visit should be re-evaluated at each subsequent visit. The participant's HS is assessed as inactive (0), almost inactive (1), mild activity (2), moderate activity (3), or severe activity (4). A higher score indicates more severe disease.

5.4.2.5. Hidradenitis Suppurativa Symptom Diary (HSSD)

The HSSD is an 8-item patient self-reported questionnaire that assesses symptoms (including pain, tenderness, pressure, itch, heat, and odor) and signs (including swelling and drainage) of HS. The participants are asked to rate the severity of each symptom on a 0 to 10 numerical rating scale, with 0 indicating no symptom experience and 10 indicating the worst possible symptom

experience. Two versions are available: one with a 24-hour recall (HSSD-24h) and one with a 7-day recall (HSSD-7d). Each individual symptom (including pain and itch) and sign scale score, ranging from 0-10, will be summarized. A total symptom score will be derived by averaging the 6 individual symptom scale scores. A total sign score will be derived by averaging the 2 individual sign scale scores. An overall total score will be derived by averaging all 8 individual items. The last item included in the HSSD is an optional item for patients to assess systemic symptoms of HS (flu-like symptoms). It will be assessed as a separate item and not included in HSSD overall total score. The psychometric properties of the HSSD will be evaluated for scale validation using the data from this study.

For the HSSD-24h rating scale, each component will be averaged into a weekly score respectively (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. The baseline is defined as the average score of last 7 days prior to Week 0 study agent administration. Similarly, if there are more than 3 days missing data, then baseline is set as missing. Missing baseline will not be imputed.

5.4.3. Estimands for Secondary Endpoints

The secondary endpoints will be analyzed using the same attributes as the primary estimand described in section 5.3.2.1 except for the Variable (Endpoint) definition. The estimands for secondary endpoints will be considered for both binary and continuous secondary endpoints.

- **Study intervention:**
  - Bermekimab 1050 mg
  - Placebo
- **Population:** adult participants with moderate to severe HS
- **Population level summary:** Difference in the proportions of participants achieving a binary response, or difference in change from baseline of a continuous endpoint at Week 16 between the bermekimab 1050 mg and placebo intervention groups.
- **Variable/endpoint:** variables defined as below, without experiencing any of the ICEs in categories 1-2 prior to the Week 16 visit.

BINARY ENDPOINTS

Variable (endpoint): Binary response variable (response/non-response) with response defined as follows at Week 16.

- The proportion of participants who achieved HiSCR75 and HiSCR90
- The proportion of participants with HS-IGA score of inactive (0), almost inactive (1), or mild (2) and with at least 2-grade improvement relative to baseline

CONTINUOUS ENDPOINTS

Variable (endpoint): Continuous variables of change from baseline at Week 16 as defined below.

- The change from baseline in AN count
- The change from baseline in number of abscesses
- The change from baseline in number of draining fistulas
- The change from baseline in number of inflammatory nodules
- The change from baseline in international hidradenitis suppurativa severity score (IHS4)
- The change from baseline in pain scale score of HSSD-24h

Intercurrent Events (ICEs)	Analysis Strategy for Intercurrent Events
1. Discontinuation of study intervention due to lack of efficacy, an AE of worsening of HS 2. Initiation of a protocol-prohibited medication or therapy during the study that could improve H S	**Composite Strategy:** Participants with these intercurrent event are considered as non-responders for binary endpoints and zero change from baseline for continuous endpoints after these events, as reflected in variable definition.
3. Discontinuation of study intervention for reasons other than ICE 1	**Treatment Policy:** observed data will be used regardless of whether or not this intercurrent event had occurred.

Note: For participants experiencing multiple ICEs, ICE 2 will override ICE 3.

5.4.4. Analysis Methods for Secondary Endpoints

The secondary endpoints at Week 16 will be analyzed using the estimand described in section 5.4.3 for mFAS. The endpoints will be summarized by intervention group. Simple descriptive statistics, such as n, mean, SD, median, IQ range, minimum and maximum for continuous variables and counts and percentages for discrete variables will be used to summarize the data.

Binary Endpoints

- The proportion of participants who achieved HiSCR75 and HiSCR90 at Week 16 in Part 1 will be compared between the bermekimab groups and the placebo group.
- The proportion of participants with HS-IGA score of inactive (0), almost inactive (1), or mild (2) and with at least 2-grade improvement relative to baseline at Week 16 in Part 1 will be compared between the bermekimab groups and the placebo group.

The analysis strategy for ICEs and missing data for binary endpoints will be handled in the same manner as the primary estimand for the primary analysis. The Cochran-Mantel-Haenszel chi-square statistic stratified by baseline Hurley stage status (II, III) at a 2-sided significance level of 0.1 will be used. Difference in response rates between each of the active and placebo groups at Week 16 adjusted for baseline Hurley stage status (II, III) using Mantel-Haenszel weight and the corresponding 90% CI will be presented.

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 treatment groups and placebo and the exact confidence intervals will be provided.

Continues Endpoints

- The change from baseline in AN count at Week 16 in Part 1 will be compared between the bermekimab groups and the placebo group.
- The change from baseline in number of abscesses at Week 16 in Part 1 will be compared between the bermekimab groups and the placebo group.
- The change from baseline in number of draining fistulas at Week 16 in Part 1will be compared between the bermekimab groups and the placebo group.
- The change from baseline in international hidradenitis suppurativa severity score (IHS4) at Week 16 in Part 1will be compared between the bermekimab groups and the placebo group.
- The change from baseline in number of inflammatory nodules at Week 16 in Part 1 will be compared between the bermekimab groups and the placebo group.
- The change from baseline in pain scale score of HSSD-24h at Week 16 in Part 1 will be compared between the bermekimab groups and the placebo group.

Unless otherwise specified, the analyses for continuous secondary endpoints at Week 16 will be based on the following strategies to handle ICEs and missing data.

- Participants experiencing ICEs 1-2 will have a zero change from baseline assigned from that point onward.

- The analysis for participants with ICE3 will be performed using observed data regardless of intercurrent events. For participants experiencing multiple ICEs, an ICE in categories 2 will override an ICE in category 3.

- Missing data will not be imputed after applying the rules for intercurrent events, and missing data will be accounted for through correlation of repeated measures in the Mixed-Effect Model Repeated Measure (MMRM) model.

Treatment comparisons for the secondary continuous endpoints at Week 16 will be performed using a MMRM model under the assumption of missing at random (MAR) with intervention group, visit, baseline Hurley stage status (II, III), baseline value for the efficacy endpoint, treatment by visit, baseline Hurley stage 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. If the model with unstructured covariance structure does not converge, alternative covariance structures will be tried in the following order, with the first structure that converges being used in the analysis: heterogeneous Toeplitz, standard Toeplitz, and autoregressive of order 1.

5.5. Exploratory Endpoints

In addition to the primary and secondary efficacy endpoints, the analyses for exploratory efficacy endpoints will be performed.

- HiSCR
- Lesion Count
- HS-IGA
- IHS4
- HASI
- HSSD pain

5.5.1. Endpoint Definitions

5.5.1.1. Hidradenitis Suppurativa Clinical Response (HiSCR)

Please also refer to Section 5.4.2.1 for the definition of the HiSCR50, HiSCR75, and HiSCR90 responder status.

5.5.1.2. Lesion Counts

Details refer to Section 5.4.2.2for the definition of the lesion counts.

5.5.1.3. International Hidradenitis Suppurativa Severity Score System (IHS4)

Details refer to Section 5.4.2.3.

5.5.1.4. Hidradenitis Suppurativa Investigator's Global Assessment (HS-IGA)

Details refer to Section 5.4.2.4.

5.5.1.5. Hidradenitis Suppurativa Symptom Diary (HSSD)

Details refer to Section 5.4.2.5.

5.5.1.6. Hidradenitis Suppurativa Activity and Severity Index (HASI)

The HASI is a clinician reported outcomes tool that assesses HS severity by incorporating signs of inflammation and surface area involved. The HASI includes 4 domains to assess the severity of HS disease activity: inflammatory color change, inflammatory induration, open skin surface. and extent of tunnels. Each of these variables is scored on a Likert Scale from 0 to 3 (0=none; 1=limited/mild, 2=moderate, 3=severe/extensive) based on the average intensity for each body site. A higher score indicates more severe disease. See Section 10.10 of the JNJ-77474462HDS2001 protocol, Appendix 10 for more details. The HASI score was the total for all body sites and ranged from 0 to 720, with higher scores indicating more severe disease activity.

5.5.2. Analysis Methods

The efficacy data from all participants in mFAS will be included and analyzed by study intervention groups from Week 0 through Week 36. The analysis strategy for ICEs and missing data will be handled in the same manner as the secondary endpoints analyses.

All exploratory endpoints over time analyses will be descriptively summarized by treatment groups using descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum and maximum for continuous variables, and counts and percentages for categorical variables.

Additionally, graphical data displays may also be used to summarize the over time data if applicable.

5.5.2.1. Analysis Related to HiSCR

- The proportion of participants who achieved HiSCR50 and the proportion of participants who achieved HiSCR50 by baseline Hurley stage (II, III) will be summarized by treatment group over time.
- The proportion of participants who achieved HiSCR75 and HiSCR90 will be summarized by treatment group over time.

5.5.2.2. Analyses Related to Lesion Count

- The change from baseline in total AN count will be summarized by treatment groups over time.
- The change from baseline in number of abscesses will be summarized by treatment group over time.
- The change from baseline in number of draining fistulas will be summarized by treatment group over time.
- The change from baseline in number of inflammatory nodules will be summarized by treatment group over time.

5.5.2.3. Analysis Related to IHS4

- The change from baseline in IHS4 score will be summarized by treatment group over time.

5.5.2.4. Analyses Related to HS-IGA

- The proportion of participants with HS-IGA score of inactive (0), HS-IGA score of inactive (0) or almost inactive (1), and the proportion of participants achieving HS-IGA score of mild activity or better (≤2) with at least 2-grade improvement from baseline will be summarized by treatment groups over time.

5.5.2.5. Analyses Related to HASI

- The change from baseline in HASI score over time will be summarized by treatment groups over time.

5.5.2.6. Analyses Related to HSSD

- The change from baseline in HSSD pain score (24 hours recall) will be summarized over time.
- The change from baseline in HSSD pain score (7 days recall) will be summarized over time.

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.

5.6.1. Extent of Exposure

The number and percentage of participants who receive study intervention (placebo, bermekimab, and adalimumab) 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 leading to discontinuation of study intervention
- AEs of severe intensity
- AEs related to study intervention
- AEs of injection site reaction

In addition to the summary tables, 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 36 will be summarized for selected chemistry, and hematology tests and displayed by intervention group.

- **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.

Applicable laboratory results will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE). Participants with toxicity grades ≥2 will be listed.

5.7. Other Analyses

5.7.1. Pharmacokinetics

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

Blood samples for measuring bermekimab concentrations will be collected from all participants 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. Samples must be collected before study agent administration at visits when a study agent administration is scheduled.

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

- Summary of bermekimab concentrations at each visit by treatment group.
- Proportion of participants without detectable bermekimab concentration (below the lower limit of quantification) at each visit by treatment group.
- Summary of bermekimab concentrations at each visit by treatment group and baseline body weight (>=95 or < 95 kg).
- Summary of bermekimab concentrations at each visit by treatment group and baseline Hurley stage status (II, III).
- Plot of median (IQ) bermekimab concentrations over time by treatment group.
- Plot of median (IQ) bermekimab concentrations over time by baseline body weight and treatment group.

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

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

- Received an additional bermekimab dose.

In addition, if a participant has an administration outside of dosing windows (± 3 days from scheduled visit from Week 0 through Week 32), the concentration data collected at and after that visit will be excluded from the by-visit data analyses. Additional exclusions for incongruous PK data to be implemented based on Janssen SOP-07948. All participants and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

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.

Immunogenicity analyses will be based on the Immunogenicity Analysis Set (Section 4). No imputation for missing concentration data will be performed.

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

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

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

5.8. Interim Analyses

An internal independent interim analysis committee (IAC) will be established to review the interim data to formulate recommended decisions and/or actions in accordance with the objectives of the interim analyses. The IAC will consist of at least a clinician and a statistician (neither of whom are involved in study conduct), one of whom will chair the committee, and other members as required.

The IAC will review the unblinded efficacy data and provide recommendations about the next step of enrollment of Part 2 portion of this study based upon the results of the first (when approximately 50% of the Part 1 participants reach Week 16) and/or second (when 100% of the Part 1participants reach Week 16) interim efficacy analyses. Both interim analyses will be performed to determine

whether the efficacy of bermekimab, as measured by the proportion of participants achieving HiSCR50 response at Week 16, is sufficient to open the enrollment of the Part 2 portion of the study. Other selected supportive efficacy endpoints could also be reviewed. Additionally, as part of both IAs, serum bermekimab concentration data available at the time of both database release will be used for PK concentration analyses and population PK analysis to support IAC data review and to inform dose regimens for Phase 2b portion of the study.

Based on the results from the first IA, consideration of termination of the study may be warranted if either the efficacy is sufficiently low based on the prespecified criteria or the efficacy is considered to be insufficient to outweigh specific safety findings observed in study participants.

Furthermore, if the study is not terminated after the 1st IA, a database lock based on all available data when 100% of participants completed Week 16 from Part a portion of the study will be planned to support the end of phase 2 meeting. The unblinded results will be limited to specific sponsor personnel not involved in the study conduct. Interim analysis results will not be disseminated to investigators or individuals associated with the conduct of the study.

Following the first IA, the study was terminated due to futility.

5.9. Data Monitoring Committee (DMC)

An external iDMC whose members are not directly involved in the conduct of 77474462HDS2001 Phase 2a/2b study, will review unblinded safety data to ensure the safety of the participants enrolled in this study. The iDMC will convene for a prespecified look at safety after at least 12 participants have received 4 weekly doses. The committee will also meet regularly to review unblinded safety data. After the review, the DMC will make recommendations to the sponsor 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

ADA	anti-drug antibody
AE	adverse event
ALT/SGPT	alanine aminotransferase
AST/SGOT	aspartate aminotransferase
ATC	anatomic and therapeutic class
BMI	body mass index
BSA	body surface area
CI	confidence interval
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
IQ	interquartile
IWRS	interactive web response system
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
NAb	neutralizing antibodies
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TEAE	treatment-emergent adverse event
US NCI	United States National Cancer Institute
WHO	World Health Organization

6.2. Appendix 2 Changes to Protocol-Planned Analyses

The IA futility criterion was met and the decision was made to terminate the study. The SAP has reduced efficacy, safety and PK analyses.

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 (<95 kg, >=95 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 HS disease, baseline Hurley stage status, baseline AN count, inflammatory nodule count, abscess count, and draining fistula, baseline IHS4, baseline HASI, HS-IGA, and PRO related measurements) will be summarized by treatment group. In addition, summaries of participants' medical history and current diagnoses, alcohol intake, and smoking status will be provided by treatment group and the distribution of participants by Hurley stage status (II, and III) will also be provided.

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

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

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. Prior HS treatment received (including prior HS related surgery) will be summarized by randomized treatment group for the FAS.

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.

In addition, a list of participants who received a protocol-prohibited medication or therapy meeting the definition of ICE 2 will be provided.

6.6. Appendix 7 Intervention Compliance

Study agent compliance will be summarized descriptively through Week 31 for the FAS. Compliance to randomized intervention versus actual intervention will be presented in a summary table. Number of the participants receiving each scheduled treatment will be summarized.

6.7. Appendix 8 Adverse Events of Special Interest

Not Applicable.

6.8. Appendix 9 Medications of Special Interest

Not Applicable.

6.9. Appendix 10 Laboratory Toxicity Grading

The grading scale use for lab assessments is based on 'Common Terminology Criteria for Adverse Events (CTCAE) v5.0'.

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.

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.