Janssen Research & Development *

Clinical Protocol

Protocol Title

A Phase 2a/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.

LYRA

Short Title

A Dose-ranging Study of Bermekimab (JNJ-77474462) in the Treatment of Subjects with Moderate to Severe Hidradenitis Suppurativa

Protocol 77474462HDS2001; Phase 2a/2b
AMENDMENT 2

JNJ-77474462 (bermekimab)

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United States (US) sites of this study will be conducted under US Food & Drug Administration Investigational New Drug (IND) regulations (21 CFR Part 312).

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GCP Compliance: This study will be conducted in compliance with Good Clinical Practice, and applicable regulatory requirements.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	12 August 2022
Amendment 1	08 July 2021
Original Protocol	26 April 2021

Amendment 2 (12 August 2022)

Overall Rationale for the Amendment: The overall rationale for the amendment is to change the prospective dose regimens in Part 2 based on the emerging Phase 1 PK information on bermekimab as well as the interest to test the q2w regimen. Since the newly proposed q2w regimen in Part 2 starts after Week 12, the timing of the primary endpoint for analysis in Part 2 was updated to Week 12 from Week 16 while keeping the Week 16 primary endpoint in Part 1. The number of dose regimens and total sample size to be studied in Part 2 will be determined in an adaptive fashion based on PK results from Part 1.

The changes made to the clinical protocol 77474462HDS2001 as part of Protocol Amendment 2 are listed below, including the rationale of each change and a list of all applicable sections. Changes made in previous protocol amendment are listed in Section 10.20 Appendix 20: Protocol Amendment History.

Section number and Name	Description of Change	Brief Rationale
Throughout the protocol	• Updated the timing of the primary, secondary, and exploratory endpoints for Part 2 to Week 12. • Modified dose regimens in Part 2. • Updated dose justification. • Added DBL at IA 2. • Modified sample size in Part 2 and associated sample size/power calculations and efficacy evaluation.	To investigate relevant dose regimens for further development based on the emerging information on bermekimab. Updated the timing of primary endpoint based on the newly proposed q2w regimens. To remove "dose response" from objectives to reflect the elimination of the lower dose arm(s).
Synopsis; 3. Objectives and Endpoints; 4.3. Justification for Dose; 9.1. Statistical Hypotheses	Removed "dose-response" from primary objectives and hypothesis.	
Throughout the protocol	• Removed active comparator, adalimumab, from Part 2. • Added EC #45 to add washout period for adalimumab.	To include adalimumab-experienced participants in Part 2 of the study.
Synopsis; 4.1. Overall Design; 9.5. Interim Analysis	• Added futility for the first IA.	To consider termination of the study if bermekimab does not provide benefit for participants.
1.3.1. Screening Through Week 16, Part 1; 1.3.2. Screening Through Week 16, Part 2	• Updated time point for medical history/demographics. • Updated footnote k for Population PK sample. • Removed footnote "s" in Amendment 1 and renumbered the footnotes after it in Amendment 2.	To correct errors.

Section number and Name	Description of Change	Brief Rationale
1.3.1. Screening Through Week 16, Part 1; 1.3.2. Screening Through Week 16, Part 2; 5.1. Inclusion Criteria; 8.2.4. Clinical Safety Laboratory Assessments; 10.3. Appendix 3	Changed "Urine pregnancy test" to "Pregnancy test" in Schedule of Activities and updated IC #15 and Clinical Laboratory Tests to cover both serum and urine pregnancy tests	To correct an error.
1.3.2. Screening Through Week 16, Part 2; 8.1.3. Lesion Counts; 8.1.11. HS Lesion Monitoring Using Medical Infrared Thermography; 10.17. Appendix 17	Reduced collection time points for lesion counts, HS-IGA, and images of skin lesions in Part 2.	To decrease burden for participants while collecting sufficient efficacy data.
1.3.2. Screening through Week 16, Part 2; 10.3. Appendix 3	Added fasting lipid panel to clinical laboratory tests in Part 2.	To further investigate the timing and the magnitude of the possible changes in lipid levels during the course of the current study. A mild elevation of serum triglycerides was observed in some participants in the bermekimab Phase 1 study.
2.2. Background; 11. References	Added 2 references for HiSCR.	References missed in original protocol and Amendment 1.
5.1. Inclusion Criteria; 5.2. Exclusion Criteria	Added IC #22 and EC #43 for BCG vaccination.	To correct an error (missing in original protocol and Amendment 1).
5.2. Exclusion Criteria; 5.3. Lifestyle Considerations	• Modified EC #12 to refer to IC #13. • Modified Criterion #3 to refer to IC #17.	To correct an error.
5.2. Exclusion Criteria	Added EC #44 for congenital conditions including Down syndrome.	To maintain consistent demographics.
5.3. Lifestyle Considerations	Modified lifestyle consideration #1	To be consistent with the labeling for adalimumab in Part 1.
6.7.1. Rescue Medication	Included the correct formulation of the rescue medication.	To correct an error in dosage form.
6.7.4. Analgesic Therapy	Modified use of NSAIDs.	To provide flexibility in compliance with local labeling recommendations.
9.4.2.1. Primary Endpoint	Changed the analysis strategy for addressing Intercurrent Event 3 (Discontinuation of study intervention due to COVID-19 related reasons [excluding COVID-19 infection]) to Treatment Policy strategy and combined it with Intercurrent Event 4.	Since COVID-19 can no longer be viewed as a temporary problem, all COVID-19 related reasons will be treated similarly to "Discontinuations of study intervention due to other reasons (excluding reasons indicative of lack of efficacy)" for which

Section number and Name	Description of Change	Brief Rationale
		treatment policy strategy was used in the past.
10.6. Appendix 6	Updated examples of contraceptives not allowed as sole method of contraception during the study.	To be consistent with IC #17 and current guidance on contraception.
10.19.2. Follow up Assessments	Added guidelines for rechallenge.	For clarification.
Throughout the protocol	Minor grammatical, formatting, or spelling errors and inconsistencies were corrected.	Minor errors were noted.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol number: 77474462HDS2001

A Phase 2a/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.

JNJ-77474462 (bermekimab) is a recombinant human immunoglobulin G1 kappa (IgG1k) monoclonal antibody (mAb) that binds with high affinity and selectivity for human interleukin-1 alpha (IL-1α) and is an effective blocker of IL-1α biological activity. Interleukin-1 alpha is a key mediator of sterile inflammatory responses. Skin is a significant reservoir of preformed IL-1α, and it has been postulated that IL-1α may play a role in the pathophysiology of multiple inflammatory skin disorders, including hidradenitis suppurativa (HS).

Bermekimab has been investigated in dermatologic clinical studies and in other indications. Two Phase 2 studies in atopic dermatitis (AD) and HS were recently completed.

Bermekimab was initially developed by XBiotech, Inc and is currently being developed by Janssen Research and Development, LLC (sponsor).

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

Objectives	Endpoints
	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. • 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.

Objectives	Endpoints
	• 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. • 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.

Objectives	Endpoints
	• 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.

Hypothesis

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, and at Week 12 in Part 2.

OVERALL DESIGN

This is a randomized, double-blind, placebo- and active-comparator-controlled, dose-ranging, multicenter study to assess the efficacy, safety, PK, and immunogenicity of subcutaneously (SC) administered bermekimab for the treatment of moderate to severe HS in adult participants. The participant population will comprise men and women ≥18 years of age, with HS, that is moderate to severe, Hurley Stage II or Hurley Stage III, and has been present for at least 1 year prior to the baseline visit as determined by the investigator through participant interview and/or review of the medical history. Participants must also have HS lesions present in at least 2 distinct anatomic areas, had an inadequate response to an adequate course of appropriate oral antibiotics for treatment of HS in the investigator's opinion and have a total abscess and inflammatory nodule (AN) count of ≥5 at the screening and baseline visit. Participants must agree to daily use (throughout the entirety of the study) of one of the following over-the-counter treatments to the body areas affected with HS lesions: either soap and water, a dilute bleach bath, or a topical antiseptic wash containing chlorhexidine gluconate or benzoyl peroxide.

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). A screening period will take approximately 6 weeks. At baseline, 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.

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 75 participants complete 16 weeks of treatment. The second interim analysis will occur when approximately 150 participants complete 16 weeks of treatment. The goal of the interim analyses is to assess efficacy and safety of bermekimab before enrollment of Part 2 of this study.

The details of the planned interim analyses will be defined in a separate statistical analysis plan (SAP). In summary, if results from Interim Analysis 1 show a positive benefit-risk assessment for bermekimab, enrollment of Part 2 of this Phase 2a/2b design study will proceed. If results from Interim Analysis 1 are inconclusive, enrollment of Part 2 will only be initiated after results from Interim Analysis 2 confirm a positive benefit-risk assessment for bermekimab. 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.

An internal Interim Analysis Committee (IAC) composed of members that are not involved with the clinical program 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.

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.

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 study is considered as the last visit for the last participant in the study.

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 interim analysis results impacting the benefit-risk considerations for the study.

NUMBER OF PARTICIPANTS

Approximately 250 or 300 participants are targeted for enrollment in this 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.

Description of Interventions

The study intervention presentation to be used in this study is a sterile liquid formulation of 175 mg/mL of bermekimab in a prefilled syringe with an injectable volume of 2.0 mL (350 mg of bermekimab per syringe). Bermekimab will be manufactured and provided under the responsibility of the sponsor. Refer to the Investigator's Brochure (IB) for a list of excipients.

Placebo and adalimumab will be provided centrally by the sponsor.

EFFICACY EVALUATIONS

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 Schedules of Activities.

PHARMACOKINETIC AND IMMUNOGENICITY EVALUATIONS

Venous blood samples will be collected for the measurement of serum bermekimab concentrations and detection of antibodies to bermekimab at the time points presented in the Schedule of Activities. Serum samples will also be collected at the final visit from participants who early terminate study participation.

BIOMARKER EVALUATIONS

Biomarker samples will be collected to evaluate the pharmacodynamics (PD) and mechanism of action of bermekimab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to the intervention.

PHARMACOGENOMIC (DNA) EVALUATIONS

A pharmacogenomic blood sample will be collected to allow for pharmacogenomic research, as necessary (where local regulations permit). Participation in the pharmacogenomic research is optional.

SAFETY EVALUATIONS

Safety evaluations conducted at each study visit will include the assessment of adverse events (AEs; at the visit and those occurring between evaluation visits), a tuberculosis evaluation and other infection assessment, clinical laboratory blood tests (complete blood count and serum chemistries), physical examinations, vital sign measurements, weight, concomitant medication review and observations for injection-site reactions and/or allergic reactions.

STATISTICAL METHODS

Sample Size Determination

This study is designed to enroll approximately 250 or 300 participants, in order to provide sufficient data to have adequate power to detect a treatment difference for 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.

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 with reference 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 adalimumab Phase 3 Studies M11-313 and M11-810 at Week 12 were 42% vs 26% and 59% vs 28% in the adalimumab weekly group and placebo group, respectively.

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

- 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 and the placebo group with 50 participants per arm.
- For 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 at Week 12, the study sample size provides:

- At least 87% power to detect a 25% treatment difference between the bermekimab 700 mg treatment groups (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 groups (n=50) and the placebo group (n=75).

Efficacy Analysis

All randomized participants who received at least 1 administration of study intervention will be included in the efficacy analyses. Participants will be analyzed according to the treatment group to which they were randomized, regardless of the treatment they actually received.

In general, treatment comparisons for binary endpoints will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline Hurley stage status. For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM will include treatment, visit, baseline value for the corresponding efficacy endpoint, baseline Hurley stage status, baseline value by visit interaction, baseline Hurley stage status by visit interaction and the treatment-by-visit interaction, if applicable. The Least Square mean (LSmean) estimates and their corresponding 95% confidence interval (CI) will be provided at each time point. In addition, the estimates of LSmean difference and 95% CIs between treatment groups will be provided.

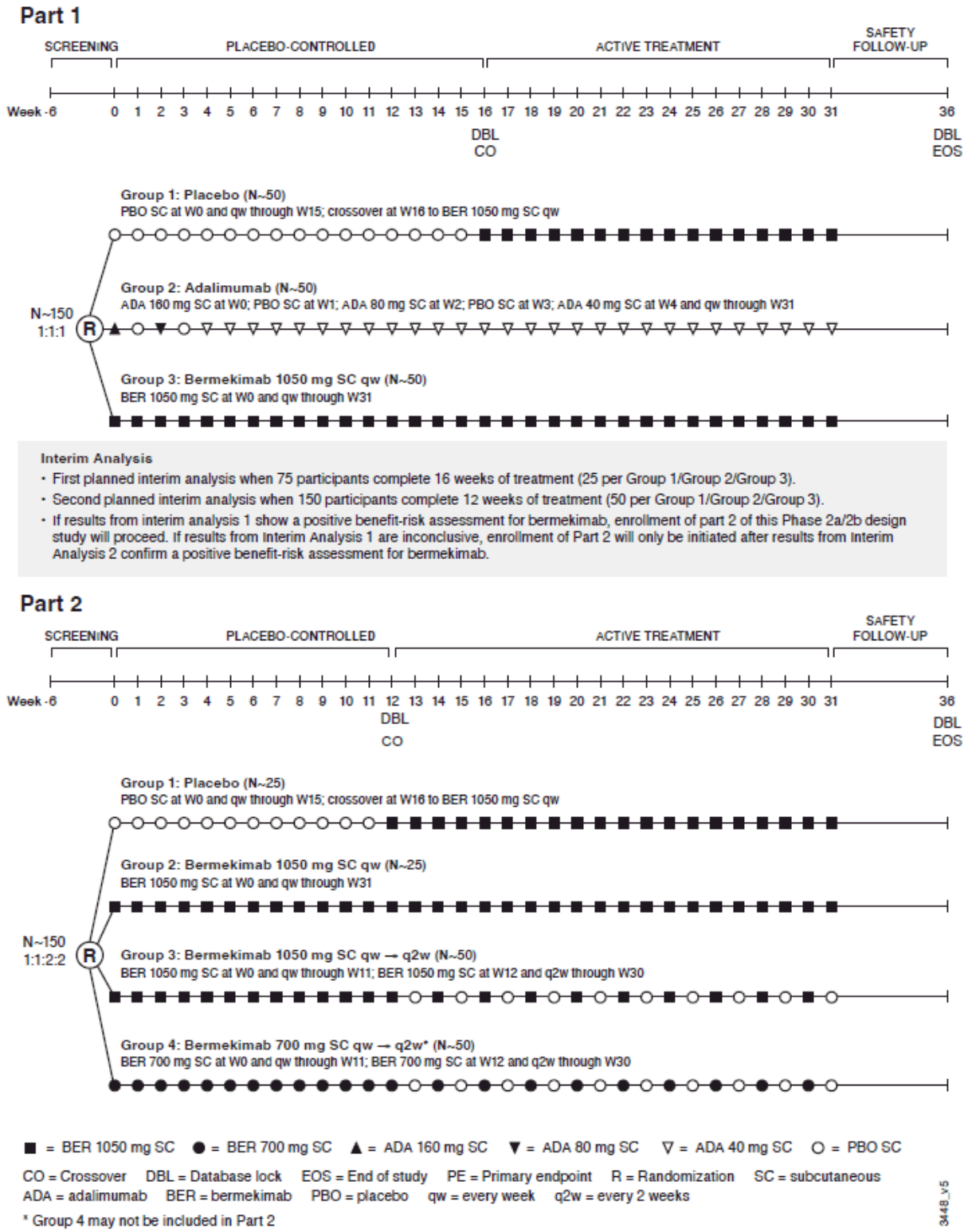
In general, all statistical testing will be performed at a significance level of 0.05 (2-sided) unless otherwise specified. Nominal p-values will be displayed for all treatment comparisons.

Safety Analysis

Safety data, including but not limited to, AEs, SAEs, AEs leading to study intervention discontinuation, changes in laboratory assessments, and changes in vital signs will be summarized. Intervention-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms.

1.2. Schema

Figure 1: Schematic Overview of the Study



1.3. Schedules of Activities

Two Schedules of Activities (SoAs) are presented below, one for the study period from screening through Week 16 and the second from Week 17 through Week 36.

1.3.1. Screening Through Week 16, Part 1

From Screening through Week 16																		
Period	Screening[a]	Blinded, Placebo-controlled Period																
Week[b]	-6 to 0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study Procedure[c]																		
Screening/Administrative																		
Informed consent (ICF)[d]	X																	
ICF for optional biomarker substudy[d]	X																	
ICF for optional pharmacogenomic[d]	X																	
ICF for imaging substudy[d]	X																	
Medical History/ Demographics	X																	
Inclusion/exclusion criteria	X	X																
Study Treatment Administration																		
Randomization		X																
Study intervention administration[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations																		
Physical examination	X	X																X
Height		X																
Weight		X																X
Waist circumference		X																
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph	X																	
12-lead ECG	X																	X
Pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Evaluations																		
Lesion Counts	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HASI		X								X				X				X
Hurley Stage	X	X				X				X				X				X

From Screening through Week 16																		
Period	Screening[a]	Blinded, Placebo-controlled Period																
Week[b]	-6 to 0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
HS-IGA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Images of Skin Lesions[m]		X	X	X		X				X				X				X
DLQI[g]		X								X				X				X
PROMIS-29[g]		X								X				X				X
HSSD-24h[g, t]	X----------																	----------X
HSSD-7d[g]		X				X				X				X				X
PGIS[g]		X								X				X				X
PGIC[g]										X				X				X
Clinical Laboratory Tests																		
QuantiFERON- TB test[h]	X																	
Hepatitis B and C serology	X																	
HIV antibody test	X																	
Hematology	X	X		X		X				X				X				X
Chemistry	X	X		X		X				X				X				X
High sensitivity C-reactive protein (hs-CRP)		X								X								X
Lipids		X																
Pharmacokinetics and Immunogenicity[i,j]																		
Serum bermekimab concentration		X	X			X				X				X				X
Population PK sample				----------X[k]----------														
Antibodies to bermekimab		X				X				X				X				X
Biomarkers																		
Serum[l]		X				X		X		X				X				X
Plasma[l]		X				X		X		X				X				X
Whole blood for RNA[l]		X				X		X										X
Whole blood for PBMC[l]		X				X		X										X
Whole Blood for genomics[l,m,n]		X																
Skin Biopsy (nodule)[m,o]		X																X
Skin Biopsy (tunnel)[m,o,p]																		X
Exudate Swab[q]		X						X										X
FibroTx[m,s]		X						X										X
Skin Swab for microbiome[m,r]		X																X

Abbreviations: DLQI=Dermatological Life Quality Index; DNA=deoxyribonucleic acid; ECG=electrocardiogram; HASI=Hidradenitis Suppurativa Activity and Severity Index; HIV=human immunodeficiency virus; HS-IGA=Hidradenitis Suppurativa Investigator's Global Assessment; HSSD-24h=Hidradenitis Suppurativa Symptom Diary-24-hour version; HSSD-7d=Hidradenitis Suppurativa Symptom Diary-7-day version; PBMC=peripheral blood mononuclear cells; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; PROMIS-29=Patient-reported Outcomes Measurement Information System-29; RNA=ribonucleic acid; TB=tuberculosis.

Footnotes:

a. The screening visit should occur no more than 6 weeks prior to and no less than 7 days before the Week 0 visit.
b. Study visit dates in Weeks 1 through 32 must be calculated from the first study intervention administration visit in Week 0. Visit and study intervention administrations should occur within +/-3 days of scheduled visit.
c. All study procedures and evaluations are to be completed before study intervention is administered except where otherwise indicated.
d. Must be signed before first study-related activity. Separate informed consents are required for participants who chose to participate in the optional biomarkers, optional imaging, and optional pharmacogenetics substudies.
e. Study intervention administrations must occur no less than 4 days apart.
f. Women of childbearing potential must have a negative pregnancy test result before randomization and before receiving study intervention at all study intervention administration visits. This assessment can be performed any other time during the study visit including prior to patient-reported outcome (PRO) collection.
g. All PROs should be collected during the study visit prior to all other assessments, unless otherwise specified
h. A tuberculin skin test is additionally required if the QuantiFERON®-TB test is not approved/registered in the country in which this study is being conducted
i. For all visits where study intervention will be administrated, all blood samples should be collected prior to study intervention administration for evaluation of serum concentration of bermekimab and/or antibodies to bermekimab.
j. Participants who terminated study participation early should have a safety follow-up visit after their last administration of study intervention. Serum samples should be collected at this visit for serum drug concentration measurement and antibody to drug assessment
k. An additional visit is necessary such that a random venous blood sample for population PK analysis will be collected from all participants on any day between Weeks 2 to 12, except on the days of the scheduled study visits. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study intervention administration. Each population PK serum sample will be divided into 2 aliquots: 1 for serum concentration of bermekimab and a back-up.
l. Blood sample will be taken pre-dose.
m. Participation is optional.
n. The pharmacogenomic (DNA) sample should be collected at the specified time point; however, if necessary, it may be collected at a later time point without constituting a protocol deviation. Blood samples for pharmacogenomics will be collected only from participants who give informed consent indicating willingness to participate in this optional component of the study.
o. Skin biopsies to be collected pre-dose. At Week 0, lesional (nodule) and non-lesional skin samples will be collected. At Week 16 and/or Week 32, lesional (nodule) skin samples will be collected.
p. Ultrasound guided deep tunnel biopsy will be collected at Week 16 and Week 32 if available.
q. Exudate will be collected if draining fistulas are present.
r. Skin swab will be collected at the time of skin biopsy. Two swabs will be collected – one from the lesional nodule from where skin biopsy will be taken and the second one from the adjacent non-lesional area, 10 cm away from the lesional margin area.
s. FibroTx Patch will be collected pre-dose. Lesional and non-lesional skin will be sampled at baseline. Lesional skin will be sampled at Week 6 and Week 16.
t. Daily administration.

1.3.2. Screening Through Week 16, Part 2

From Screening through Week 16																		
Period	Screening[a]	Blinded, Placebo-controlled Period													Blinded Active Treatment Phase			
Week[b]	-6 to 0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study Procedure[c]																		
Screening/Administrative																		
Informed consent (ICF)[d]	X																	
ICF for optional biomarker substudy[d]	X																	
ICF for optional pharmacogenomic[d]	X																	
ICF for imaging substudy[d]	X																	
Medical History/ Demographics	X																	
Inclusion/exclusion criteria	X	X																
Study Treatment Administration																		
Randomization		X																
Study intervention administration[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Evaluations																		
Physical examination	X	X												X				
Height		X																
Weight		X												X				
Waist circumference		X																
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest radiograph	X																	
12-lead ECG	X													X				
Pregnancy test[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Evaluations																		
Lesion Counts	X	X		X		X		X		X		X		X		X		X
HASI		X								X				X				X
Hurley Stage	X	X				X				X				X				X

From Screening through Week 16																	
Period	Screening[a]	Blinded, Placebo-controlled Period												Blinded Active Treatment Phase			
Week[b]	-6 to 0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
HS-IGA		X		X		X		X		X		X		X		X		X
Images of Skin Lesions[m]		X				X				X				X				X
DLQI[g]		X								X				X				X
PROMIS-29[g]		X								X				X				X
HSSD-24h[g, t]	X----------													X				
HSSD-7d[g]		X				X				X				X				X
PGIS[g]		X								X				X				X
PGIC[g]										X				X				X
Clinical Laboratory Tests																		
QuantiFERON- TB test[h]	X																	
Hepatitis B and C serology	X																	
HIV antibody test	X																	
Hematology	X	X		X		X				X				X				X
Chemistry	X	X		X		X				X				X				X
High sensitivity C-reactive protein (hs-CRP)		X								X				X				
Fasting lipid panel		X	X											X				
Pharmacokinetics and Immunogenicity[i,j]																		
Serum bermekimab concentration		X	X			X				X				X				X
Population PK sample				----------X[k]----------														
Antibodies to bermekimab		X				X				X				X				X
Biomarkers																		
Serum[l]		X				X		X		X				X				X
Plasma[l]		X				X		X		X				X				
Whole blood for RNA[l]		X				X		X						X				
Whole blood for PBMC[l]		X				X		X						X				
Whole Blood for genomics[l,m,n]		X																
Skin Biopsy (nodule)[m,o]		X												X				
Skin Biopsy (tunnel)[m,o,p]														X				
Exudate Swab[q]		X						X						X				
FibroTx[m,s]		X						X						X				

From Screening through Week 16																		
Period	Screening[a]	Blinded, Placebo-controlled Period													Blinded Active Treatment Phase			
Week[b]	-6 to 0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Skin Swab for microbiome[m,r]		X												X				

Abbreviations: DLQI=Dermatological Life Quality Index; DNA=deoxyribonucleic acid; ECG=electrocardiogram; HASI=Hidradenitis Suppurativa Activity and Severity Index; HIV=human immunodeficiency virus; HS-IGA=Hidradenitis Suppurativa Investigator's Global Assessment; HSSD-24h=Hidradenitis Suppurativa Symptom Diary-24-hour version; HSSD-7d=Hidradenitis Suppurativa Symptom Diary-7-day version; PBMC=peripheral blood mononuclear cells; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PK=pharmacokinetics; PROMIS-29=Patient-reported Outcomes Measurement Information System-29; RNA=ribonucleic acid; TB=tuberculosis.

Footnotes:

a. The screening visit should occur no more than 6 weeks prior to and no less than 7 days before the Week 0 visit.
b. Study visit dates in Weeks 1 through 32 must be calculated from the first study intervention administration visit in Week 0. Visit and study intervention administrations should occur within +/-3 days of scheduled visit.
c. All study procedures and evaluations are to be completed before study intervention is administered except where otherwise indicated.
d. Must be signed before first study-related activity. Separate informed consents are required for participants who chose to participate in the optional biomarkers, optional imaging, and optional pharmacogenetics substudies.
e. Study intervention administrations must occur no less than 4 days apart.
f. Women of childbearing potential must have a negative pregnancy test result before randomization and before receiving study intervention at all study intervention administration visits. This assessment can be performed any other time during the study visit including prior to patient-reported outcome (PRO) collection.
g. All PROs should be collected during the study visit prior to all other assessments, unless otherwise specified
h. A tuberculin skin test is additionally required if the QuantiFERON®-TB test is not approved/registered in the country in which this study is being conducted
i. For all visits where study intervention will be administrated, all blood samples should be collected prior to study intervention administration for evaluation of serum concentration of bermekimab and/or antibodies to bermekimab.
j. Participants who terminated study participation early should have a safety follow-up visit after their last administration of study intervention. Serum samples should be collected at this visit for serum drug concentration measurement and antibody to drug assessment
k. An additional visit is necessary such that a random venous blood sample for population PK analysis will be collected from all participants on any day between Weeks 2 to 12, except on the days of the scheduled study visits. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study intervention administration. Each population PK serum sample will be divided into 2 aliquots: 1 for serum concentration of bermekimab and a back-up.
l. Blood sample will be taken pre-dose.
m. Participation is optional.
n. The pharmacogenomic (DNA) sample should be collected at the specified time point; however, if necessary, it may be collected at a later time point without constituting a protocol deviation. Blood samples for pharmacogenomics will be collected only from participants who give informed consent indicating willingness to participate in this optional component of the study.
o. Skin biopsies to be collected pre-dose. At Week 0, lesional (nodule) and non-lesional skin samples will be collected. At Week 12 and/or Week 32, lesional (nodule) skin samples will be collected.
p. Ultrasound guided deep tunnel biopsy will be collected at Week 12 and Week 32 if available.
q. Exudate will be collected if draining fistulas are present.
r. Skin swab will be collected at the time of skin biopsy. Two swabs will be collected – one from the lesional nodule from where skin biopsy will be taken and the second one from the adjacent non-lesional area, 10 cm away from the lesional margin area.
s. FibroTx Patch will be collected pre-dose. Lesional and non-lesional skin will be sampled at baseline. Lesional skin will be sampled at Week 6 and Week 12.
t. Daily administration.

1.3.3. Week 17 Though Week 36, Part 1 and Part 2

From Week 17 through Week 36																		
Period	Blinded Active Treatment Phase																Safety Follow-up (EOS)[b]	Early Termination Visit (ET)[b]
Week[a]	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	36	
Study Procedure[c]																		
Study Treatment Administration																		
Study intervention administration[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Safety Evaluations																		
Physical examination																X	X	X
Weight																X	X	X
Waist circumference																X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tuberculosis evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Evaluations																		
Lesion Counts				X				X				X				X	X	X
HASI				X				X				X				X		X
Hurley Stage				X				X				X				X		X
HS-IGA				X				X				X				X	X	X
Images of Skin Lesions[j]				X				X				X				X	X	X
DLQI[f]				X				X				X				X	X	X
PROMIS-29[f]				X				X				X				X		X
HSSD-7d[f]				X				X				X				X		X
PGIS[f]				X				X				X				X		X
PGIC[f]				X				X				X				X		X
Clinical Laboratory Tests																		
Hematology				X				X				X				X	X	X
Chemistry				X				X				X				X	X	X
Pharmacokinetics and Immunogenicity[g,h]																		
Serum bermekimab concentration				X				X				X				X	X	X
Antibodies to bermekimab								X								X	X	X

From Week 17 through Week 36																		
Period	Blinded Active Treatment Phase																Safety Follow-up (EOS)[b]	Early Termination Visit (ET)[b]
Week[a]	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	36	
Biomarkers																		
Serum[l]				X				X				X				X		X
Plasma[i]				X				X				X				X		
Whole blood for RNA[i]				X												X		
Whole blood for PBMC[i]				X												X		
Skin Biopsy (nodule)[j,k]																X		
Skin Biopsy (tunnel)[j,k,l]																X		
Exudate Swab[m]				X												X		X
FibroTx[j,n]				X												X		
Skin Swab for microbiome[j,o]				X												X		

Abbreviations: DLQI=Dermatological Life Quality Index; HASI=Hidradenitis Suppurativa Activity and Severity Index; HS-IGA=Hidradenitis Suppurativa Investigator's Global Assessment; HSSD-7d=Hidradenitis Suppurativa Symptom Diary-7-day version; PBMC=peripheral blood mononuclear cells; PGIC=Patient Global Impression of Change; PGIS=Patient Global Impression of Severity; PROMIS-29=Patient-reported Outcomes Measurement Information System-29; RNA=ribonucleic acid.

Footnotes:

a. Study visit dates in Weeks 1 through 32 must be calculated from the first study intervention administration visit in Week 0. Visit and study intervention administrations should occur within +/-3 days of scheduled visit.
b. Study visit dates in for the safety follow-up visit or study termination visit should be calculated from the date of the last administration of study intervention. The safety follow-up visit should occur within -1 to +3 days of scheduled visit.
c. All study procedures and evaluations are to be completed before study intervention is administered except where otherwise indicated.
d. Study intervention administrations must occur no less than 4 days apart.
e. Women of childbearing potential must have a negative urine pregnancy test result before randomization and before receiving study intervention at all study intervention administration visits. This assessment can be performed any other time during the study visit including prior to PRO collection.
f. All PROs should be collected during the study visit prior to all other assessments, unless otherwise specified
g. For all visits where study intervention will be administrated, all blood samples should be collected prior to study intervention administration for evaluation of serum concentration of bermekimab and/or antibodies to bermekimab.
h. Participants who terminated study participation early should have a safety follow-up visit after their last administration of study intervention. Serum samples should be collected at this visit for serum drug concentration measurement and antibody to drug assessment
i. Blood samples will be collected pre-dose
j. Participation is optional.
k. Skin biopsies to be collected pre-dose. Week 32, lesional (nodule) skin samples will be collected.
l. Ultrasound guided deep tunnel biopsy will be collected at Week 32 if available
m. Exudate will be collected if draining fistula is present.
n. FibroTx patch will be collected pre-dose from lesional skin.
o. Skin swab will be collected at the time of skin biopsy. Two swabs will be collected – one from the lesional nodule from where skin biopsy will be taken and the second one from the adjacent non-lesional area, 10 cm away from the lesional margin area.

2. INTRODUCTION

JNJ-77474462 (bermekimab) is a recombinant human immunoglobulin G1 kappa (IgG1k) monoclonal antibody (mAb) that binds with high affinity and selectivity for human interleukin-1 alpha (IL-1α) and is an effective blocker of IL-1α biological activity. Interleukin-1 alpha is a key mediator of sterile inflammatory responses. Skin is a significant reservoir of preformed IL-1α, and it has been postulated that IL-1α may play a role in the pathophysiology of multiple inflammatory skin disorders, including hidradenitis suppurativa (HS).

Bermekimab is not currently approved for any therapeutic indications. Fourteen clinical studies to date have been conducted using bermekimab including 2 recently completed studies in HS and atopic dermatitis (AD). Bermekimab has previous been administered intravenously (IV) at doses ranging from 0.25 mg/kg to 7.5 mg/kg and subcutaneously (SC) at doses from 100 mg to 800 mg.

For the most comprehensive nonclinical and clinical information regarding bermekimab, refer to the latest version of the Investigator's Brochure (IB) for bermekimab.

The term “study intervention” throughout the protocol, refers to bermekimab as defined in Section 6.1, Study Interventions Administered.

The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided as a separate document.

The term "participant" throughout the protocol refers to the common term "subject".

2.1. Study Rationale

This is a Phase 2a/2b randomized, placebo- and active-comparator-controlled, parallel-group, multicenter, dose-ranging study to assess the safety and efficacy of bermekimab in adult participants with moderate to severe HS by means of:

- Assessing efficacy across all treatment groups through Week 16 in Part 1, and through Week 12 combining Part 1 and Part 2.
- Evaluating the longer-term efficacy resulting from the SC dose regimens of bermekimab through 32 weeks.
- Evaluating safety and tolerability data for bermekimab in these HS participants.

In addition, this study will evaluate the pharmacokinetics (PK), immunogenicity and pharmacodynamics (PD) of bermekimab therapy in participants with HS.

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

An overview of the protocol design and supportive rationale is described in Section 4.

2.2. Background

Hidradenitis suppurativa (HS) is a chronic skin disease of unclear etiology that affects 1% to 4% of the general population (Jemec 2012, Margesson 2014, Vekic 2018b, Zouboulis 2018). HS typically manifests as recurrent, inflamed, tender, SC nodules that are generally restricted to the axillary, inguinal, and anogenital regions (Jemec 2012, Margesson 2014, Vekic 2018b). While some nodules resolve spontaneously, others progress to form sterile abscesses, which then rupture into the skin, leading to the formation of fistulas and sinus tracts that can spontaneously release purulent drainage (Jemec 2012, Margesson 2014, Vekic 2018b). Over time, chronic inflammation can lead to irreversible scarring and fibrosis, which in severe cases can result in contractures and limitations in limb mobility, especially in the axilla. Disease onset is typically after puberty and women are affected 2 to 5 times more commonly than men (Jemec 2012, Margesson 2014). Multiple factors including genetics, cigarette smoking, and obesity are believed to predispose a person to HS (Jemec 2012, Zouboulis 2018).

The chronic pain, drainage, and progressive, irreversible scarring associated with HS has been shown to have a particularly profound effect on patients' health-related quality of life relative to other common skin disorders (Zouboulis 2018). Patients with HS experience considerable impact on activities of daily living, work/school attendance and productivity, physical activities, and emotional state (Vekic 2018a).

The biologic anti-TNF inhibitor adalimumab (Humira®) has been approved to treat moderate to severe HS, but even this agent has not shown satisfactory treatment effects in many patients. Across 2 Phase 3 studies, the primary endpoint of Hidradenitis Suppurativa Clinical Response (HiSCR) 50, defined as at least 50% reduction in total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to baseline, was achieved in 42% and 59%, respectively, of adalimumab-treated patients compared with 26% and 28%, respectively, of placebo-treated patients (Ingram 2016; Kimball 2014; Kimball 2016a; Kimball 2016b; Okun 2013). Therefore, a substantial, unmet medical need exists for safe and more effective HS management options with alternative mechanisms of action.

Bermekimab is a recombinant human IgG1 mAb that binds the cytokine IL-1α with high affinity and is an effective blocker of IL-1α biological activity. IL-1α is a key mediator of sterile inflammatory responses and has been implicated in the pathology of advanced cancer, cardiovascular disease, and rheumatologic disease. Clinical evidence generated to date suggests that targeting IL-1α may be an effective treatment in undermining the inflammatory process that drives a wide array of diseases, including dermatologic conditions.

To date, there have been 14 clinical studies using bermekimab in a wide range of therapeutic areas. Bermekimab has been studied in both IV and SC formulations in several dose levels and dosing schedules to evaluate safety and efficacy.

Nonclinical Studies

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

This section provides a summary of the sponsor's assessment of how the overall nonclinical data support the safety of the proposed dosing for bermekimab in this Phase 2 program in HS.

Bermekimab binds with high affinity and specificity to human IL-1α with a dissociation constant (K_D) of 0.059 nM. No binding to human IL-1β or interleukin-1 receptor antagonist (IL-1Ra) was detected up to the highest concentrations tested. In addition, bermekimab was shown to effectively neutralize the ability of human IL-1α to induce endothelial cell expression of adhesion molecules and fibroblast expression of interleukin-6 (IL-6). Bermekimab was bound by cynomolgus monkey IL-1α with a K_D of 1.3 nM and did not bind with mouse, rat, or pig IL-1α at the highest concentrations tested.

A 1-month repeat intraperitoneal dose mouse study tested bermekimab up to 3 doses of 312 mg/kg/week. No treatment-related adverse effects were observed.

The potential toxicity of bermekimab was also evaluated in a 6-week, repeat IV and SC exploratory and tolerability study with toxicokinetics in female cynomolgus monkeys, at dose levels of 0, 50 (IV), 300 (IV), and 300 (SC) mg/kg/week for 6 weeks. The toxicology evaluations included mortality, clinical observation, body weight, food consumption, veterinary physical examination, ophthalmology, clinical pathology (hematology, chemistry, coagulation and urinalysis), organ weight, gross necropsy and histopathology. In addition, safety pharmacology and physiology endpoints (electrocardiogram [ECG], blood pressure, heart rate, respiratory rate, and body temperature) were evaluated. There was a transient decrease in blood pressure only at the high dose for both IV and SC administrations on Day 6 and the values returned to baseline at the end of dosing period (Day 37). There were no other treatment-related findings at any dose levels. The no observed adverse effect level (NOAEL) was 300 mg/kg for both IV and SC administrations. At the NOAEL dose, the exposures C_{max} and AUC for IV administration were 9050 µg/mL and 26300 µg·day/mL respectively and C_{max} and AUC for SC administration were 4480 µg/mL and 22800 µg·day/mL respectively following dosing on Day 36.

Clinical Studies

Five Phase 2 studies sponsored by XBiotech have been completed in dermatologic indications (psoriasis [NCT01384630], acne vulgaris [NCT01474798], pyoderma gangrenosum [NCT01965613], AD [NCT03496974], and HS [NCT03512275]), along with one investigator sponsored study in HS.

The investigator-initiated Phase 2 randomized-controlled study among patients not eligible for treatment with adalimumab (EudraCT number 2015-002321-20; ClinicalTrials.gov NCT02643654) was first completed and showed promising results for activity of bermekimab in HS. Twenty patients with severe HS and with either primary or secondary failure of previous anti-TNF agents, or who were unwilling to receive SC adalimumab treatment, were randomly allocated (1:1) to receive, in a blinded fashion, every other week treatment with placebo or bermekimab at a dose of 7.5 mg/kg IV. Treatment was administered intravenously for 12 weeks. The primary efficacy endpoint was the HiSCR50 score, which is defined as achieving at least a 50% reduction in the total nodule and abscess counts with no worsening in abscess or draining fistulae count, that

was achieved among 10% of patients allocated to placebo and 60% of patients allocated to bermekimab. The odds ratio for positive HiSCR50 after 12 weeks of treatment was 13.50 (95% confidence intervals [CIs] 1.19-152.51, p=0.035; Kanni, 2018).

Data from XBiotech's 2018-PT045 open-label Phase 2 study of bermekimab treating HS corroborated the positive results generated from the investigator led study. Twenty-four patients who had failed previous anti-TNF treatment (Group A) and 18 patients with no prior treatment with anti-TNF treatment (Group B) were enrolled into the study and received 400 mg bermekimab SC weekly. A HiSCR50 response at Week 12 was again used as the primary efficacy endpoint. At Week 12, HiSCR50 was achieved in 63% of patients in Group A, and 61% of in Group B. In addition to patients achieving a meaningful clinical response, patients also experienced a marked reduction in pain, with Group A patients reporting a 54% reduction in pain and Group B Patients reports a 64% reduction in pain (Gottlieb 2020).

Data from a recently completed Phase 2 study, 77474462HDS2002 (PT-047) have recently become available, and were used to inform the dose regimens of this study. Study 77474462HDS2002 (PT-047) is a double-blind, placebo-controlled, study of bermekimab in moderate to severe adult HS patients. The primary endpoint of this trial was the proportion of patients achieving HiSCR50 at Week 12. The primary endpoint from this trial was analyzed at the Week 16 database lock (DBL). Bermekimab 400 mg weekly and 400 mg q2w were both safe and well-tolerated in participants with HS through Week 36. A numerically higher response rate was observed in the bermekimab 400 mg weekly group relative to the placebo group on the primary endpoint of HiSCR50 at Week 12. Statistical superiority, however, was not achieved. At Week 12, a numerically greater proportion of treated subjects randomized to bermekimab 400 mg q2w and 400 mg qw groups achieved a HiSCR50 compared with placebo. These results suggest that bermekimab 400 mg weekly and q2w may have modest efficacy in participants with HS.

In addition, in clinical studies completed to date in psoriasis, acne, pyoderma gangrenosum, and AD, bermekimab was well-tolerated. For more information regarding completed clinical studies, see the IB.

2.3. Benefit-Risk Assessment

Based on the available data and the proposed safety measures discussed below, the risks of the dose regimens of bermekimab to be investigated in this protocol appear to be acceptable relative to the potential benefit.

Bermekimab has undergone previous clinical development in diseases such as psoriasis, AD, HS, acne vulgaris, pyoderma gangrenosum and cancer, as summarized in the latest version of the IB. The collective efficacy and safety results of the Phase 1 and Phase 2 clinical studies in healthy volunteers and patients in dermatologic indications have indicated a favorable benefit-risk profile for further bermekimab development to date. In addition, nonclinical evidence that IL-1a may be an important component for inducing chronic skin inflammation (Abdel-Razzak 1993, Murphy 2000).

Unblinded safety will be evaluated on an ongoing basis throughout this study by an independent Data Monitoring Committee (iDMC), in addition to the standard safety oversight performed by the sponsor.

The risks for bermekimab are infections, hypersensitivity reactions and injection-site reactions. More detailed information about the known and expected benefits and risks of bermekimab may be found in the IB.

The important risks for adalimumab are:

1. serious infections which may be fatal and include opportunistic infections such as tuberculosis (TB) and invasive fungal infection (patients over 65 years of age were found to be at higher risk for infection);
2. malignancies which may be fatal (including lymphoma and hepatosplenic T-cell lymphoma);
3. anaphylaxis or serious allergic reactions;
4. Hepatitis B virus (HBV) reactivation;
5. demyelinating disease;
6. cytopenias and pancytopenia;
7. heart failure;
8. Lupus-like syndrome;
9. Concomitant administration of adalimumab with anakinra (human interleukin-1 receptor antagonist) is not recommended based on the possible increased risk for infections, including serious infections which were observed with anakinra and etanercept (another TNF-blocker) studies (Humira SmPC 2021). Bermekimab has not been evaluated in clinical studies with TNF blockers.

The safety plan for bermekimab and adalimumab includes monitoring of AEs and safety laboratory results, using sites adequately prepared for managing hypersensitivity reactions and patient education for recognizing signs of a serious hypersensitivity reaction such as anaphylaxis. In addition, participants will be screened for TB prior to study entry (Section 8.2.8.1) and receive regular ongoing evaluation (Section 8.2.8.2).

Taking into account the measures taken to minimize risk to participants of this study, the potential risks identified in association with bermekimab are justified by the anticipated benefits that may be afforded to participants with HS.

3. 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.

Objectives	Endpoints
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. • 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

Objectives	Endpoints
	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.

Objectives	Endpoints
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. • 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.

Objectives	Endpoints
	• 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.

Refer to Section 8, for evaluations related to endpoints.

HYPOTHESIS

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, and at Week 12 in Part 2.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo- and active-comparator-controlled, dose-ranging, multicenter study to assess the efficacy, safety, PK, and immunogenicity of 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 will employ 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.

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).

A screening period will take approximately 6 weeks. 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.

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 75 participants complete 16 weeks of treatment. The second interim analysis will occur when approximately 150 participants complete 16 weeks of treatment. The goal of the interim analyses is to assess efficacy and safety of bermekimab at the doses evaluated prior to enrollment of Part 2 of this study.

The details of the planned interim analyses will be defined in a separate statistical analysis plan (SAP). In summary, if results from Interim Analysis 1 show a positive benefit-risk assessment for bermekimab, enrollment of Part 2 of this Phase 2a/2b design study will proceed. If results from Interim Analysis 1 are inconclusive, enrollment of Part 2 will only be initiated after results from Interim Analysis 2 confirm a positive benefit-risk assessment for bermekimab. 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.

An internal Interim Analysis Committee (IAC) composed of members that are not involved with the clinical program will be established to review the interim data and recommend actions to the study team in accordance with the objectives of the interim analyses. Refer to Section 9.5 for details.

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, 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.

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.

In addition to the 2 interim analyses described above (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 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 time points in the SoA (Section 1.3).

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 interim analysis results impacting the benefit-risk considerations for the study. Refer to Section 9.5 and Section 9.6 for details.

4.2. Scientific Rationale for Study Design

Blinding, Control, Study Phase/Periods, Intervention Groups

A placebo control will be used to establish the frequency and magnitude of changes in clinical endpoints that may occur in the absence of active intervention. Adalimumab (HUMIRA) is approved for the treatment of moderate to severe HS and was selected as a reference arm to benchmark bermekimab efficacy relative to adalimumab. Randomization will be used to minimize bias in the assignment of participants to intervention groups, to increase the likelihood that known and unknown participant attributes (e.g., demographic and baseline characteristics) are evenly balanced across intervention groups, and to enhance the validity of statistical comparisons across intervention groups. Blinded intervention will be used to reduce potential bias during data collection and evaluation of clinical endpoints.

DNA and Biomarker Collection

It is recognized that genetic variation can be an important contributory factor to interindividual differences in intervention distribution and response and can also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research may help to explain interindividual

variability in clinical outcomes and may help to identify population subgroups that respond differently to an intervention. The goal of the pharmacogenomic component is to collect DNA to allow the identification of genetic factors that may influence the PK, PD, efficacy, or safety, of bermekimab and to identify genetic factors associated with HS.

Biomarker samples will be collected to evaluate the mechanism of action of bermekimab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to an intervention. The goal of the biomarker analyses is to evaluate the PD of bermekimab and aid in evaluating the intervention-clinical response relationship.

DNA and biomarker samples may be used to help address emerging issues and to enable the development of safer, more effective, and ultimately individualized therapies.

4.2.1. Study-Specific Ethical Design Considerations

Potential participants will be fully informed of the risks and requirements of the study and, during the study, participants will be given any new information that may affect their decision to continue participation. They will be told that their consent to participate in the study is voluntary and may be withdrawn at any time with no reason given and without penalty or loss of benefits to which they would otherwise be entitled. Only participants who are fully able to understand the risks, benefits, and potential adverse events (AEs) of the study and provide their consent voluntarily will be enrolled.

The maximum amount of blood drawn from each participant in this study will not exceed 500 mL as per the standard of the American Red Cross. For more details regarding blood collection see Section 8.

There is a high unmet medical need for novel, effective treatments for Hidradenitis Suppurativa. A placebo control arm is needed to assess the efficacy and safety of the investigational product (IP). Placebo subjects will cross over to active treatment after Week 16 in Part 1 and Week 12 in Part 2. The protocol allows for lesion intervention(s) for painful lesions as well as the use of certain analgesics. In addition, subjects have the option of discontinuing from the study at any time for any reason.

4.3. Justification for Dose

Three bermekimab dose regimens were originally selected to be evaluated in this study: 350 mg SC qw, 700 mg SC qw, and 1050 mg SC qw. These dose regimens were chosen based on bermekimab PK, efficacy, and safety data from a Phase 2 open-label study (2018-PT045, NCT03512275) and a Phase 2 placebo-controlled study (2019-PT047/77474462HDS2002, NCT03512275) in participants with HS.

Results from the open-label study (2018-PT045) of bermekimab demonstrated evidence of clinical activity in participants with HS. The HiSCR50 responses at Week 12 were achieved by 63% and 61% of anti-TNF failure and anti-TNF naïve patients with HS, respectively, following bermekimab 400 mg SC qw injection for 13 weeks. Based on these findings, a Phase 2 placebo-controlled study

(77474462HDS2002) was conducted to further evaluate the 400 mg SC qw and 400 mg SC q2w dose regimens in participants with HS. At Week 12, the proportion of participants who achieved a HiSCR50 response was numerically higher in the bermekimab 400 mg qw group compared with the placebo group (54.8% vs 44.2%), while comparable HiSCR50 response was observed between the 400 mg q2w group and the placebo group (44.0% vs 44.2%, respectively). Since the 400 mg qw dose regimen suggested clinical efficacy in these 2 HS studies, a similar dose regimen of 350 mg qw (350 mg x 1 SC injection) was selected as a dose to assess the minimally effective dose in this Phase 2b study. The formulation for 350 mg SC (175 mg/mL in 2 mL) is less viscous compared to the formulation for 400 mg SC (200 mg/mL in 2 mL). The 350 mg qw dose is expected to result in only slightly lower PK exposure compared with the 400 mg qw dose.

In the Phase 2 placebo-controlled study (77474462HDS2002), an E-R trend for HiSCR50 response at Weeks 12 and 16 was observed in the 400 mg qw group, albeit a small sample size. This E-R trend indicated that higher PK exposure may result in higher efficacy. As such, 2 higher dose regimens of 700 mg qw (350 mg x 2 SC injections) and 1050 mg qw (350 mg x 3 SC injections) were also selected to support evaluation of dose-response in this Ph2b study. The dose regimens of 700 mg qw and 1050 mg qw will provide 2- and 3-fold higher exposure than 350 mg qw and are anticipated to achieve higher efficacy in HS.

The weekly dose frequency was selected based on bermekimab half-life ($T_{1/2}$). Bermekimab $T_{1/2}$ was estimated to be approximately 1 week so that a weekly dose regimen would maintain adequate drug exposure over the entire dosing interval. Given that the initial intensive treatment with weekly doses of bermekimab for 12 weeks is expected to reduce participants' inflammatory burden, a less frequent dose regimen may be sufficient for maintenance therapy. In addition, less frequent dosing interval will decrease participant burden. Therefore, instead of testing 700 mg qw and 350 mg qw regimens in Part 2, bermekimab 1050 mg qw→q2w (starting at Week 12) or 700 mg qw→q2w (starting at Week 12) regimens will be implemented. Whether 700 mg qw→q2w will be included in Part 2 will be based on interim analysis results from Part 1. Details will be described in the interim analysis plan.

Bermekimab was well-tolerated in the 2018-PT045 study (400 mg SC qw for 13 weeks) with no safety concerns. In the completed Phase 2 AD and HS studies 77474462HDS2002 (NCT04019041) study and 77474462ADM2002 (NCT04021862), bermekimab 800 mg at Week 0, 1 followed by 400 mg qw or 400 mg q2w were both safe and well-tolerated in participants with HS through Week 36. The highest dose of bermekimab studied was 7.5 mg/kg IV q2w for 12 weeks in HS (10 participants; Kanni, 2018), with no safety concerns. The 7.5 mg/kg IV dose is equivalent to a 1125 mg SC dose for a 90 kg (average body weight of HS patients, 77474462HDS2002) individual assuming an SC bioavailability of 60%. Based on the preliminary PK simulation, the median C_{max} for the highest dose of 1050 mg SC qw would be lower (0.83-fold) than that for the 7.5 mg/kg IV q2w dose regimen while the median AUC_{2weeks} would be higher (1.85-fold) than that for the 7.5 mg/kg IV q2w dose regimen. Given the safety margins calculated based on predicted human PK exposure at 1050 mg SC qw (ie., 40-fold for $C_{max,ss}$ and 33-fold for $AUC_{1week,ss}$) relative to that at monkey NOAEL (300 mg/kg SC qw, Section 2.2), dose

regimens of up to 1050 mg SC qw proposed in this Phase 2 study would have adequate safety margins.

To actively monitor unblinded safety data on ongoing basis, an independent DMC will be commissioned in this study (Section 9.6, Data Monitoring Committee).

Overall, the 3 proposed dose regimens are expected to have an acceptable safety profile. The inclusion of 3 different active dose regimens of bermekimab in this study would provide an opportunity to explore PK/PD relationships to enable optimal dose selection for subsequent clinical trials in participants with moderate to severe HS.

4.4. End of Study Definition

End of Study Definition

The end of study is considered as the last visit for the last participant in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final participant visit at that study site, in the time frame specified in the Clinical Trial Agreement.

Study Completion Definition

A participant will be considered to have completed the study if he or she has completed all scheduled study interventions through Week 31 and has completed all assessments at Week 36 of the safety follow-up period.

5. STUDY POPULATION

A target of 250 or 300 participants will be enrolled under the 77474462HDS2001 protocol.

Screening for eligible participants will be performed within 6 weeks before administration of the study intervention. Refer to Section 5.4, for conditions under which the repeat of any screening procedures are allowed.

The inclusion and exclusion criteria for enrolling participants in this study are described below. If there is a question about these criteria, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a participant in the study. Waivers are not allowed.

For a discussion of the statistical considerations of participant selection, refer to Section 9.2.

5.1. Inclusion Criteria

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

1. Be a male or female 18 (or the legal consent in the jurisdiction in which the study is taking place) years of age or older.

2. Be otherwise healthy on the basis of physical examination, medical history, vital signs, and 12-lead ECG performed at screening. Any abnormalities, must be consistent with the

underlying illness in the study population and this determination must be recorded in the participant's source documents and initialed by the investigator.

3. Have HS for at least 1 year (365 days) prior to the baseline visit as determined by the investigator through participant interview and/or review of the medical history.

4. Have HS lesions present in at least 2 distinct anatomic areas (examples include but are not limited to left and right axilla; or left axilla and left inguinocrural fold) at screening and baseline visits.

5. Have Hurley Stage II or Hurley Stage III HS as determined by the investigator at screening and baseline visits.

6. Had an inadequate response to a course of appropriate oral antibiotics for treatment of HS (or demonstrated intolerance to or had a contraindication to oral antibiotics for treatment of their HS) in the investigator's opinion.

7. Criterion modified per Amendment 2.

   7.1. Be considered, in the opinion of the investigator, a suitable candidate for adalimumab (HUMIRA®) therapy according to their country's approved HUMIRA product labeling. This criterion only applies to participants enrolling in Part 1 of the study, where adalimumab is one of the possible randomization arms. This criterion does not apply to participants enrolling in Part 2.

8. Have stable HS for at least 60 days prior to the screening visit and at baseline as determined by the investigator through patient interview and/or review of the medical history.

9. Have a total AN count of ≥5 at the screening and baseline visit.

10. Have screening laboratory test results within the following parameters, if one or more of the laboratory parameters is out of range, a single retest of laboratory values is permitted:

    a. Hemoglobin ≥10 g/dL (SI: ≥100 g/L)
    b. White blood cells ≥3.5 x 10^3/μL (SI: ≥3.5 GI/L)
    c. Neutrophils ≥1.5 x 10^3/μL (SI: ≥1.5 GI/L)
    d. Platelets ≥100 x 10^3/μL (SI: ≥100 GI/L)
    e. Serum creatinine ≤1.5 mg/dL (SI: ≤137 μmol/L)
    f. Aspartate aminotransferase ≤2 × upper limit of normal (ULN)
    g. Alanine aminotransferase ≤2 × ULN
    h. Alkaline phosphatase ≤2 × ULN

11. Must agree to daily use (throughout the entirety of the study) of one of the following over-the-counter treatments to the body areas affected with HS lesions: either soap and water, or a topical antiseptic wash containing chlorhexidine gluconate, or benzoyl peroxide, or a dilute bleach bath.

12. Criterion modified per Amendment 1:

    12.1. Agree not to receive a live virus or live bacterial vaccination during the study and for 90 days after the last administration of study intervention.

13. Are considered eligible according to the following TB screening criteria:

    a. Have no history of latent or active TB before screening. An exception is made for participants who have a history of latent TB and
        - are currently receiving treatment for latent TB,

          OR

        - will initiate treatment for latent TB before the first administration of study intervention,

          OR

        - have documentation of having completed appropriate treatment for latent TB within 5 years before the first administration of study intervention. It is the responsibility of the investigator to verify the adequacy of previous anti-TB treatment and provide appropriate documentation. Participants with a history and documentation of having completed appropriate treatment for latent TB more than 5 years before the first administration of study intervention are not eligible.

    b. Have no signs or symptoms suggestive of active TB upon medical history and/or physical examination.

    c. Have had no recent close contact with a person with active TB or, if there has been such contact, will be referred to a physician specializing in TB to undergo additional evaluation and, if warranted, receive appropriate treatment for latent TB before the first administration of study intervention.

    d. Within 2 months before the first administration of study intervention, have a negative QuantiFERON®-TB (or T-SPOT® for sites in Japan) test result, or have a newly identified positive QuantiFERON®-TB (or T-SPOT® for sites in Japan) test result (see laboratory manual) in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study intervention. Within 2 months before the first administration of study intervention, a negative tuberculin skin test, or a newly identified positive tuberculin skin test in which active TB has been ruled out and for which appropriate treatment for latent TB has been initiated before the first administration of study intervention, is additionally required if the QuantiFERON®-TB test is not approved/registered in that country or the tuberculin skin test is mandated by local health authorities.

NOTE: A negative tuberculin skin test result (see Section 10.8) is additionally required if the QuantiFERON-TB® test is not approved/registered in the country in which this protocol is being conducted. The QuantiFERON®-TB (or T-SPOT® for sites in Japan) test and the tuberculin skin test are not required at screening for participants with a history of latent TB and ongoing treatment for latent TB, if active TB has been ruled out, and if appropriate treatment has been initiated/completed as described above in Inclusion Criterion 13a.

e. Have a chest radiograph (both posterior-anterior and lateral views, or per country regulations where applicable), or a chest CT scan taken within 3 months before the first administration of study intervention and read by a qualified radiologist or pulmonologist, with no evidence of current, active TB or old, inactive TB.

14. Before randomization, a woman must be either:

- Not of childbearing potential.
- Of childbearing potential and practicing a highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) and agrees to remain on a highly effective method while receiving study intervention and until 12 weeks after last dose - the end of relevant systemic exposure. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first administration of study intervention. Examples of highly effective methods of contraception are located in Section 10.6.

15. Criterion modified per Amendment 2.

15.1. A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [β-hCG]) at screening and a negative urine pregnancy test at Week 0 prior to administration of study intervention.

16. A woman must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for at least 12 weeks administration of study intervention.

17. A man who is sexually active with a woman of childbearing potential and who has not had a vasectomy must agree to use a barrier method of birth control (eg, either a condom [with spermicidal foam/gel/film/cream/suppository if available in their locale] or a partner with an occlusive cap [diaphragm or cervical/vault caps] plus spermicidal foam/gel/film/cream/suppository if available in their locale), during the study and for at least 12 weeks intervention.

18. All men must also agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of study intervention.

19. Be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

20. Must sign an informed consent form (ICF) indicating that he or she understands the purpose of, and procedures required for, the study and is willing to participate in the study.

21. Must sign a separate ICF if he or she agrees to provide an optional DNA sample for research (where local regulations permit) or participate in one of the substudies. Refusal to give consent for the optional DNA research sample does not exclude a participant from participation in the study.

22. Agree not to receive a Bacille Calmette-Guérin (BCG) vaccination during the study, and for 12 months after the last administration of study intervention.

5.2. Exclusion Criteria

Any potential participant who meets any of the following criteria will be excluded from participating in the study:

1. Has a current diagnosis or signs or symptoms of severe, progressive, or uncontrolled renal, cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, rheumatologic, psychiatric, or metabolic disturbances.

2. Has unstable cardiovascular disease, defined as a recent clinical deterioration (eg, unstable angina, rapid atrial fibrillation) in the last 3 months or a cardiac hospitalization within the last 3 months.

3. Has a history of lymphoproliferative disease, including lymphoma; a history of monoclonal gammopathy of undetermined significance; or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy or splenomegaly.

4. A history of malignancy within 5 years before screening (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy, which is considered cured with no evidence of recurrence for at least 3 months prior to the first administration of study intervention and with minimal risk of recurrence).

5. Has a history of chronic or recurrent infectious disease, including but not limited to chronic renal infection, chronic chest infection (e.g., bronchiectasis), recurrent urinary tract infection (recurrent pyelonephritis or chronic nonremitting cystitis), fungal infection (mucocutaneous candidiasis), or open, draining, or infected skin wounds or ulcers (not related to HS).

6. Has or has had a serious infection (e.g., sepsis, pneumonia, or pyelonephritis), or has been hospitalized or received IV antibiotics for an infection during the 2 months before screening.

7. Has or has had herpes zoster within the 2 months before screening.

8. Has a history of an infected joint prosthesis or has received antibiotics for a suspected infection of a joint prosthesis, if that prosthesis has not been removed or replaced.

9. Is infected with human immunodeficiency virus (HIV), positive serology for HIV antibody).

10. Tests positive for HBV infection (see Section 10.7) or who are seropositive for antibodies to hepatitis C virus (HCV) at screening.

11. Criterion modified per Amendment 1:

    11.1. During the 6 weeks prior to baseline, have had any of (a) confirmed SARS-CoV-2 (COVID-19) infection (test positive), **OR** (b) suspected SARS-CoV-2 infection (clinical features without documented test results), **OR** (c) close contact with a person with known or suspected SARS-CoV-2 infection.

    An exception to this criterion may be granted if a participant has a documented negative result for a validated SARS-CoV-2 test:

    (i) Obtained at least 2 weeks after conditions (a), (b), and (c) above (timed from resolution of key clinical features if present, eg, fever, cough, dyspnea)

    AND

    (ii) with absence of ALL conditions (a), (b), (c) above during the period between the negative test result and the baseline study visit.

    NOTES on COVID-related exclusion:

    - The field of COVID-related testing (for presence of, and immunity to, the SARS-CoV-2 virus) is rapidly evolving. Additional testing may be performed as part of screening and/or during the study if deemed necessary by the investigator and in accordance with current regulations / guidance from authorities / standards of care.
    - Precaution: for those who may carry a higher risk for severe COVID-19 illness, follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

12. Criterion modified per Amendment 2.

    12.1. Has a history of latent or active granulomatous infection, including histoplasmosis or coccidioidomycosis, before screening. Participants with radiographic evidence of possible prior histoplasmosis or coccidioidomycosis will be

excluded. Refer to Inclusion Criterion 13 for information regarding eligibility with a history of latent TB.

13. Has a chest radiograph or a chest CT scan within 3 months before the first administration of study intervention that shows an abnormality suggestive of a malignancy or current active infection, including TB.

14. Has ever had a nontuberculous mycobacterial infection or opportunistic infection (eg, cytomegalovirus, pneumocystis, aspergillosis).

15. Has 2 indeterminate (on repeat sampling) QuantiFERON -TB test results.

16. Has had major surgery (e.g., requiring general anesthesia and hospitalization) within 8 weeks before screening, or has not fully recovered from such surgery, or has such surgery planned during the time the participant is expected to participate in the study.

    NOTE: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

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

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

19. Criterion modified per Amendment 2.

    19.1. Has previously received adalimumab. This criterion only applies to participants enrolling in Part 1 of the study, where adalimumab is one of the possible randomization arms. This criterion does not apply to participants enrolling in Part 2.

20. The participant is deemed ineligible according to the following TB screening criteria:

    - A diagnosis of active TB is made.
    - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not continue to undergo additional evaluation.
    - A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON-TB® (or T-SPOT® for sites in Japan) test result (and/or a positive tuberculin skin test result in countries in which the QuantiFERON-TB® test is not approved/registered or the tuberculin skin test is mandated by local health authorities), unless active TB can be ruled out and appropriate treatment for latent TB can be initiated prior to the next study intervention administration and continued to completion (see also Section 8.2.8.1 and Section 10.8). Indeterminate QuantiFERON-TB® (or

borderline T-SPOT® for sites in Japan) test results should be handled as described in Section 8.2.8.1. Participants with persistently indeterminate QuantiFERON-TB® (or borderline T-SPOT® for sites in Japan) test results may continue without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

- A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.

21. Has received an immunomodulating biology therapy within the previous 3 months of study intervention administration (including, but not limited to, anti-cytokine, anti-complement antibodies, anti-Ig antibodies, etc).

22. Has received phototherapy or any systemic medications/treatments that could affect HS or IGA evaluations within 4 weeks of the first administration of any study intervention.

23. Has any other active skin disease or condition (e.g., bacterial, fungal or viral infection) that could have interfered with assessment of HS.

24. Has a draining fistula count of >20 at the baseline visit.

25. Receipt of prescription topical therapies for the treatment of HS within 14 days prior to the baseline visit.

26. Receipt of systemic non-biologic therapies for the treatment of HS within 28 days prior to the baseline visit.

27. Receipt of any oral antibiotic treatment for HS or inflammatory disorders within 28 days prior to the baseline visit.

28. Receipt of opioid analgesics (including tramadol) within 14 days prior to the baseline visit, or if it is anticipated that the participant will require initiation of opioid analgesics (excluding tramadol) for any reason during the study period.

29. Receipt of PRN or “as needed” dose of oral concomitant analgesics for HS-related pain within14 days prior to the baseline visit. (participants may be receiving non-opioid analgesics for treatment of chronic HS-related pain but must be on a stable dose/regimen for at least 14 days prior to the baseline visit and be expected to continue use throughout the study).

30. Receipt of "PRN" or "as needed" non-opioid analgesics for treatment of a chronic pain condition other than HS within 14 days prior to the baseline visit (participants may be receiving non-opioid analgesics for treatment of chronic non-HS-related pain, but must be on a stable dose/regimen for at least 14 days prior to the baseline visit and be expected to continue use throughout the study).

31. Has ever received any IL-1 antagonist (e.g. including but not limited to anakinra, rilonacept).

32. Has received any non-biologic investigational therapy within 30 days or 5 half-lives (whichever is longer) of study intervention administration or is currently enrolled in another study using an investigational agent, device, or procedure.

33. Has received immune-cell depleting therapy (including rituximab) within 6 months of the first administration of study intervention.

34. Has received any systemic immunosuppressants (eg, methotrexate [MTX], azathioprine, cyclosporine, 6-thioguanine, mercaptopurine, mycophenolate mofetil, tacrolimus) within 4 weeks of the first administration of study intervention.

35. Has received, or is expected to receive, any live virus or bacterial vaccination within 12 weeks before the first administration of study intervention.

36. Has known intolerance or hypersensitivity to any biologic medication, or known allergies or clinically significant reactions to murine, chimeric, or human proteins, mAbs, or antibody fragments.

37. Is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study or within 12 weeks after the last administration of study intervention.

38. Plans to father a child while enrolled in this study or within 12 weeks after the last administration of study intervention.

39. Is known to have had a substance abuse (drug or alcohol) disorder within the previous 12 months.

40. Lives in an institution on court or authority order.

41. Has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the participant (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

42. Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator.

43. Has had a BCG vaccination within 12 months of screening.

44. Has congenital conditions including Down syndrome that may impact the clinical course of HS.

45. Has received an anti-TNF drug such as adalimumab within 3 months of the first administration of study intervention. This criterion only applies to participants enrolling in Part 2 of the study. In Part 1, participants previously exposed to adalimumab are excluded.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a participant's clinical status changes (including any available laboratory results or receipt of additional medical records) after screening but before the first administration of study intervention is given such that he or she no longer meets all eligibility criteria, then the participant should be excluded from participation in the study. Section 5.4, Screen Failures, describes options for retesting. The required source documentation to support meeting the enrollment criteria are noted in Section 10.4.

5.3. Lifestyle Considerations

Potential participants must be willing and able to adhere to the following lifestyle restrictions during the course of the study to be eligible for participation:

1. Criterion modified per Amendment 2.

   1.1. A woman of childbearing potential who is heterosexually active must remain on a highly effective method of birth control (Inclusion Criterion 14) during the study and after receiving the last administration of study intervention for at least 5 months if participating in Part 1 (due to potential exposure to adalimumab) and for at least 12 weeks if participating in Part 2.

2. A woman must agree not to donate eggs (ova, oocytes) during the study and for a period of at least 12 weeks following the last administration of study intervention.

3. Criterion modified per Amendment 2.

   3.1. A man who is sexually active with a female of childbearing potential and has not had a vasectomy must agree to use a barrier method of birth control (See Inclusion Criterion 17) during the study and for at least 12 weeks after receiving the last administration of study intervention.

4. A man must agree to not donate sperm during the study and for at least 12 weeks after receiving the last administration of study intervention.

5. Participants must comply with restrictions on concomitant medications and therapies specified in the protocol (see Section 6.7.5).

6. Participants are required to use a daily antiseptic wash on their HS lesions before randomization and continue the treatment throughout the study (including the safety follow-up period) (see Section 6.7.2).

7. Participants must not receive a live virus or bacterial vaccination during the study and for 3 months after the last administration of any study intervention.

8. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (e.g., contraceptive requirements).

9. It is recommended that participants are up-to-date on age-appropriate vaccinations prior to screening as per routine local medical guidelines. For study participants who received locally-approved (and including emergency use-authorized) COVID-19 vaccines recently prior to study entry, follow applicable local vaccine labelling, guidelines, and standards of care for patients receiving immune-targeted therapy when determining an appropriate interval between vaccination and study enrolment (see also Section 6.7 concomitant medications).

5.4. Screen Failures

If, during the screening phase, the subject has not met all inclusion criteria or met any exclusion criteria, or is unable or unwilling to adhere to the prohibitions and restrictions of the study, the subject is considered to be a screen failure and is not eligible to be randomized at that time.

Retesting of abnormal laboratory values that may lead to exclusion will be allowed once. Retesting can occur at an unscheduled visit during the specified screening period of 6 weeks.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Rescreened participants will be assigned a new participant number, undergo the informed consent process, and then start a new screening period.

Completion of screening and randomization procedures within the specified screening window of approximately 6 weeks is required.

Participant Identification, Enrollment, and Screening Logs

The investigator agrees to complete a participant identification and enrollment log to permit easy identification of each participant during and after the study. This document will be reviewed by the sponsor study-site contact for completeness.

The participant identification and enrollment log will be treated as confidential and will be filed by the investigator in the study file. To ensure participant confidentiality, no copy will be made. All reports and communications relating to the study will identify participants by participant identification and age at initial informed consent. In cases where the participant is not randomized into the study, the date seen and age at initial informed consent will be used.

6. STUDY INTERVENTION AND CONCOMITANT THERAPY

6.1. Study Interventions Administered

The study intervention presentation to be used in this study is a sterile liquid formulation of 175 mg/mL of bermekimab in a prefilled syringe with an injectable volume of 2.0 mL (350 mg of bermekimab per syringe). Bermekimab will be manufactured and provided under the responsibility of the sponsor. Refer to the IB for a list of excipients.

Placebo will be provided centrally by the sponsor.

Commercially available adalimumab will be provided by the sponsor as a sterile liquid containing 40 mg/0.4 mL per vial for SC injection in a PFS.

Part 1:

All participants will receive 4 SC injections at the Week 0 visit (either 4 active, 3 active and 1 placebo, 2 active and 2 placebo, 1 active and 3 placebo, or 4 placebo). From Weeks 1 through 31, all participants will receive 3 SC injections at each administration visit (either 3 active, 2 active and 1 placebo, 1 active and 2 placebo, or 3 placebo). Since 4 SC injections at the Week 0 visit and 3 SC injections will be administered at each administration visit thereafter, each SC injection should be given at a different location of the body. Participants randomized to placebo will receive bermekimab 1050 mg beginning at Week 16 and continuing through Week 31.

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.

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

For details on rescue medications, refer to Section 6.7.1. For a definition of study intervention overdose, refer to Section 6.6.

Guidelines for study intervention administrations affected by the COVID-19 pandemic are found in Section 10.17.

6.2. Preparation/Handling/Storage/Accountability

Preparation/Handling/Storage

Study intervention labels will contain information to meet the applicable regulatory requirements.

Bermekimab (JNJ-77474462) and placebo PFS must be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C) and protected from light according to the product label.

Adalimumab must be stored as indicated on the product-specific labeling.

Refer to the Site IP Binder for additional guidance, including instructions for use, on study intervention preparation, handling, and storage.

Accountability

The investigator is responsible for ensuring that all study intervention received at the site is inventoried and accounted for throughout the study. The study intervention administered to the participant must be documented on the intervention accountability form. All study intervention will be stored and disposed of according to the sponsor's instructions. Study-site personnel must not combine contents of the study intervention containers.

The dispensing of study intervention to the participant, and the return of study intervention from the participant (if applicable), must be documented on the intervention accountability form. Participants must be instructed to return all original containers, whether empty or containing study intervention.

If rescue medication or other medication is also supplied by the sponsor, inclusion of this medication on the intervention accountability form is required. The participants must return unused study intervention to the study site.

Study intervention must be handled in strict accordance with the protocol and the container label and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study intervention, and study intervention returned by the participant, must be available for verification by the sponsor's study site monitor during on-site monitoring visits. The return to the sponsor of unused study intervention, or used returned study intervention for destruction, will be documented on the intervention return form. When the study site is an authorized destruction unit and study intervention supplies are destroyed on-site, this must also be documented on the intervention return form.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids, should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes. The study intervention boxes will be retained for inventory by the sponsor.

Study intervention should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study intervention will be supplied only to participants participating in the study. Returned study intervention must not be dispensed again, even to the same participant. Study intervention may not be relabeled or reassigned for use by other participants. The investigator agrees neither to dispense the study intervention from, nor store it at, any site other than the study sites agreed upon with the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

Intervention Allocation

Procedures for Randomization and Stratification

Dynamic central randomization will be implemented in this study.

The randomization method will be a minimization procedure with biased-coin assignment for both randomizations, which minimizes the imbalance in the distribution of the number of participants across treatment groups within the levels of each individual stratification factor: investigational site and baseline Hurley stage status (II, III). Based on the algorithm, each participant will be assigned to the treatment group which will produce minimum total imbalance score with a high probability, where the total imbalance score is a weighted average of the imbalance scores for each stratification factor and for the whole study. The Interactive Web Response System (IWRS) will assign a unique treatment code, which will dictate the treatment assignment and matching study drug for the participant.

At first, approximately 150 participants in Part 1 will be randomized to receive bermekimab 1050 mg, adalimumab, or placebo in a 1:1:1 ratio. Enrollment will pause once approximately 150 participants are randomized. Two interim analyses will be performed. The first interim analysis will be performed when approximately 75 participants have completed Week 16 or have terminated study participation. The objective of this interim analysis is to assess whether favorable efficacy is seen in the 1050 mg bermekimab dose group.

The second planned interim analysis will take place once the 150 participants have completed study participation to Week 16 or have terminated study participation. The objectives of the second interim analysis are to assess whether a favorable efficacy is seen in the 1050 mg bermekimab dose group if not determined as favorable at the first interim analysis or confirm the favorable efficacy observed from the first interim analysis, or efficacy is low enough to consider termination of the study or the observed efficacy suggests modification to study.

If favorable efficacy is observed in either the first or the second interim analysis, screening and randomization of participants will resume in Part 2 as planned, with additional participants being randomized to receive bermekimab 1050 mg qw, placebo, bermekimab 1050 mg qw→q2w, or 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).

However, if 700 mg qw→q2w is not included in Part 2 based on PK results from Part 1, screening and randomization of participants will resume with additional participants being randomized to receive bermekimab 1050 mg qw, placebo, or bermekimab 1050 mg qw→q2w in a 1:1:2 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). Thus, if the study continues, a total number of approximately 250 or 300 participants will be enrolled in the study.

Otherwise, 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.

The requestor must use his or her own user identification and personal identification number when contacting the IWRS and will then give the relevant participant details to uniquely identify the participant.

Blinding

Active study intervention and placebo will be prepared by an unblinded pharmacist or an unblinded qualified member of the investigational staff. The volume of the placebo will match the volume of the active intervention within each group. Prepared doses will be covered to mask potential visual differences between the active study intervention and placebo. The participants and other site staff members, including the investigator, will be blinded to study intervention allocation through study completion to reduce bias in the assessment of efficacy, safety, and tolerability data.

To ensure that no unintentional unblinding occurs during study intervention administration, at least one qualified site staff member will be designated to perform all SC injections of the IP. This unblinded administrator will have no other contact with the participant during the study and will not discuss the participant's treatment with the participant, the investigator, or other site personnel at any time. The unblinded administrator(s) will be documented in the source documents at each dosing day.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS, which has the functionality to allow the investigator to break the blind for an individual participant.

Data that may potentially unblind the intervention assignment (i.e., study intervention serum concentrations, antibodies to bermekimab, and intervention allocation) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized. This can include making special provisions, such as segregating the data in question from view by the investigators, clinical team, or others as appropriate until the time of database lock and unblinding.

Under normal circumstances, the blind should not be broken until all participants have completed the study and the database is finalized. However, selected sponsor personnel will be unblinded for analysis after the Week 12 DBL from Part 2 has occurred. All site personnel and participants will remain blinded to the treatment assignments until the last participant completes Week 36 evaluations and the database has been locked.

The investigator may in an emergency determine the identity of the intervention by contacting the IWRS. While the responsibility to break the intervention code in emergency situations resides solely with the investigator, it is recommended that the investigator contact the sponsor or its designee if possible, to discuss the particular situation, before breaking the blind. Telephone contact with the sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the sponsor must be informed as soon as possible. The date and reason for the unblinding must be documented in the appropriate section of the eCRF and in the source document. The documentation received from the IWRS indicating the code break must be retained with the participant's source documents in a secure manner.

Participants who have had their intervention assignment unblinded by the investigator will not be eligible to receive further study intervention but should continue complete evaluations specified in the SoA (Section 1.3).

For the planned interim analyses and the DMC, the randomization codes and the translation of randomization codes into intervention and control groups will be disclosed to those authorized and only for those participants included in the interim analysis. For more information, see Sections 9.5 and 9.6.

6.4. Study Intervention Compliance

Because study intervention will be administered at the investigational site for all randomized participants, intervention compliance will be ensured by site personnel.

When study intervention is administered as an SC injection by qualified staff, the details of each administration will be recorded in the eCRF. These will include date, body location, and time of SC injection.

All visits through Week 32 should occur within ±3 days of the scheduled visit throughout the study. Study intervention administration should not occur within 4 days of the last administration of study intervention. If a study visit occurs outside this window, the sponsor should be consulted about how the participant should resume his/her normal dosing schedule relative to the baseline visit (Week 0).

Information regarding study intervention administrations that are administered outside of the scheduled windows or missed will be recorded. Source data will be reviewed and compared with the data entries on the eCRFs to ensure accuracy. Although it is understood that intervention may be interrupted for many reasons, compliance with the intervention schedule is strongly encouraged.

6.5. Dose Modification

No treatment/dose adjustment will be permitted through the study.

6.6. Treatment of Overdose

For this study, any dose of bermekimab greater than the highest dose at a single dosing visit will be considered an overdose. The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AE/serious adverse event (SAE) and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

6.7. Concomitant Therapy

Prestudy therapies administered up to 30 days before first administration of study intervention must be recorded at screening.

Concomitant therapies must be recorded throughout the study from Week 0 through Week 36 or continuing until 5 weeks after the last administration of study intervention. Concomitant therapies on randomized participants should also be recorded beyond that point only in conjunction with SAEs that meet the criteria outlined Section 8.3.1.

When considering use of locally-approved (and including emergency use-authorized) COVID-19 vaccines in study participants, follow applicable local vaccine labelling, guidelines, and standards of care for participants receiving immune-targeted therapy. For study participants receiving a locally-approved (and including emergency use-authorized) COVID-19 vaccine, in order to help identify acute reactions potentially related to COVID-19 vaccine, it is recommended where possible that vaccine and study drug be administered on different days, separated by as large an interval as is practical within the protocol.

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation) different from the study intervention must be recorded in the CRF. If a medication is temporarily discontinued because of abnormal laboratory values, side effects, concurrent illness, or the performance of a procedure, the change and reason for it should be clearly documented in the participant's medical records. Modification of an effective preexisting therapy should not be made for the explicit purpose of entering a participant into the study.

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

6.7.1. Rescue Medication

Rescue interventions are not allowed during the study. However, in the event that a particularly painful HS lesion occurs that necessitates an acute intervention, investigators will have the option to perform protocol-allowed interventions starting at Week 2. Otherwise, the use of rescue interventions should be avoided during the study.

When necessary, 2 types of interventions may be used as rescue:

- Injection with intralesional triamcinolone acetonide suspension (at a concentration of 10 mg/mL, up to 0.5 mL)
- Incision and drainage of the lesion

If incision and drainage is performed, the required over-the-counter soap and water or antiseptic wash should continue to be used. New systemic and topical therapies following incision and drainage (including antibiotics) are prohibited. Concomitant use of wound care dressings is allowed; however, options are limited to alginates, hydrocolloids, and hydrogels. Participants should continue using any ongoing oral and topical therapies (as described in Section 6.7) during the study.

Concomitant therapies associated with the lesion intervention(s) must be captured in the source documentation and on the appropriate eCRF.

The number of interventions allowed during the 32 weeks of the study is defined by the number of lesions present at baseline:

- For participants with an AN count of 5-8 at baseline, it is permissible to perform a single lesion intervention. If a participant with 5-8 lesions at baseline, requires more than 1 intervention during the study, then he or she must be discontinued from IP but continued for follow-up for approximately 5 weeks after last administration of IP.
- For subjects with an AN count >8 at baseline, a total of 2 rescue interventions are permissible. An intervention can occur maximally on 2 different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same visit. If a participant requires more than 2 interventions during the study, then he or she must be discontinued from IP but continued for follow-up for approximately 5 weeks after last administration of study intervention.

All study visit evaluations must occur before any interventions are performed. Any lesion that undergoes an intervention will be documented in the source.

6.7.2. Antiseptic Therapy

Participants must agree to daily use (throughout the entirety of the study) of one of the following over-the-counter treatments to the body areas affected with HS lesions: either soap and water, a dilute bleach bath, or a topical antiseptic wash containing chlorhexidine gluconate or benzoyl peroxide.

6.7.3. Wound Care

Concomitant use of wound care dressings on HS wounds is allowed; however, options are limited to alginates, hydrocolloids, and hydrogels.

6.7.4. Analgesic Therapy

Use of opioid analgesics is prohibited for 14 days prior to the baseline visit regardless of HS or non-HS reasons. During the study, concomitant use of opioid analgesics is also prohibited, except for tramadol as detailed below.

If a participant is on a stable dose/regimen of a non-opioid analgesic (PRN is not considered stable) for a HS-related condition or non- HS medical condition (e.g., osteoarthritis), the participant may continue the analgesic, provided the dose is stable for 14 days prior to baseline and is anticipated to remain stable throughout study participation.

If a participant's pain (HS-related or non-HS-related) worsens after baseline, they may initiate analgesic therapy at any time as follows:

For HS-related pain, permitted analgesics are limited to:

- Non-steroidal anti-inflammatory drugs (NSAIDs, such as Ibuprofen) as per local labeling; AND/OR
- Acetaminophen (paracetamol) as per local labeling; AND/OR
- If HS-related pain is uncontrolled with ibuprofen and/or acetaminophen at the above dosing regimens after the baseline visit, participants can be prescribed tramadol (at a dose of up to 100 mg by mouth every 4 hours), not to exceed 400 mg/24 hours.

Dose adjustments of ibuprofen, acetaminophen, or tramadol, and use of these analgesics on an "as needed" (PRN) basis for HS-related pain up to the maximum permitted dose and frequency, are allowed during the study.

All analgesics and dose adjustments will be captured in the source and on the appropriate eCRF.

For Non-HS-related Pain:
All other non-opioid analgesics and tramadol are allowed at the recommended or prescribed dose.

6.7.5. Prohibited Therapy

Participants who initiate the following treatments during study participation must have their study intervention discontinued:

- Phototherapy (PUVA and/or UVB)
- All biologic therapy with a potential therapeutic impact on the disease being studied, including but not limited to the following:
  - TNF αblockers (adalimumab, etanercept, certolizumab, infliximab, golimumab)
  - IL 1 blockers (anakinra, canakinumab, rilonacept)
  - IL 6 blockers (tocilizumab, sarilumab)
  - IL 23 blockers (ustekinumab, guselkumab, tildrakizumab)
  - IL 17 blockers (secukinumab, ixekizumab, brodalumab)
  - CD20- directed cytolytic antibody (rituximab)
  - Inhibitor of B-Lymphocyte stimulator-specific (belimumab)
  - Integrin receptor antagonist (natalizumab)
  - Inhibitor of T cell activation (abatacept)
  - JAK inhibitor (systemic and topical)
- Any investigational agents for the treatment of HS.
- Any other systemic drug therapies for HS, including but not limited to MTX, cyclosporine, and retinoids.

- Concomitant use of oral antibiotic therapy for HS or inflammatory disorders. Systemic antibiotic use (including oral) is allowed for the treatment of AEs other than a worsening of HS.
- Oral or injectable corticosteroids for the treatment of HS, except for protocol-allowed intralesional rescue therapy as outlined in Section 6.7.1.
- Surgical or laser intervention for an HS lesion except as outlined in Section 6.7.1.

6.7.6. Concomitant Corticosteroid use for Conditions Other than HS

The use of systemic corticosteroids for indications other than HS should be limited to situations for which, in the opinion of the treating physician, there are no adequate alternatives. They should be used on a short-term basis, preferably for ≤2 weeks. Longer-term use of corticosteroids should be discussed with the medical monitor or designee and may require discontinuation of study drug. Intra-articular, or routes of delivery of corticosteroids such as inhaled, otic, ocular, nasal, or other routes of mucosal delivery are allowed throughout the study.

6.7.7. Drugs Metabolized by Cytochrome P450

In vitro studies have shown that IL-1 could impact cytochrome (CYP) enzyme expression and activities (Renton 2005; Abdel-Razzak 1993). As such, suppression of IL-1α by bermekimab, a cytokine modulator, may potentially alter the hepatic metabolism and clearance of drugs that are substrates for CYP enzymes (FDA Guidance 2020). Therefore, upon initiation or discontinuation of bermekimab in patients being treated with CYP substrates with a narrow therapeutic index, monitoring of the effect (eg, warfarin) or drug concentration (eg, theophylline) is recommended and the individual dose of the drug may be adjusted as needed.

6.8. Intervention After the End of the Study

No long-term extension is provided in this Phase 2 study. Participants and investigators will be informed that study intervention will not be made available to them beyond this protocol and that they should return to their treating physician for guidance

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

A participant's study intervention must be discontinued if:

- The participant withdraws consent to receive study intervention.
- The participant or their legally acceptable representative withdraws consent/assent for administration of study intervention.
- The investigator believes that for safety reasons or tolerability reasons (e.g., AE) it is in the best interest of the participant to discontinue study intervention.
- The participant has a serious adverse reaction that is related to an injection including a hypersensitivity reaction. In general, discontinuation of study intervention administration

must be considered for participants who develop a nonserious but severe injection-site reaction.

- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- The participant becomes pregnant or plans a pregnancy during the study period. Refer to Section 10.6.
- The initiation of protocol-prohibited medications, treatments, or interventions (outlined in Section 6.7) that have an impact on HS efficacy evaluations.
- The participant has a malignancy including squamous cell skin cancer. Consideration may be given to allow participants, who develop ≤2 basal cell skin cancers and who are adequately treated with no evidence of residual disease, to continue to receive study intervention.
- A systemic opportunistic infection.
- A recurrent or chronic serious infection.
- The participant is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A participant has symptoms suggestive of active TB based on follow-up assessment questions and/or physical examination or has had recent close contact with a person with active TB and cannot or will not undergo additional evaluation.
  - A participant undergoing evaluation has a chest radiograph with evidence of current active TB and/or a positive QuantiFERON®-TB test result and/or 2 indeterminate QuantiFERON®-TB test results on repeat testing (refer to Section 8.2.8) (and/or a positive tuberculin skin test result in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities).
  - A participant receiving treatment for latent TB discontinues this treatment prematurely or is noncompliant with the therapy.
- The participant is unable to adhere to the study visit schedule or comply with protocol requirements.
- The participant has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness and not representative of signs and symptoms of other recognized clinical syndromes) occurring 1 to 14 days after an injection of study intervention. These may be accompanied by other events including pruritus, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and/or headache.
- The participant has his/her treatment assignment unblinded by the investigator.
- Sponsor decision.

Participants who decide to discontinue study intervention administration for reasons other than those outlined above must be interviewed by the investigator to determine if a specific reason for discontinuing study intervention can be identified. Participants should be explicitly asked about

the possible contribution of AEs to their decision to discontinue study intervention; investigators should confirm that any AE information elicited has been documented. If a participant elects to discontinue study intervention due to an AE, the event should be recorded as the reason for study intervention discontinuation, even if the investigator's assessment is that the AE would not require study intervention discontinuation. The reason for study intervention discontinuation must be documented in the eCRF and in source documents. Study intervention assigned to a participant who discontinues may not be assigned to another participant.

A participant will not be automatically withdrawn from the study if he or she must discontinue treatment before the end of the treatment regimen. Participants who discontinue study intervention but do not terminate study participation will continue to return for protocol-specified procedures and evaluations for approximately 5 weeks following the last administration of study intervention. The procedures and evaluations listed for the Early Termination Visit should also be performed approximately 5 weeks after the last administration of study intervention.

All procedures and evaluations must be conducted prior to a participant's withdrawal of consent.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant will be withdrawn from the study for any of the following reasons:

- Lost to follow-up
- Withdrawal of consent
- Death

To ensure access for participant follow-up, study sites should try to obtain both primary and secondary telephone contact numbers from participants (e.g., home, work, and mobile phones), as well as other contact information such as email addresses, and emphasize the importance of follow-up information to the participant, before randomization. For participants who withdraw from study participation, every effort should be made to conduct the Early Termination Visit assessments, as indicated in the SoA (Section 1.3). If the reason for withdrawal from the study is withdrawal of consent, then no additional assessments are allowed.

Withdrawal of consent should be a very unusual occurrence in a clinical trial; the investigator should make every effort to maintain good participant relationships to avoid withdrawals of consent. For participants who truly request withdrawal of consent, it is recommended that the participant withdraw consent in writing; if the participant or the participant's representative refuses to do so or is physically unavailable, the study-site should document the reason for the participant's failure to withdraw consent in writing, sign the documentation, and maintain it with the participant's source records. When a participant withdraws before completing the study, the reason for withdrawal is to be documented in the eCRF and in the source document. Study intervention assigned to the withdrawn participant may not be assigned to another participant. Participants who withdraw will not be replaced.

7.2.1. Withdrawal From the Use of Research Samples

A participant who withdraws from the study will have the following options regarding the optional research samples:

- The collected samples will be retained and used in accordance with the participant's original separate informed consent for optional research samples.
- The participant may withdraw consent for optional research samples, in which case the samples will be destroyed, and no further testing will take place. To initiate the sample destruction process, the investigator must notify the sponsor study site contact of withdrawal of consent for the optional research samples and to request sample destruction. The sponsor study site contact will, in turn, contact the biomarker representative to execute sample destruction. If requested, the investigator will receive written confirmation from the sponsor that the samples have been destroyed.

Withdrawal From the Optional Research Samples While Remaining in the Main Study

The participant may withdraw consent for optional research samples while remaining in the study. In such a case, the optional research samples will be destroyed. The sample destruction process will proceed as described above.

Withdrawal From the Use of Samples in Future Research

The participant may withdraw consent for use of samples for research (refer to Section 10.4.5). In such a case, samples will be destroyed after they are no longer needed for the clinical study. Details of the sample retention for research are presented in the main ICF and in the separate ICF for optional research samples.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. A participant cannot be deemed lost to follow-up until all reasonable efforts made by the study-site personnel to contact the participant are deemed futile. The following actions must be taken if a participant fails to return to the study site for a required study visit:

- The study-site personnel must attempt to contact the participant to reschedule the missed visit as soon as possible, to counsel the participant on the importance of maintaining the assigned visit schedule, to ascertain whether the participant wishes to or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every reasonable effort to regain contact with the participant (where possible, 3 telephone calls, e-mails, text, and, if necessary, a certified letter to the participant’s last known mailing address, or local equivalent methods). These contact attempts should be documented in the participant’s medical records.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Should a study site close, e.g., for operational, financial, or other reasons, and the investigator cannot reach the participant to inform them, their contact information will be transferred to another study site.

8. STUDY ASSESSMENTS AND PROCEDURES

Overview

The SoA (Section 1.3) summarizes the frequency and timing of efficacy, PK, immunogenicity, biomarker, pharmacogenomic, and safety measurements applicable to this study.

During screening, each participant will be provided with an electronic device to enter patient-reported outcome (PRO) data. Study-site personnel will train the participants on how to use the electronic device (ePRO), including instructions to capture the data according to the study design and not to wait until the study-site visit to record information. Participants will be provided with written instructions on how to get 24-hour technical support, if needed, for operation of the ePRO device.

All visit-specific PRO assessments should be conducted/completed before any tests, procedures or other clinical assessments, except for a urine pregnancy test, to prevent influencing participant perceptions.

Electrocardiograms (ECGs) should precede vital signs and both procedures should be completed prior to any invasive procedures. Vital signs should be recorded from the opposite arm from which blood samples are being taken.

All samples (including safety, efficacy, PK and biomarkers) must be obtained after the PRO and ECG assessments but prior to study intervention administration. Blood collections for PK and biomarker assessments should be kept as close to the specified time as possible. Actual dates of all assessments will be recorded in the source documentation; in addition, times of all blood collections will be recorded in the source documentation (laboratory requisition form).

Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participation in the study. Results of all pregnancy testing should be documented in the participants' source documents.

Guidelines for handling of assessments affected by the COVID-19 pandemic are found in Section 10.18.

Blood Sample Collection

The maximum amount of blood drawn from each participant in this study will not exceed 500 mL as per the standard of the American Red Cross.

In addition, repeat or unscheduled samples may be collected for safety reasons or for technical issues with the samples.

Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the CRF or laboratory requisition form. Refer to the SoA (Section 1.3) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided.

Study-Specific Materials

The investigator will be provided with the following supplies:

- Protocol
- IB for bermekimab
- Site IP Binder
- Laboratory Manual
- Laboratory Kits
- IWRS Manual
- Sample CRF
- eCRF Completion Guidelines
- ePRO equipment (tablet device questionnaires, completion instructions)
- Patient Diary
- Participant Study Participation Card
- Investigative Site File
- Recruitment materials, as needed

8.1. Efficacy Assessments

Efficacy evaluations are consistent with those used to evaluate other therapies for HS and will include the following:

8.1.1. Hidradenitis Suppurativa Investigator's Global Assessment

The HS-IGA (refer to Section 10.9) documents the investigator's assessment of the participant's HS at a given time point. 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.

8.1.2. Hidradenitis Suppurativa Activity and Severity Index

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, Appendix 10 for more details.

8.1.3. Lesion Counts

Lesion counts are defined as the counting of abscesses, inflammatory nodules, non-inflammatory nodules, draining fistulas, and non-draining fistulas.

8.1.4. Images of Skin Lesions

Images of selected HS lesions of the axilla will be taken at a subset of study sites in participants who provide additional consent. Consult the Trial Center File for instruction manual.

8.1.5. Hurley Staging

Hurley staging consists of 3 stages of disease that will be used to determine stratification:

- Stage I: Abscess formation, single or multiple, without sinus tracts and scarring
- Stage II: One or more widely separated recurrent abscesses with tract formation and scarring
- Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement.

Only participants with Hurley Stage II and Hurley Stage III will be enrolled in this study.

8.1.6. Hidradenitis Suppurativa Symptom Diary (HSSD)

The HSSD (refer to Section 10.11 and Section 10.12) 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; see Section 10.12) and one with a 7-day recall (HSSD-7d; see Section 10.11). 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.

8.1.7. Dermatological Life Quality Index (DLQI)

The DLQI (refer to Section 10.13) is a dermatology-specific health-related quality of life (HRQoL) instrument designed to assess the impact of the disease on a participant's HRQoL (Finlay 1994). It is a 10-item questionnaire that assesses HRQoL over the past week and in addition to evaluating overall HRQoL, can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work or school performance, personal relationships, and treatment. The total score ranges from 0 to 30 with a higher score indicating greater impact on QoL (Finlay 1994).

8.1.8. Patient Global Impression of Change (PGIC) of Hidradenitis Suppurativa Severity

The PGIC of HS Severity (refer to Section 10.14) is a questionnaire that measures participants' perceived change (improvement or deterioration) in severity of their HS. Participants will rate how his/her HS has changed since the beginning of the study using a 7-point scale ranging from "a lot better now" to "a lot worse now" with a neutral center point ("neither better nor worse"). PGIC will be used as an anchor to test reliability and establish a clinical response criterion of other patient or physician reported outcomes for future reference.

8.1.9. Patient Global Impression of Severity (PGIS) of Hidradenitis Suppurativa

The PGIS of HS (refer to Section 10.15) is a one-item questionnaire that measures participants' perceived severity of HS. Participants will rate the severity of their HS using a 5-point scale ranging from "none" to "very severe". PGIS will be used as an anchor to establish a clinical response criterion of other patient or physician reported outcomes for future reference. The questionnaire will be administered at time points according to the SoA (Section 1.3).

8.1.10. Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29)

The PROMIS-29 (refer to Section 10.16) is a 29 item generic HRQoL survey, assessing each of the 7 PROMIS domains (depression; anxiety; physical function; pain interference; fatigue; sleep disturbance; and ability to participate in social roles and activities) with 4 questions. The questions are ranked on a 5-point Likert Scale. There is also one 11-point rating scale for pain intensity (PROMIS -29). Participants will undergo this assessment at time points according to the SoA (Section 1.3).

8.1.11. HS Lesion Monitoring Using Medical Infrared Thermography

Medical imaging can be used in the clinical assessment of HS to complement manual palpation (Elkin 2020). As part of the 77474462HDS2001 study, visible light photography and medical infrared thermography (MIT) will be used to acquire images of lesions in HS participants. At baseline and throughout the study, sites will collect images from both axillae (left and right), regardless of presence of HS lesions. Images will be analyzed by computer vision-based algorithms to understand if the images can be used to identify lesion features and lesion heat distribution, which may be indicative of the levels of inflammation in lesions. Finally, imaging

derived metrics will be compared to clinical evaluations of HS axilla lesions to determine the suitability of imaging for objective clinical assessment of HS. Imaging will be conducted in a limited number of participants who consent to this optional substudy at some clinical sites. Details are provided in Appendix 17 (Section 10.17) and instructions for acquiring photographs and completing assessments are provided in the imaging manual. At visits when images are collected, imaging should be completed prior to clinical disease assessment by the investigator. The results of these analyses will be presented in a separate report.

8.2. Safety Assessments

Details regarding the internal independent DMC are provided in Sections 10.4.1 and 10.4.6.

AEs will be reported and followed by the investigator as specified in Sections 8.3 and 10.5.

Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the CRF.

Any clinically significant abnormalities persisting at the end of the study/early withdrawal will be followed by the investigator until resolution or until a clinically stable condition is reached.

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

8.2.1. Physical Examinations

Physical Examination

Physical examinations will be performed by the investigator or designated physician, nurse practitioner or physician assistant as specified in the SoA (Section 1.3). Any new, clinically significant finding (in the opinion of the investigator) must be captured as an AE. In addition, resolution of any abnormal findings during the study will be noted in the source document and in the eCRF.

Height and Weight

Height and weight will be measured as specified in the SoA (Section 1.3). Participants will be instructed to remove shoes and outdoor apparel and gear prior to these measurements.

8.2.2. Vital Signs

Vital signs (including temperature, pulse/heart rate, respiratory rate, and blood pressure) will be obtained before prior to study intervention administration at visits specified in the SoA (Section 1.3).

8.2.3. Electrocardiograms

A single 12-lead ECG will be performed at screening and at Week 16 in Part 1 and Week 12 in Part 2.

8.2.4. Clinical Safety Laboratory Assessments

Blood samples for serum chemistry and hematology will be collected as noted in Section 10.3. The investigator must review the laboratory results, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The laboratory reports must be filed with the source documents.

The tests that will be performed by the central laboratory unless otherwise specified or approved by the medical monitor are specified in Section 10.3.

Female participants of childbearing potential will undergo a pregnancy test at screening, before each study intervention administration, and at the Week 36 or Early Termination Visit.

8.2.5. Concomitant Medication

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

8.2.6. Allergic Reactions

Before any SC injection, appropriately trained personnel and medications must be available to treat allergic reactions, including anaphylaxis. All participants must be observed carefully for symptoms of an allergic reaction (e.g., urticaria, itching, hives). If a mild or moderate allergic reaction is observed, acetaminophen (paracetamol), non-steroidal anti-inflammatory drugs, and/or diphenhydramine may be administered.

In the case of a severe allergic reaction (eg, anaphylaxis), IM or SC aqueous epinephrine, corticosteroids, respiratory assistance, and other proper resuscitative measures may be essential and must be available at the study site where the injections or infusions are being administered (Sampson 2006).

Participants who experience serious adverse reactions related to an injection should be discontinued from further study intervention administrations (see Section 7.1).

8.2.7. Injection-site Reactions

A study intervention injection-site reaction is any adverse reaction at an SC study intervention injection-site. The injection sites will be evaluated for reactions and any injection-site reactions will be recorded as an AE. Participants should be monitored for the occurrence of injection-site reactions for 30 minutes after the study intervention administration.

8.2.8. Tuberculosis Evaluation(s)

8.2.8.1. Initial Tuberculosis Evaluation

Participants must undergo testing for TB (refer to laboratory manual for QuantiFERON®-TB test or Section 10.8 for tuberculin skin test) and their medical history assessment must include specific questions about a history of TB or known occupational or other personal exposure to individuals with active TB. The participant should be asked about past testing for TB, including chest

radiograph results and responses to tuberculin skin or other TB testing. Investigators have the option to use both the QuantiFERON®-TB test and the tuberculin skin test to screen for latent TB if they believe, based on their judgment, that the use of both tests is clinically indicated in order to evaluate a participant who has high risk of having latent TB. If either the QuantiFERON®-TB test or the tuberculin skin test is positive, the participant is considered to have latent TB infection for the purposes of eligibility for this study.

Participants with a negative QuantiFERON-TB® (or T-SPOT® for sites in Japan) test result (and a negative tuberculin skin test result in countries in which the QuantiFERON-TB® test is not approved/registered or the tuberculin skin is mandated by local health authorities) are eligible to continue with pre-randomization procedures. Participants with a newly identified positive QuantiFERON-TB® (or T-SPOT® for sites in Japan or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study.

A participant whose first QuantiFERON-TB® test result is indeterminate should have the test repeated. In the event that the second QuantiFERON-TB® test result is also indeterminate, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. For sites in Japan, a participant whose first T-SPOT® test result is borderline should have the test repeated. In the event that the second T-SPOT® (for sites in Japan) test result is also borderline, the participant may be enrolled without treatment for latent TB if active TB is ruled out, their chest radiograph shows no abnormality suggestive of TB (active or old, inactive TB) and the participant has no additional risk factors for TB as determined by the investigator. This determination must be promptly reported to the medical monitor or designee and recorded in the participant's source documents and initialed by the investigator.

8.2.8.2. Ongoing Tuberculosis Evaluation

Early Detection of Active Tuberculosis

To aid in the early detection of TB reactivation or new TB infection during study participation, participants must be evaluated for signs and symptoms of active TB at scheduled visits (refer to the SoA in Section 1.3). The following series of questions is suggested for use during the evaluation:

- “Have you had a new cough of >14 days’ duration or a change in a chronic cough?”
- “Have you had any of the following symptoms:
  - Persistent fever?
  - Unintentional weight loss?
  - Night sweats?”

- "Have you had close contact with an individual with active TB?" (If there is uncertainty as to whether a contact should be considered "close," a physician specializing in TB should be consulted.)

If the evaluation raises suspicion that a participant may have TB reactivation or new TB infection, an immediate and thorough investigation should be undertaken, including, where possible, consultation with a physician specializing in TB.

Investigators should be aware that TB reactivation in immunocompromised participants may present as disseminated disease or with extrapulmonary features. Participants with evidence of active TB should be referred for appropriate treatment.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment for latent TB is warranted.

Participants who experience close contact with an individual with active TB during the conduct of the study must have a repeat chest radiograph, a repeat QuantiFERON®-TB (or T-SPOT® for sites in Japan) test, a repeat tuberculin skin test in countries in which the QuantiFERON®-TB test is not approved/registered or the tuberculin skin test is mandated by local health authorities, and, if possible, referral to a physician specializing in TB to determine the participant's risk of developing active TB and whether treatment is warranted. Study intervention administration should be interrupted during the investigation. A positive QuantiFERON®-TB (or T-SPOT® for sites in Japan) test or tuberculin skin test result should be considered detection of latent TB. Participants with a newly identified positive QuantiFERON-TB® (or T-SPOT® for sites in Japan or tuberculin skin) test result must undergo an evaluation to rule out active TB and initiate appropriate treatment for latent TB. Appropriate treatment for latent TB is defined according to local country guidelines for immunocompromised patients. If no local country guidelines for immunocompromised patients exist, US guidelines should be followed, or the participant will be excluded from the study. If the QuantiFERON-TB® test result is indeterminate, the test should be repeated. For sites in Japan, a participant whose first T-SPOT® test result is borderline should have the test repeated. Participants should be encouraged to return for all subsequent scheduled study visits according to the protocol. Participants who discontinue treatment for latent TB prematurely or who are noncompliant with therapy must immediately discontinue further administration of study intervention and be encouraged to return for all subsequent scheduled study visits according to the SoA (Section 1.3).

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

Timely, accurate, and complete reporting and analysis of safety information, including AEs, SAEs, and product quality complaints (PQCs), from clinical studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide.

The sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally acceptable representative) for the duration of the study.

Anticipated events related to HS exacerbation will be recorded and reported as described in Section 10.2.

Further details on AEs, SAEs and PQC can be found in Section 10.5.

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All Adverse Events

All adverse events and special reporting situations, whether serious or non-serious, will be reported from the time a signed and dated ICF is obtained until completion of the participant's last study-related procedure, which may include contact for follow-up of safety.

Serious Adverse Events

All serious adverse events, as well as PQC, occurring during the study must be reported to the appropriate sponsor contact person by study-site personnel within 24 hours of their knowledge of the event.

Serious adverse events, including those spontaneously reported to the investigator within 12 weeks after the last administration of study intervention, must be reported using the Serious Adverse Event Form. The sponsor will evaluate any safety information that is spontaneously reported by an investigator beyond the time frame specified in the protocol.

A possible Hy's law Case is defined by the occurrence of alanine transaminase/aspartate transaminase ≥3 x upper limit of normal (ULN), alkaline phosphatase <2 x ULN together with total bilirubin ≥2 x ULN or international normalized ratio >1.5 (if measured). Any possible Hy's Law case is considered an important medical event and should be reported to the sponsor in an expedited manner, even before all other possible causes of liver injury have been excluded.

Information regarding SAEs will be transmitted to the sponsor using the Serious Adverse Event Form and Safety Report Form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted to the sponsor within 24 hours. The initial and follow-up reports of an SAE should be transmitted electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Solicited Adverse Events

Solicited AEs are predefined local at the injection site and systemic events for which the participant is specifically questioned and which are noted by participants in their diary (see Section 8).

Unsolicited Adverse Events

Unsolicited AEs are all AEs for which the participant is not specifically questioned in the participant diary.

8.3.3. Follow-up of Adverse Events and Serious Adverse Events

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and evaluations as medically indicated to elucidate the nature and causality of the AE, SAE or PQC as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. AEs, including pregnancy, will be followed by the investigator as specified in Section 10.5.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events and Anticipated Events

The sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities. The sponsor will also report to the investigator (and the head of the investigational institute where required) all suspected unexpected serious adverse reactions (SUSARs). The investigator (or sponsor where required) must report SUSARs to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB. A SUSAR will be reported to regulatory authorities unblinded. Participating investigators and IEC/IRB will receive a blinded SUSAR summary, unless otherwise specified.

An anticipated event is an AE that commonly occurs in the study population independent of exposure to the drug under investigation. For the purposes of this study the following SAEs will be considered anticipated events:

- Worsening of HS

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

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

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

8.3.5. Pregnancy

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using a serious adverse event reporting form. Any participant who becomes pregnant during the study must discontinue further study intervention (see Section 7.1).

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

8.3.6. Adverse Events of Special Interest

Any newly identified malignancy or case of active TB occurring after the first study intervention administration(s) in participants participating in this clinical study must be reported by the investigator according to the procedures in Section 10.5. Investigators are also advised that active TB is considered a reportable disease in most countries. These events are to be considered serious only if they meet the definition of an SAE.

8.4. Pharmacokinetics and Immunogenicity

Blood samples will be collected for the measurement of serum bermekimab concentrations and antibodies to bermekimab at the time points presented in the SoA.

At visits in which serum bermekimab concentration and/or antibodies to bermekimab will be evaluated, 1 venous blood sample of sufficient volume should be collected, and each serum sample should be divided into 3 aliquots: 1 for serum concentration of bermekimab and a back-up. Each serum sample will be divided into 3 aliquots: 1 for serum concentration of bermekimab, 1 for antibodies to bermekimab, and 1 back-up.

Blood samples should also be collected at the final visit or at the Early Termination Visit from participants who are discontinued from intervention or withdrawn from the study. Blood samples collected for serum bermekimab concentrations may also be used for exploratory biomarker analyses.

A random venous blood sample for population PK analysis will be collected from all participants on any day between Weeks 2 to 12, except on the days of the scheduled study visits. Additionally, this blood sample must be collected at least 24 hours prior to or after the actual time of study intervention administration. Each population PK serum sample will be divided into 2 aliquots: 1 for serum concentration of bermekimab and a back-up.

The exact dates and times of blood sample collection must be recorded in the laboratory requisition form. See the laboratory manual for further information regarding collection, handling, and shipment of biological samples. Genetic analyses will not be performed on these serum samples. Participant confidentiality will be maintained.

Pharmacokinetic Analytical Procedures

Serum samples will be analyzed to determine serum bermekimab concentrations using a validated, specific, and sensitive immunoassay method under the supervision of the sponsor. The sponsor, or its designee, under conditions in which the participants' identity remains blinded, will assay these samples.

Immunogenicity Analytical Procedures

The detection and characterization of antibodies to bermekimab will be performed using a validated, drug-tolerant immunoassay method by or under the supervision of the sponsor. Serum samples will be screened for antibodies binding to bermekimab and the titer of confirmed positive samples will be reported. Antibodies to bermekimab may be further characterized and/or evaluated for their ability to neutralize the activity of bermekimab.

8.5. Genetics and Pharmacogenomics

Genetic and epigenetic variation can be an important contributory factor to interindividual differences in drug disposition and response and may also serve as a marker for disease susceptibility and prognosis. Pharmacogenomic research consists of the analysis of one or more candidate genes or of the analysis of markers throughout the genome (as appropriate) in relation to bermekimab or HS clinical endpoints. The goal of the pharmacogenomic/epigenomic component is to explore factors that may influence the PK, PD, efficacy, or tolerability of bermekimab and to evaluate genetic factors previously reported to be associated with HS or help identify new associations. These DNA samples may be used to help address emerging issues and to enable the development of safer, more effective, and more precisely applied therapies.

A pharmacogenomic blood sample will be collected from participants who consent separately to this component of the study to allow for pharmacogenomic research, as necessary (where local regulations permit). Genotyping or sequencing techniques will be used to assess variation genome-wide. Participation in pharmacogenomic research is optional.

8.6. Biomarkers

Biomarker samples will be collected to evaluate the PD and mechanism of action of bermekimab or help to explain interindividual variability in clinical outcomes or may help to identify population subgroups that respond differently to the intervention. The goal of the biomarker analyses is to evaluate the PD of and aid in evaluating the intervention-clinical response relationship.

Biomarker assessments will include the evaluation of relevant markers in blood and wound exudate (when present) for all participants. Genetic analysis, skin biopsies, FibroTx Transdermal Patch analysis (when kits are available), and skin swabs will also be collected from participants who consent to this optional part of the study. The samples will be used to better understand the biology of HS; to provide biological assessment of the response of participants to treatment with bermekimab; to analyze differences between responders and nonresponders; and to determine if the markers can be used to classify participants as potential responders prior to treatment. Blood samples will be separated into serum, plasma, and peripheral blood mononuclear cells (PBMCs)

for biomarker analysis. Samples for serum biomarkers, flow cytometry and gene expression from blood will be collected at time points according to the SoA (Section 1.3). Instructions for the collection and shipment of these samples are found in the Laboratory Reference Manual and Biopsy Collection Manual.

8.6.1. Skin Biomarkers

Wound exudates (from all participants when present) and FibroTx Patch assessments (from participants who consent to this optional part of the study and when kits are available) will be collected at time points specified in the SoA (Section 1.3). Protein analysis will be done to monitor the PD effect and to understand mechanism of action of bermekimab.

Participants may participate in collection of biopsies (nodule and ultrasound guided deep tunnel biopsy) and/or skin swabs for microbiome analysis in this optional part of the study.

Skin biopsy samples will be collected from participants that consent to this optional part of the study at time points specified in the SoA (Section 1.3). At baseline, biopsy samples will be collected from both lesional (nodule) and adjacent non-lesional areas (10 cm away from the lesional nodule). At subsequent time points (Week 16 and Week 32 in Part 1, and Week 12 and Week 32 in Part 2), only lesional areas will be sampled. At Week 16 in Part 1 and Week 12 in Part 2, 2 nodules and 1 tunnel (if present) will be sampled. If a participant consents to undergoing Week 32 biopsies, 1 nodule and 1 tunnel biopsy will be sampled at Week 32. Gene expression analysis of skin biopsy samples will be performed to investigate differential gene expression during treatment compared to baseline to explore PD, mechanism of action, and differences in responders versus nonresponders. Proteomic analysis will be used to explore the target occupancy and the treatment effect on the affected skin. All skin biopsies and sampling should be completed after completion of the disease severity assessments by the investigator/sub-investigator. In addition, the tissue biopsies may be analyzed for histological readouts and immunohistochemistry to explore the effects of study intervention on cellular composition within skin tissue. Skin swabs will be collected to study the effect of intervention on microbiome composition on affected skin.

8.6.2. Serum Biomarkers

Serum samples will be collected from all participants at time points specified in the SoA (Section 1.3). Potential circulating factors to be evaluated may include cytokines and other inflammatory markers (eg, IL-6, IL-8, TNFα, SAA), and other categories of biomarkers potentially associated with HS or related to the mechanism of action of bermekimab.

8.6.3. Plasma Biomarkers

Plasma samples will be collected from all participants at time points specified in the SoA (Section 1.3). Potential circulating factors to be evaluated may include complements and other biomarkers potentially associated with HS or related to the mechanism of action of bermekimab.

8.6.4. Flow Cytometry Analysis

Whole blood samples will be collected from all participants at time points specified in the SoA (Section 1.3), and PBMC will be isolated. Flow cytometry analysis of blood cell samples will be

utilized to monitor the effects of bermekimab on circulating immune cell populations. Cell surface markers such as, but not limited to, those for T cell subsets (eg, Th1, Th2), dendritic cells, and B cells will be assessed.

8.6.5. Gene Expression Analysis in Whole Blood

Whole blood samples will be collected from all participants at time points specified in the SoA (Section 1.3). Total RNA will be isolated and used for differential gene expression analyses to better understand the pathologic mechanisms involved in HS and to potentially identify a treatment response signature to bermekimab.

Stopping Analysis

Biomarker analyses are dependent upon the availability of appropriate biomarker assays and clinical response rates. Biomarker analysis may be deferred or not performed, if during or at the end of the study, it becomes clear that the analysis will not have sufficient scientific value for biomarker evaluation, or if there are not enough samples or responders to allow for adequate biomarker evaluation. In the event the study is terminated early or shows poor clinical efficacy, completion of biomarker assessments is based on justification and intended utility of the data.

8.7. Health Economics

Health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the SAP.

9.1. Statistical Hypotheses

The 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, and at Week 12 in Part 2.

- 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.

9.2. 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%

9.3. Populations for Analysis Sets

For the efficacy analyses in this study, the full analysis set (FAS) will be used according to the participants' assigned treatment to which they were randomized, regardless of the treatment they actually received. The FAS includes all randomized participants who receive at least one administration of study intervention. The FAS will be used for all primary and secondary efficacy analyses.

Safety analyses will include all participants who received at least 1 administration of study intervention and participants will be analyzed based on the treatment they actually received, regardless of the treatment groups to which they were assigned.

Pharmacokinetics analyses for bermekimab will include participants who receive at least one administration of bermekimab and have at least one post-dose sample collection. Antibodies to bermekimab will be analyzed for participants who receive at least one dose of bermekimab and have at least one post-dose sample collection.

9.4. Statistical Analyses

9.4.1. Statistical Methods

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

In general, treatment comparisons for binary endpoints will be performed using a Cochran-Mantel-Haenszel (CMH) test stratified by baseline Hurley stage status. For continuous efficacy endpoints, treatment comparisons will be performed using a Mixed-Effect Model Repeated Measure (MMRM) model. The MMRM will include treatment, visit, baseline value for the corresponding efficacy endpoint, baseline Hurley stage status, baseline value by visit interaction, baseline Hurley stage status by visit interaction and the treatment-by-visit interaction, if applicable. The Least Square mean (LSmean) estimates and their corresponding 95% CIs will be provided at each time point. In addition, the estimates of LSmean difference and 95% CIs between treatment groups will be provided.

In general, all statistical testing will be performed at a significance level of 0.05 (2-sided) unless otherwise specified. Nominal p-values will be displayed for all treatment comparisons.

9.4.2. Efficacy Analyses

9.4.2.1. Primary Endpoint

The primary efficacy endpoint is the proportion of participants with a clinical response at Week 16 in Part 1, and at Week 12 in Part 2, defined according to the HiSCR50 measure as at least a 50% reduction from baseline in the total abscess and inflammatory- nodule count, with no increase in the abscess or draining fistula count.

9.4.2.1.1. Primary Estimand 1

Primary Estimand 1: The primary estimand 1 (ie, a precise definition of the primary targeted treatment effect) is defined by the following 5 attributes:

- **Population:** adult participants with moderate to severe HS.
- **Variable/endpoint:** HiSCR50 binary responder variable at Week 16 in Part 1.
- **Treatment:**
  - Experimental: Bermekimab1050 mg qw.
  - Active Comparator: Adalimumab
  - Control: Placebo

- **Intercurrent Events and Corresponding Analysis Strategies:**

Intercurrent Events	Analysis Strategy for Addressing Intercurrent Events
1. Discontinuation of study intervention due to lack of efficacy or an AE of worsening of HS. 2. Initiation of a protocol-prohibited medication or therapy that could improve H S during the study.	**Composite Strategy:** Participants are considered HiSCR50 nonresponders at the time of primary endpoint if they experience this intercurrent event prior to Week 16 in Part 1.
3. Discontinuation of study intervention for other reasons.	**Treatment policy strategy:** Observed data will be used regardless of whether or not this intercurrent event had occurred.

Note: For participants experiencing multiple intercurrent events (ICEs), ICE 2 will override ICE 3.

- **Population level summary:** Difference in the proportions of participants achieving HiSCR50 at Week 16 in Part 1, between the bermekimab and placebo treatment groups.

9.4.2.1.2. Primary Estimand 2

Primary Estimand 2: The primary estimand 2 is also defined by the following 5 attributes as the primary estimand 1:

- **Population:** adult participants with moderate to severe HS.
- **Variable/endpoint:** HiSCR50 binary responder variable at Week 12 based on the combined data from Part1 and Part 2.
- **Treatment:**
  - Experimental: Bermekimab 700 mg qw→q2w (starting at Week 12), 1050 mg qw→q2w (starting at Week 12), and 1050 mg qw. For the primary analysis, bermekimab 1050 mg qw →q2w and 1050 mg qw groups will be combined as 1050 mg group and bermekimab 700 mg qw → q2w group will be denoted as 700 mg group.
  - Control: Placebo
- **Intercurrent Events and Corresponding Analysis Strategies:**

Intercurrent Events	Analysis Strategy for Addressing Intercurrent Events
1 Discontinuation of study intervention due to lack of efficacy or an AE of worsening of HS. 2 Initiation of a protocol-prohibited medication or	**Composite Strategy:** Participants are considered HiSCR50 nonresponders at the time of primary endpoint if they experience this intercurrent event prior to Week 12 in Part 1 and Part 2

	therapy that could improve H S during the study.	
3	Discontinuation of study intervention for other reasons.	**Treatment policy strategy:** 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.

- **Population level summary:** Difference in the proportions of participants achieving HiSCR50 at Week 12 based on the combined data from both Part 1 and Part 2 of the study between the bermekimab and placebo treatment groups.

9.4.2.1.3. Primary Endpoint Analysis

In the primary efficacy analysis, data from all randomized participants who received at least 1 administration of study intervention will be analyzed according to their assigned treatment group.

In this primary analysis, the proportion of participants who achieve a HiSCR50 at Week 16 in Part 1, and at Week 12 based on the combined data from Part 1 and Part 2 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.

There will be 3 comparisons for the primary analyses. The proportion of participants who achieve HiSCR50 will be compared between bermekimab treatment groups and the placebo group based on the fixed-sequence testing approach. To maintain an overall Type I error rate of 0.1, the 3-pairwise comparisons will be performed sequentially at a two-sided alpha level of 0.1 in the following order:

1. Bermekimab 1050 mg group versus Placebo at Week 12 based on the combined data from Part 1 and Part 2

2. Bermekimab 1050 mg group versus Placebo at Week 16 based on the data from Part 1

3. Bermekimab 700 mg group versus Placebo at Week 12 based on the combined data from Part 1 and Part 2

With the pre-specified sequential analyses, whenever a prior comparison is not significant at a two-sided alpha level of 0.1, the remaining treatment group comparisons will be considered nonsignificant and the p-values from the remaining treatment group comparison will be considered nominal.

In addition, the comparison between adalimumab and placebo for the primary endpoint at Week 16 in Part 1 will also be performed.

This method is to control the type-1 error at 10% level or less and will only be implemented for the primary efficacy analysis. The study will be considered positive if one of the hypotheses is tested as significant at a 2-sided alpha level of 0.10.

To examine the robustness of the primary endpoint analysis, additional analyses will be conducted using different missing data approaches; these analyses will be described in the SAP. In addition, sensitivity analyses will be performed for the primary endpoint using the per-protocol population, which includes participants who are generally compliant with the protocol.

To evaluate the consistency of the efficacy, subgroup analyses of the primary endpoint will be performed.

9.4.2.2. Secondary Endpoints

In addition to the primary endpoint analysis, the analyses for secondary efficacy endpoints will be performed. No adjustments for multiple comparisons will be made for the secondary endpoints and nominal p-values will be provided. The efficacy endpoints will also be summarized over time. Additional efficacy analyses may be performed and will be documented in the SAP.

- The proportion of participants who achieved HiSCR75 and HiSCR90 at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in AN count at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The 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 will be compared between each of the bermekimab groups and the placebo group.
- The proportion of participants achieving AN count of 0/1 and 0/1/2 at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The proportion of participants who achieved complete elimination of abscesses at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group among participants who had any abscess at baseline.
- The change from baseline in number of abscesses at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The proportion of participants who achieved complete elimination of draining fistulas at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group among those with draining fistulas at baseline.
- The change from baseline in number of draining fistulas at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The proportion of participants who achieved complete elimination of inflammatory nodules at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group among those with inflammatory nodules at baseline.

- The change from baseline in international hidradenitis suppurativa severity score (IHS4) at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in number of inflammatory nodules at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of 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, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The proportion of participants with HS-IGA score of inactive (0), 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 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in DLQI at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in HSSD-24h total symptom score at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in pain scale score of HSSD-24h at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in itch scale score of HSSD-24h at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.

The comparison between the adalimumab and placebo groups for the secondary endpoints at Week 16 in Part 1 listed above will also be performed at a 2-sided significance level of 0.1. Nominal p-values will be reported. No adjustments for multiple comparisons will be made for the secondary endpoints.

In addition, to assess the relative efficacy between the bermekimab and adalimumab groups, for selected binary endpoints (including HiSCR50 at Week 16), the difference in proportion of participants achieving these endpoints at Week 16 and Week 32 in Part 1 between the bermekimab group and the adalimumab group, and the corresponding 80% CIs, will be calculated. No hypothesis testing will be performed.

9.4.2.3. Exploratory Endpoints

The following endpoints will be explored as exploratory endpoints. The secondary efficacy endpoints specified in Section 9.4.2.2 and selected efficacy endpoints in this section will also be summarized over time as exploratory analyses based on the combined data from Part 1 and Part 2. Detailed analyses will be specified in the SAP.

- The change from baseline in HASI at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.

- The distribution of the PGIS scale at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The distribution of the PGIC scale at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- The change from baseline in PROMIS-29 total score and sub-scores at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- Change from baseline in HSSD-7d score at Week 16 in Part 1, and at Week 12 in Part 2 will be compared between each of the bermekimab groups and the placebo group.
- Change in high-sensitivity C-reactive protein (hs-CRP) from baseline to Week 16 in Part 1, and at Week 12 in Part 2.

9.4.3. Safety Analyses

Safety data, including but not limited to, AEs, SAEs, discontinuation of study intervention due to AEs, changes in laboratory assessments, changes in vital signs, and changes in weight will be summarized. Intervention-emergent AEs will be summarized by treatment group and Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred terms. Details will be specified in the SAP.

Safety Definition

Injection-Site Reactions

An injection-site reaction is any unfavorable or unintended sign that occurs at an injection-site and will be recorded as an AE. Detailed instructions for the evaluation of injection-site reactions are in the Trial Center File.

Adverse Events

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the MedDRA. Intervention-emergent AEs are AEs with onset during the intervention period or that are a consequence of a preexisting condition that has worsened since baseline. All intervention-emergent AEs will be included in the analysis. For each AE, the percentage of participants who experience at least 1 occurrence of the given event will be summarized by intervention group. In addition, comparisons between intervention groups will be provided if appropriate.

The following analyses will also be used to assess the safety of participants in the study:

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of severe AEs.
- The incidence and type of reasonably related AEs as assessed by the investigator.
- The incidence and type of AEs leading to discontinuation of study.
- The incidence and type of injection-site reactions.

Listings of participants with SAEs, severe AEs, AEs leading to discontinuation of study and anaphylactic reaction/serum sickness reactions will also be provided. All safety analyses will be based on the population of participants who received at least 1 administration of study intervention; participants will be summarized by the intervention they received.

Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test (eg, hematology, clinical chemistry). Selected laboratory parameters will be summarized by treatment groups. Common Terminology Criteria (CTC) will be used to identify abnormal laboratory test results, and the incidence and severity of abnormal laboratory parameters (hematology and chemistry) will be summarized by treatment group.

In addition, a listing of participants with Grade 2 or higher laboratory test results (based on the CTC criteria) will also be provided.

Vital Signs

Descriptive statistics of heart rate and blood pressure (systolic and diastolic) values and changes from baseline will be summarized at each scheduled time point.

Weight

Descriptive statistics of changes from baseline will be summarized at selected scheduled time points.

9.4.4. Other Analyses

Pharmacokinetic Analyses

The PK evaluable population is defined as all the participants who received at least 1 complete dose of bermekimab and had at least 1 valid blood sample drawn for PK analysis after their first dose of bermekimab.

Serum bermekimab concentrations will be summarized by visit and treatment group. Descriptive statistics will be calculated at each sampling time point. Concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All serum concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration database. PK data may also be displayed graphically.

If feasible, population PK analysis of serum concentration-time data of bermekimab may be performed using nonlinear mixed-effects modeling. Data may be combined with those of other selected studies to support a relevant structural model. Available baseline participant characteristics (demographics, laboratory variables, genotypes, race, etc.) will be tested as potential covariates affecting PK parameters. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

If data permit, the relationships between serum bermekimab concentration and efficacy may be examined when appropriate. If a relationship is observed, a suitable PK/PD model may be developed to describe the exposure-response relationship and will be presented in a separate technical report.

Immunogenicity Analyses

The incidence and titers of antibodies to bermekimab will be summarized for all participants who receive at least 1 dose of bermekimab and have appropriate samples for detection of antibodies to bermekimab (i.e., participants with at least 1 sample obtained after their first dose of bermekimab).

A listing of participants who are positive for antibodies to bermekimab will be provided. The maximum titers of antibodies to bermekimab will be summarized for participants who are positive for antibodies to bermekimab.

The incidence of neutralizing antibodies (NAbs) to bermekimab will be summarized for participants who are positive for antibodies to bermekimab and have samples evaluable for NAbs to bermekimab.

Other immunogenicity analyses may be performed to further characterize the immune responses that are generated.

Biomarkers Analyses

Planned biomarker analyses may be deferred if emerging study data show no likelihood of providing useful scientific information. Any biomarker samples received by the contract vendor or sponsor after the cutoff date will not be analyzed, and therefore, excluded from the biomarker analysis.

Changes in biomarkers over time will be summarized by treatment group. Associations between baseline levels and changes from baseline in select markers and response to treatment will be explored. The analyses will aim to identify biomarker relevant to treatment. Results of biomarker analyses will be reported in separate technical reports.

Pharmacogenomic Analyses

DNA samples will be used for research related to bermekimab or HS. They may also be used to develop tests/assays related to bermekimab and HS. Pharmacogenomic research may consist of the analysis of one or more candidate genes or of the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate) in relation to bermekimab or HS clinical endpoints.

Results will be presented in a separate report.

9.5. Interim Analysis

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

The IAC will review the unblinded efficacy data and provide recommendations about the next step of study conduct based upon the results of the first (approximately n=75) and/or second (approximately n=150) interim efficacy analyses. Interim analyses will be performed based on the primary endpoint, which is the proportion of participants achieving HiSCR50 at Week 16, and other selected efficacy endpoints. PK and biomarker analyses may also be performed at the interim analysis. Details of the plan for the interim analyses will be specified in the Interim Analysis SAP. The unblinded results will be limited to specific sponsor personnel not involved in the study. Interim analysis results will be not disseminated to investigators or individuals associated with the conduct of the study.

As specified in Section 4.1, this study will employ 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 2 interim analyses.

At first, approximately 150 participants will be randomized to receive bermekimab 1050 mg, adalimumab, or placebo in a 1:1:1 ratio. Enrollment will pause once approximately 150 participants are randomized. Two interim analyses will be performed. The first analysis will be performed when approximately 75 participants have completed Week 16 or have terminated study participation. The objective of this interim analysis is to assess whether favorable efficacy is seen in the 1050 mg bermekimab dose group or efficacy is low enough to consider termination of the study. Details will be specified in Interim Analysis Plan.

The second planned interim analysis will take place once the 150 participants have completed study participation to Week 16 or have terminated study participation. The objectives of the second interim analysis are to assess whether a favorable efficacy is seen in the 1050 mg bermekimab dose group if not determined as favorable at the first interim analysis or confirm the favorable efficacy observed from the first interim analysis, or efficacy is low enough to consider termination of the study or the observed efficacy suggests modification to study. Additional interim analysis for PK may take place based on the available PK samples when 150 participants reach Week 8 to enable coordinating output with efficacy at Week 16.

9.6. Data Monitoring Committee

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.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Abbreviations

AD	atopic dermatitis
AE	adverse event
AN	Abscess and inflammatory nodule
ARC	Anticipated Event Review Committee
BCG	Bacille Calmette-Guérin
β-hCG	Beta-human chorionic gonadotropin
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CRF	case report form(s) (paper or electronic as appropriate for this study)
CTC	Common Terminology Criteria
CYP	cytochrome
DBL	database lock
DLQI	Dermatological Life Quality Index
ECG	Electrocardiogram
eDC	electronic data capture
FAS	full analysis set
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HASI	Hidradenitis Suppurativa Activity and Severity Index
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HiSCR	Hidradenitis Suppurativa Clinical Response
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
HRT	hormonal replacement therapy
HS	hidradenitis suppurativa
hs-CRP	high-sensitivity-C-reactive protein
HS-IGA	Hidradenitis Suppurativa Investigator's Global Assessment
HSSD	Hidradenitis Suppurativa Symptom Diary
HSSD-24h	Hidradenitis Suppurativa Symptom Diary 24-hour recall
HSSD-7d	Hidradenitis Suppurativa Symptom Diary 7-day recall
IAC	Interim Analysis Committee
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG1k	immunoglobulin G1 kappa
IHS4	International Hidradenitis Suppurativa Severity Score System
IL-1α	interleukin-1 alpha
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous(ly)
IWRS	interactive web response system
LSmean	Least Square mean
mAb	monoclonal antibody
MCP-Mod	Multiple Comparison Procedures with modeling
MedDRA	Medical Dictionary for Regulatory Activities
MIT	medical infrared thermography
MMRM	Mixed-Effect Model Repeated Measure
MTX	methotrexate
NABs	neutralizing antibodies

NSAIDs	non-steroidal anti-inflammatory drugs
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamic(s)
PFS	prefilled syringe
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PQC	Product Quality Complaint
PRO	patient-reported outcome(s)
PROMIS-29	Patient-Reported Outcomes Measurement Information System-29
QoL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous(ly)
SD	standard deviation
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
TB	tuberculosis
TEAE	treatment-emergent adverse events
TNF	tumor necrosis factor

10.2. Appendix 2: Anticipated Events

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease-related) or background regimen.

For the purposes of this study the following events will be considered anticipated events:

- Worsening of hidradenitis suppurativa

Reporting of Anticipated Events

All AEs will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described under All Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described under Serious Adverse Events in Section 8.3.1, Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information. These anticipated events are exempt from expedited reporting as individual single cases to health authorities. However, if based on an aggregate review, it is determined that an anticipated event is possibly related to study intervention, the sponsor will report these events in an expedited manner.

Anticipated Event Review Committee

An Anticipated Event Review Committee (ARC) will be established to perform reviews of prespecified anticipated events at an aggregate level. The ARC is a safety committee within the sponsor's organization that is independent of the sponsor's study team. The ARC will meet to aid in the recommendation to the sponsor's study team as to whether there is a reasonable possibility that an anticipated event is related to the study intervention.

Statistical Analysis

Details of statistical analysis of anticipated events, including the frequency of review and threshold to trigger an aggregate analysis of anticipated events will be provided in a separate Anticipated Events Safety Monitoring Plan.

10.3. Appendix 3: Clinical Laboratory Tests

The following tests will be performed according to the SoA by the central laboratory:

Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet count Red blood cell count Hemoglobin Hematocrit	RBC Indices: MCV MCH % Reticulocytes	White Blood Cell (WBC) count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	Sodium Potassium Chloride Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic Alanine aminotransferase (ALT)/Serum glutamic-oxaloacetic	Total bilirubin Indirect bilirubin Alkaline phosphatase Calcium Phosphate Albumin Total protein Lactate dehydrogenase (LDH)	
	Note: Details of the liver chemistry stopping criteria and required actions and follow-up are given in Section 10.19, Liver Safety. Potential Hy's Law case (ALT or AST ≥3 x ULN and Tbili ≥2 x ULN) reporting requirements are defined in Section 8.3.1.		
Other Laboratory Tests	• Urine pregnancy testing for women of childbearing potential only • Serum Pregnancy Testing for women of childbearing potential only (at Screening only) • Lipids (Week 0 only: Part 1) • Fasting lipid panel: high-density lipoprotein, low-density lipoprotein (calculated), total cholesterol, triglycerides (Weeks 0, 1, and 12: Part 2) • High-sensitivity C-reactive protein Serology (HIV antibody, hepatitis B surface antigen [HBsAg], hepatitis B surface antibody [anti-HBs], hepatitis B core antibody [anti-HBc], and hepatitis C virus antibody)		

10.4. Appendix 4: Regulatory, Ethical, and Study Oversight Considerations

10.4.1. Regulatory and Ethical Considerations

Investigator Responsibilities

The investigator is responsible for ensuring that the study is performed in accordance with the protocol, current ICH guidelines on Good Clinical Practice (GCP), and applicable regulatory and country-specific requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of study participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible.

Protocol Amendments

Neither the investigator nor the sponsor will modify this protocol without a formal amendment by the sponsor. All protocol amendments must be issued by the sponsor and signed and dated by the investigator. Protocol amendments must not be implemented without prior IEC/IRB approval, or when the relevant competent authority has raised any grounds for non-acceptance, except when necessary to eliminate immediate hazards to the participants, in which case the amendment must be promptly submitted to the IEC/IRB and relevant competent authority. Documentation of amendment approval by the investigator and IEC/IRB must be provided to the sponsor. When the change(s) involve only logistic or administrative aspects of the study, the IEC/IRB (where required) only needs to be notified.

During the course of the study, in situations where a departure from the protocol is unavoidable, the investigator or other physician in attendance will contact the appropriate sponsor representative listed in the Contact Information page(s), which will be provided as a separate document. Except in emergency situations, this contact should be made before implementing any departure from the protocol. In all cases, contact with the sponsor must be made as soon as possible to discuss the situation and agree on an appropriate course of action. The data recorded in the CRF and source documents will reflect any departure from the protocol, and the source documents will describe this departure and the circumstances requiring it.

Regulatory Approval/Notification

This protocol and any amendment(s) must be submitted to the appropriate regulatory authorities in each respective country, if applicable. A study may not be initiated until all local regulatory requirements are met.

Required Prestudy Documentation

The following documents must be provided to the sponsor before shipment of study intervention to the study site:

- Protocol and amendment(s), if any, signed and dated by the principal investigator.
- A copy of the dated and signed (or sealed, where appropriate per local regulations), written IEC/IRB approval of the protocol, amendments, ICF, any recruiting materials, and if applicable, participant compensation programs. This approval must clearly identify the specific protocol by title and number and must be signed (or sealed, where appropriate per local regulations) by the chairman or authorized designee.
- Name and address of the IEC/IRB, including a current list of the IEC/IRB members and their function, with a statement that it is organized and operates according to GCP and the applicable laws and regulations. If accompanied by a letter of explanation, or equivalent, from the IEC/IRB, a general statement may be substituted for this list. If an investigator or a member of the study-site personnel is a member of the IEC/IRB, documentation must be obtained to state that this person did not participate in the deliberations or in the vote/opinion of the study.
- Regulatory authority approval or notification, if applicable.
- Signed and dated statement of investigator (eg, Form FDA 1572), if applicable.
- Documentation of investigator qualifications (eg, curriculum vitae).
- Completed investigator financial disclosure form from the principal investigator, where required.
- Signed and dated clinical trial agreement, which includes the financial agreement.
- Any other documentation required by local regulations.

The following documents must be provided to the sponsor before enrollment of the first participant:

- Completed investigator financial disclosure forms from all subinvestigators
- Documentation of subinvestigator qualifications (eg, curriculum vitae)
- Name and address of any local laboratory conducting tests for the study, and a dated copy of current laboratory normal ranges for these tests, if applicable
- Local laboratory documentation demonstrating competence and test reliability (eg, accreditation/license), if applicable

Independent Ethics Committee or Institutional Review Board

Before the start of the study, the investigator (or sponsor where required) will provide the IEC/IRB with current and complete copies of the following documents (as required by local regulations):

- Final protocol and, if applicable, amendments
- Sponsor-approved ICF (and any other written materials to be provided to the participants)

- IB (or equivalent information) and amendments/addenda
- Sponsor-approved participant recruiting materials
- Information on compensation for study-related injuries or payment to participants for participation in the study, if applicable
- Investigator's curriculum vitae or equivalent information (unless not required, as documented by the IEC/IRB)
- Information regarding funding, name of the sponsor, institutional affiliations, other potential conflicts of interest, and incentives for participants
- Any other documents that the IEC/IRB requests to fulfill its obligation

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for participants, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and participant compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

Approval for the collection of optional samples for research and for the corresponding ICF must be obtained from the IEC/IRB. Approval for the protocol can be obtained independent of this optional research component.

During the study the investigator (or sponsor where required) will send the following documents and updates to the IEC/IRB for their review and approval, where appropriate:

- Protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct)
- Revision(s) to ICF and any other written materials to be provided to participants
- If applicable, new or revised participant recruiting materials approved by the sponsor
- Revisions to compensation for study-related injuries or payment to participants for participation in the study, if applicable
- New edition(s) of the IB and amendments/addenda
- Summaries of the status of the study at intervals stipulated in guidelines of the IEC/IRB (at least annually)
- Reports of adverse events that are serious, unlisted/unexpected, and associated with the study intervention
- New information that may adversely affect the safety of the participants or the conduct of the study
- Deviations from or changes to the protocol to eliminate immediate hazards to the participants
- Report of deaths of participants under the investigator's care
- Notification if a new investigator is responsible for the study at the site

- Development Safety Update Report and Line Listings, where applicable
- Any other requirements of the IEC/IRB

For all protocol amendments (excluding the ones that are purely administrative, with no consequences for participants, data or study conduct), the amendment and applicable ICF revisions must be submitted promptly to the IEC/IRB for review and approval before implementation of the change(s).

At least once a year, the IEC/IRB will be asked to review and reapprove this study, where required.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion (if applicable, the notification will be submitted through the head of investigational institution).

Country Selection

This study will only be conducted in those countries where the intent is to launch or otherwise help ensure access to the developed product if the need for the product persists, unless explicitly addressed as a specific ethical consideration in Section 4.2.1, Study-Specific Ethical Design Considerations.

Other Ethical Considerations

For study-specific ethical design considerations, refer to Section 4.2.1.

10.4.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information in accordance with local regulations to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Refer to Required Prestudy Documentation (above) for details on financial disclosure.

10.4.3. Informed Consent Process

Each participant must give written consent according to local requirements after the nature of the study has been fully explained. The ICF(s) must be signed before performance of any study-related activity. The ICF(s) that is/are used must be approved by both the sponsor and by the reviewing IEC/IRB and be in a language that the participant can read and understand. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and sponsor policy.

Before enrollment in the study, the investigator or an authorized member of the study-site personnel must explain to potential participants the aims, methods, reasonably anticipated benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Participants will be informed that their participation is voluntary and that they may withdraw

consent to participate at any time. They will be informed that choosing not to participate will not affect the care the participant will receive. Finally, they will be told that the investigator will maintain a participant identification register for the purposes of long-term follow up if needed and that their records may be accessed by health authorities and authorized sponsor personnel without violating the confidentiality of the participant, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the participant is authorizing such access. It also denotes that the participant agrees to allow his or her study physician to recontact the participant for the purpose of obtaining consent for additional safety evaluations and subsequent disease-related treatments, if needed.

The participant will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the participant's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the participant.

Participants who are rescreened are required to sign a new ICF.

Participants will be asked for consent to provide optional samples for research (where local regulations permit). After informed consent for the study is appropriately obtained, the participant will be asked to sign and personally date a separate ICF indicating agreement to participate in the optional research component. Refusal to participate in the optional research will not result in ineligibility for the study. A copy of this signed ICF will be given to the participant.

Completion of screening and randomization procedures within the specified approximately 6-week window is required. If a participant is approaching the completion of that period, the medical monitor can be contacted to discuss eligibility.

If any delay leads to the expiration of time-specific assessments (eg, TB, chest radiograph), the participant will be considered a screen failure because he/she will not meet eligibility criteria, and the expired assessments (along with the non-time-specific laboratory tests) will have to be repeated on rescreening.

10.4.4. Data Protection

Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant includes explicit consent for the processing of personal data and for the investigator/institution to allow direct access to his or her original medical records (source data/documents) for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.

The participant has the right to request through the investigator access to his or her personal data and the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

Exploratory DNA, biomarker, PK and immunogenicity research is not conducted under standards appropriate for the return of data to participants. In addition, the sponsor cannot make decisions as to the significance of any findings resulting from exploratory research. Therefore, exploratory research data will not be returned to participants or investigators, unless required by law or local regulations. Privacy and confidentiality of data generated in the future on stored samples will be protected by the same standards applicable to all other clinical data.

10.4.5. Long-Term Retention of Samples for Additional Future Research

Samples collected in this study may be stored for up to 15 years (or according to local regulations) for additional research. Samples will only be used to understand bermekimab, to understand hidradenitis suppurativa, to understand differential intervention responders, and to develop tests/assays related to bermekimab and hidradenitis suppurativa. The research may begin at any time during the study or the post-study storage period.

Stored samples will be coded throughout the sample storage and analysis process and will not be labeled with personal identifiers. Participants may withdraw their consent for their samples to be stored for research (refer to Section 7.2.1, Withdrawal From the Use of Research Samples).

10.4.6. Committees Structure

Details regarding the DMC are presented in Section 9.6.

10.4.7. Publication Policy/Dissemination of Clinical Study Data

All information, including but not limited to information regarding bermekimab or the sponsor's operations (eg, patent application, formulas, manufacturing processes, basic scientific data, prior clinical data, formulation information) supplied by the sponsor to the investigator and not previously published, and any data, including pharmacogenomic or exploratory biomarker research data, generated as a result of this study, are considered confidential and remain the sole property of the sponsor. The investigator agrees to maintain this information in confidence and use this information only to accomplish this study and will not use it for other purposes without the sponsor's prior written consent.

The investigator understands that the information developed in the study will be used by the sponsor in connection with the continued development of bermekimab, and thus may be disclosed

as required to other clinical investigators or regulatory agencies. To permit the information derived from the clinical studies to be used, the investigator is obligated to provide the sponsor with all data obtained in the study.

The results of the study will be reported in a Clinical Study Report generated by the sponsor and will contain data from all study sites that participated in the study as per protocol. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator for the study. Results of pharmacogenomic or exploratory biomarker analyses performed after the Clinical Study Report has been issued will be reported in a separate report and will not require a revision of the Clinical Study Report.

Study participant identifiers will not be used in publication of results. Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the investigator as provided for below) shall be the property of the sponsor as author and owner of copyright in such work.

Consistent with Good Publication Practices and International Committee of Medical Journal Editors (ICMJE) guidelines, the sponsor shall have the right to publish such primary (multicenter) data and information without approval from the investigator. The investigator has the right to publish study site-specific data after the primary data are published. If an investigator wishes to publish information from the study, a copy of the manuscript must be provided to the sponsor for review at least 60 days before submission for publication or presentation. Expedited reviews will be arranged for abstracts, poster presentations, or other materials. If requested by the sponsor in writing, the investigator will withhold such publication for up to an additional 60 days to allow for filing of a patent application. In the event that issues arise regarding scientific integrity or regulatory compliance, the sponsor will review these issues with the investigator. The sponsor will not mandate modifications to scientific content and does not have the right to suppress information. For multicenter study designs and sub-study approaches, secondary results generally should not be published before the primary endpoints of a study have been published. Similarly, investigators will recognize the integrity of a multicenter study by not submitting for publication data derived from the individual study site until the combined results from the completed study have been submitted for publication, within 18 months after the study end date, or the sponsor confirms there will be no multicenter study publication. Authorship of publications resulting from this study will be based on the guidelines on authorship, such as those described in the ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which state that the named authors must have made a significant contribution to the conception or design of the work; or the acquisition, analysis, or interpretation of the data for the work; and drafted the work or revised it critically for important intellectual content; and given final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and disclose the existence of and the results of clinical studies as required by law. The disclosure of the final study results will be performed after the end of study in order to ensure the statistical analyses are relevant.

10.4.8. Data Quality Assurance

Data Quality Assurance/Quality Control

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and study-site personnel before the study, periodic monitoring visits by the sponsor, and direct transmission of clinical laboratory data from a central laboratory into the sponsor's data base. Written instructions will be provided for collection, handling, storage, and shipment of samples.

Guidelines for CRF completion will be provided and reviewed with study-site personnel before the start of the study. The sponsor will review CRF for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the study database they will be verified for accuracy and consistency with the data sources.

10.4.9. Case Report Form Completion

Case report forms are prepared and provided by the sponsor for each participant in electronic format. All data relating to the study must be recorded in CRF. All CRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the CRF are accurate and correct.

The study data will be transcribed by study-site personnel from the source documents onto an eCRF, if applicable. Study-specific data will be transmitted in a secure manner to the sponsor.

Worksheets may be used for the capture of some data to facilitate completion of the CRF. Any such worksheets will become part of the participant's source documents. Data must be entered into the eCRF in English. The CRF must be completed as soon as possible after a participant visit and the forms should be available for review at the next scheduled monitoring visit.

If necessary, queries will be generated in the eDC tool. If corrections to a CRF are needed after the initial entry into the CRF, this can be done in either of the following ways:

- Investigator and study-site personnel can make corrections in the eDC tool at their own initiative or as a response to an auto query (generated by the eDC tool).
- Sponsor or sponsor delegate can generate a query for resolution by the investigator and study-site personnel.

10.4.10. Source Documents

At a minimum, source documents consistent in the type and level of detail with that commonly recorded at the study site as a basis for standard medical care must be available for the following: participant identification, eligibility, and study identification; study discussion and date of signed informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of all adverse events and follow-up of adverse events; concomitant medication; intervention receipt/dispensing/return records; study intervention administration information; and date of study completion and reason for early discontinuation of study intervention or withdrawal from the study, if applicable.

The author of an entry in the source documents should be identifiable. Given that PROs are reports of a patient's health condition that come directly from the patient, without interpretation by a clinician or anyone else, the responses to PRO measures entered by trial participants into source records cannot be overridden by site staff or investigators.

Specific details required as source data for the study and source data collection methods will be reviewed with the investigator before the study and will be described in the monitoring guidelines (or other equivalent document).

The minimum source documentation requirements for Section 5.1, Inclusion Criteria and Section 5.2, Exclusion Criteria that specify a need for documented medical history are as follows:

- Referral letter from treating physician or
- Complete history of medical notes at the site
- Discharge summaries

Inclusion and exclusion criteria not requiring documented medical history must be verified at a minimum by participant interview or other protocol-required assessment (eg, physical examination, laboratory assessment) and documented in the source documents.

An electronic source (eSource) system may be utilized, which contains data traditionally maintained in a hospital or clinic record to document medical care (eg, electronic source documents) as well as the clinical study-specific data fields as determined by the protocol. This data is electronically extracted for use by the sponsor. If eSource is utilized, references made to the CRF in the protocol include the eSource system, but information collected through eSource may not be limited to that found in the CRF.

10.4.11. Monitoring

The sponsor designee will perform on-site monitoring visits as frequently as necessary. This will include blinded site monitors who will perform source data verification and review drug preparation and dispensation. The monitor will record dates of the visits in a study-site visit log that will be kept at the study-site, as allowed by local regulation. The first post-initiation visit will be made as soon as possible after enrollment has begun. At these visits, the monitor will compare the data entered into the eCRF (as defined in the monitoring guidelines) with the source documents

(eg, hospital/clinic/physician's office medical records). The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the sponsor and study-site personnel and are accessible for verification by the sponsor study-site contact. If electronic records are maintained at the study-site, the method of verification must be discussed with the study-site personnel.

Direct access to source documents (medical records) must be allowed for the purpose of verifying that the recorded data are consistent with the original source data. Findings from this review will be discussed with the study-site personnel. The sponsor expects that, during monitoring visits, the relevant study-site personnel will be available, the source documents will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the investigator on a regular basis during the study to provide feedback on the study conduct.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

10.4.12. On-Site Audits

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. These audits will require access to all study records, including source documents, for inspection. Participant privacy must, however, be respected. The investigator and study-site personnel are responsible for being present and available for consultation during routinely scheduled study-site audit visits conducted by the sponsor or its designees.

Similar auditing procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance program or to review the results of this study in support of a regulatory submission. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

10.4.13. Record Retention

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRF and all source documents that support the data collected from each participant, as well as all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period

if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

If it becomes necessary for the sponsor or the appropriate regulatory authority to review any documentation relating to this study, the investigator/institution must permit access to such reports.

10.4.14. Study and Site Start and Closure

First Act of Recruitment

The first site open is considered the first act of recruitment and it becomes the study start date.

Study/Site Termination

The sponsor reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IEC/IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

10.5. Appendix 5: Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.5.1. Adverse Event Definitions and Classifications

Adverse Event

An adverse event is any untoward medical occurrence in a clinical study participant administered a pharmaceutical (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the intervention. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product. (Definition per International Council for Harmonisation [ICH])

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

Note: The sponsor collects adverse events starting with the signing of the ICF (refer to All Adverse Events under Section 8.3.1, Time Period and Frequency for Collecting Adverse Events and Serious Adverse Events Information, for time of last adverse event recording).

Serious Adverse Event

A serious adverse event based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  (The participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Is Medically Important*

*Medical and scientific judgment should be exercised in deciding whether expedited reporting is also appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should usually be considered serious.

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or severity is not consistent with the applicable product reference safety information. For bermekimab, the expectedness of an adverse event will be determined by whether or not it is listed in the IB.

10.5.2. Attribution Definitions

Assessment of Causality

The causal relationship to study intervention is determined by the Investigator. The following selection should be used to assess all AEs.

Related

There is a reasonable causal relationship between study intervention administration and the AE.

Not Related

There is not a reasonable causal relationship between study intervention administration and the AE.

The term "reasonable causal relationship" means there is evidence to support a causal relationship.

10.5.3. Severity Criteria

An assessment of severity grade will be made using the following general categorical descriptors:

Mild: Awareness of symptoms that are easily tolerated, causing minimal discomfort and not interfering with everyday activities.

Moderate: Sufficient discomfort is present to cause interference with normal activity.

Severe: Extreme distress, causing significant impairment of functioning or incapacitation. Prevents normal everyday activities.

The investigator should use clinical judgment in assessing the severity of events not directly experienced by the participant (eg, laboratory abnormalities).

10.5.4. Special Reporting Situations

Safety events of interest on a sponsor study intervention in an interventional study that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of a sponsor study intervention
- Suspected abuse/misuse of a sponsor study intervention
- Accidental or occupational exposure to a sponsor study intervention
- Medication error, intercepted medication error, or potential medication error involving a Johnson & Johnson medicinal product (with or without patient exposure to the Johnson &

Johnson medicinal product, eg, product name confusion, product label confusion, intercepted prescribing or dispensing errors)

- Exposure to a sponsor study intervention from breastfeeding

Special reporting situations should be recorded in the CRF. Any special reporting situation that meets the criteria of a serious adverse event should be recorded on the serious adverse event page of the CRF.

10.5.5. Procedures

All Adverse Events

All adverse events, regardless of seriousness, severity, or presumed relationship to study intervention, must be recorded using medical terminology in the source document and the CRF. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the adverse event to study therapy. All measures required for adverse event management must be recorded in the source document and reported according to sponsor instructions.

For all studies with an outpatient phase, including open-label studies, the participant must be provided with a "wallet (study) card" and instructed to carry this card with them for the duration of the study indicating the following:

- Study number
- Statement, in the local language(s), that the participant is participating in a clinical study
- Investigator's name and 24-hour contact telephone number
- Local sponsor's name and 24-hour contact telephone number (for medical personnel only)
- Site number
- Participant number
- Any other information that is required to do an emergency breaking of the blind

Serious Adverse Events

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon the participant's discontinuation from the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study intervention or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (participant or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

Suspected transmission of an infectious agent by a medicinal product will be reported as a serious adverse event.

Any event requiring hospitalization (or prolongation of hospitalization) that occurs during the course of a participant's participation in a study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (eg, social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study (must be documented in the CRF). Note: Hospitalizations that were planned before the signing of the ICF, and where the underlying condition for which the hospitalization was planned has not worsened, will not be considered serious adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.

The cause of death of a participant in a study within 4 weeks of the last administration of study intervention, whether or not the event is expected or associated with the study intervention, is considered a serious adverse event.

Information regarding serious adverse events will be transmitted to the sponsor using a serious adverse event reporting form and safety report form of the CRF, which must be completed and reviewed by a physician from the study site and transmitted in a secure manner to the sponsor within 24 hours. The initial and follow-up reports of a serious adverse event should be transmitted in a secure manner electronically or by facsimile (fax). Telephone reporting should be the exception and the reporter should be asked to complete the appropriate form(s) first.

10.5.6. Product Quality Complaint Handling

Definition

A PQC is defined as any suspicion of a product defect related to manufacturing, labeling, or packaging, ie, any dissatisfaction relative to the identity, quality, durability, reliability, or performance of a distributed product, including its labeling, drug delivery system, or package integrity. A PQC may have an impact on the safety and efficacy of the product. In addition, it includes any technical complaints, defined as any complaint that indicates a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product or the drug delivery system.

Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of participants, investigators, and the sponsor, and are mandated by regulatory agencies worldwide. The sponsor has established procedures in conformity with regulatory

requirements worldwide to ensure appropriate reporting of PQC information; all studies conducted by the sponsor or its affiliates will be conducted in accordance with those procedures.

Procedures

All initial PQCs must be reported to the sponsor by the study-site personnel within 24 hours after being made aware of the event.

A sample of the suspected product should be maintained under the correct storage conditions until a shipment request is received from the sponsor.

10.5.7. Contacting Sponsor Regarding Safety, Including Product Quality

The names (and corresponding telephone numbers) of the individuals who should be contacted regarding safety issues, PQC, or questions regarding the study are listed in the Contact Information page(s), which will be provided as a separate document.

10.6. Appendix 6: Contraceptive Guidance

Participants must follow contraceptive measures as outlined in Section 5.1, Inclusion Criteria. Pregnancy information will be collected and reported as noted in Section 8.3.5, Pregnancy and Appendix 3 Adverse Events, Serious Adverse Events, Product Quality Complaints, and Other Safety Reporting: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Woman Not of Childbearing Potential

- **premenarchal**
  A premenarchal state is one in which menarche has not yet occurred.
- **postmenopausal**
  A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level (>40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT), however in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. If there is a question about menopausal status in women on HRT, the woman will be required to use one of the non-estrogen-containing hormonal highly effective contraceptive methods if she wishes to continue HRT during the study.
- **permanently sterile (for the purpose of this study)**
  Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Note: If the childbearing potential changes after start of the study (eg, a premenarchal woman experiences menarche) or the risk of pregnancy changes (eg, a woman who is not heterosexually active becomes active), a woman must begin a highly effective method of contraception, as described throughout the inclusion criteria.

If reproductive status is questionable, additional evaluation should be considered.

Contraceptive (birth control) use by men or women should be consistent with local regulations regarding the acceptable methods of contraception for those participating in clinical studies.

Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

Examples of Contraceptives

EXAMPLES OF CONTRACEPTIVES[a] ALLOWED FOR FEMALE PARTICIPANTS DURING THE STUDY INCLUDE:
USER INDEPENDENT **Highly Effective Methods That Are User Independent** *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[b]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Tubal closure (eg, bilateral tubal occlusion, bilateral tubal ligation)
• Azoospermic partner *(vasectomized or due to medical cause)* *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 74 days.)*
USER DEPENDENT **Highly Effective Methods That Are User Dependent** *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal – injectable
• Progestogen-only hormone contraception associated with inhibition of ovulation[b] – oral – injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
NOT ALLOWED AS SOLE METHOD OF CONTRACEPTION DURING THE STUDY (not considered to be highly effective- failure rate of ≥1% per year)
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
• Female condom with or without spermicide[c]
• Cap, diaphragm, or sponge with spermicide
• Periodic abstinence (calendar, symptothermal, post-ovulation methods)
• Withdrawal (coitus-interruptus)
• Spermicides alone
• Lactational amenorrhea method (LAM)

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b) Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In addition, consider if the hormonal contraception may interact with the study intervention.
c) Male condom and female condom should not be used together (due to risk of failure with friction).

Pregnancy During the Study

All initial reports of pregnancy in female participants or partners of male participants must be reported to the sponsor or designee by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and must be reported using the Serious Adverse Event Form. Any participant who becomes pregnant during the study must discontinue further study intervention. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

10.7. Appendix 7: Hepatitis B Virus (HBV) Screening with HBV DNA Testing

Participants must undergo screening for hepatitis B virus (HBV). At a minimum, this includes testing for HBsAg (HBV surface antigen), anti-HBs (HBV surface antibody), and anti-HBc total (HBV core antibody total):

- Participants who test negative for all HBV screening tests (ie, HBsAg-, anti-HBc-, and anti-HBs-) ***are eligible*** for this study.
- Participants who test **negative** for surface antigen (HBsAg-) and test **positive** for core antibody (anti-HBc+) ***and*** surface antibody (anti-HBs+) ***are eligible*** for this study. If required by local guidelines, only subjects who have undergone HBV DNA testing and confirmed negative will be eligible.
- Participants who test **positive only** for **surface antibody** (anti-HBs+) ***are eligible*** for this study. If required by local guidelines, only subjects who have undergone HBV DNA testing and confirmed negative will be eligible.
- Participants who test **positive** for surface antigen (HBsAg+) ***are NOT eligible*** for this study, regardless of the results of other hepatitis B tests.
- Participants who test **positive only** for **core antibody** (anti-HBc+) must undergo further testing for the presence of hepatitis B virus deoxyribonucleic acid (HBV DNA test). If the HBV DNA test is **positive**, the subject ***is NOT eligible*** for this study. If the HBV DNA test is **negative**, the subject ***is eligible*** for this study. In the event the HBV DNA test cannot be performed, the subject ***is NOT eligible*** for this study.

For participants who **are not eligible for this study due to HBV test results**, consultation with a physician with expertise in the treatment of hepatitis B virus infection is recommended. For subjects who are eligible with surface antigen (HBsAg) negative, core antibody (anti-HBc) and/or surface antibody (anti-HBs) positive, and HBV DNA test is negative, HBV DNA quantitation should be monitored according to local guidelines.

For Japan sites only: Participants with surface antigen (HBsAg) negative, core antibody (anti-HBc), and/or surface antibody (anti-HBs) positive test results must undergo further HBV DNA testing. If the HBV DNA test is negative, the participant is eligible for this study and the HBV DNA testing should be performed every 4 weeks.

Eligibility based on hepatitis B virus test results			
	Hepatitis B test result		
Action	**Hepatitis B surface antigen (HBsAg)**	**Hepatitis B surface antibody (anti-HBs)**	**Hepatitis B core antibody (anti-HBc total)**
Include	—	—	—
	—	+**	—
	—	+**	+
Exclude	+	— *or* +	— *or* +
Require testing for presence HBV DNA*	—	—	+

* If HBV DNA is detectable, exclude from the clinical study. If HBV DNA testing cannot be performed, or there is evidence of chronic liver disease, exclude from the clinical study.
**If required by local guidelines, only subjects who have undergone HBV DNA testing and confirmed negative will be eligible.

10.8. Appendix 8: Tuberculin Skin Testing

Administering the Mantoux Tuberculin Skin Test

The Mantoux tuberculin skin test (CDC, 2000) is the standard method of identifying persons infected with *Mycobacterium tuberculosis*. Multiple puncture tests (Tine and Heaf) should not be used to determine whether a person is infected because the amount of tuberculin injected intradermally cannot be precisely controlled. Tuberculin skin testing is both safe and reliable throughout the course of pregnancy. The Mantoux tuberculin test is performed by placing an intradermal injection of 0.1 mL of tuberculin into the inner surface of the forearm. The test must be performed with tuberculin that has at least the same strength as either 5 tuberculin units (TU) of standard purified protein derivative (PPD)-S or 2 TU of PPD-RT 23, Statens Seruminstitut, as recommended by the World Health Organization. PPD strengths of 1 TU or 250 TU are not acceptable (Menzies, 2000). Using a disposable tuberculin syringe with the needle bevel facing upward, the injection should be made just beneath the surface of the skin. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter. To prevent needle-stick injuries, needles should not be recapped, purposely bent or broken, removed from disposable syringes, or otherwise manipulated by hand. After they are used, disposable needles and syringes should be placed in puncture-resistant containers for disposal. Institutional guidelines regarding universal precautions for infection control (eg, the use of gloves) should be followed. A trained health care worker, preferably the investigator, should read the reaction to the Mantoux test 48 to 72 hours after the injection. Participants should never be allowed to read their own tuberculin skin test results. If a participant fails to show up for the scheduled reading, a positive reaction may still be measurable up to 1 week after testing. However, if a participant who fails to return within 72 hours has a negative test, tuberculin testing should be repeated. The area of induration (palpable raised hardened area) around the site of injection is the reaction to tuberculin. For standardization, the diameter of the induration should be measured transversely (perpendicular) to the long axis of the forearm. Erythema (redness) should not be measured. All reactions should be recorded in millimeters, even those classified as negative.

Interpreting the Tuberculin Skin Test Results

In the US and many other countries, the most conservative definition of positivity for the tuberculin skin test is reserved for immunocompromised patients, and this definition is to be applied in this study to maximize the likelihood of detecting latent TB, even though the participants may not be immunocompromised at baseline.

In the US and Canada, an induration of 5 mm or greater in response to the intradermal tuberculin skin test is considered to be a positive result and evidence for either latent or active TB.

In countries outside the US and Canada, country-specific guidelines **for immunocompromised patients** should be consulted for the interpretation of tuberculin skin test results. If no local country guidelines for immunocompromised patients exist, US guidelines must be followed.

Treatment of Latent Tuberculosis

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

References

Centers for Disease Control and Prevention. Core curriculum on tuberculosis: What the clinician should know (Fourth Edition). Atlanta, GA: Department of Health and Human Services; Centers for Disease Control and Prevention; National Center for HIV, STD, and TB Prevention; Division of Tuberculosis Elimination; 2000:25-86.

Menzies RI. Tuberculin skin testing. In: Reichman LB, Hershfield ES (eds). *Tuberculosis, a comprehensive international approach*. 2nd ed. New York, NY: Marcel Dekker, Inc; 2000:279-322.

10.9. Appendix 9: Hidradenitis Suppurativa Investigator's Global Assessment

HS-IGA

Select a single unique category that best captures the subject's HS global assessment

☐ 0=Inactive – no erythema, hypopigmentation or hyperpigmentation may be present; no drainage, areas are dry following palpation; no pain and/or tenderness with palpation.

☐ 1=Almost inactive – faint, barely perceptible erythema; scant amount of drainage or discharge with palpation; slight pain and/or tenderness with palpation.

☐ 2=Mild activity – light red color; mild spontaneous drainage; mild pain and/or tenderness with palpation.

☐ 3=Moderate activity - moderate red color; moderate amount of spontaneous drainage; moderate pain and/or tenderness with palpation, participant winces.

☐ 4= Severe activity - bright red coloration; severe spontaneous drainage occurring over broad area(s); severe pain and/or tenderness with palpation, participant winces and attempts to withdraw

After the selection of the most appropriate IGA category, select the score that best captures each individual HS attribute most appropriately for the subject. The individual attribute numeric scores should not be utilized for calculating the overall IGA category score.

Erythema

☐ 0=no erythema, hypopigmentation or hyperpigmentation may be present

☐ 1= faint, barely perceptible erythema

☐ 2= light red color

☐ 3= moderate red color

☐ 4= bright red coloration

Drainage

☐ 0= no drainage, areas are dry following palpation

☐ 1= scant amount of discharge with palpation

☐ 2= mild spontaneous drainage

☐ 3= moderate amount of spontaneous drainage

☐ 4= severe spontaneous drainage occurring over broad area(s)

Pain and/or tenderness to gentile palpation (excluding scarring area)

☐ 0=no pain and/or tenderness with palpation

☐ 1= slight pain and/or tenderness with palpation

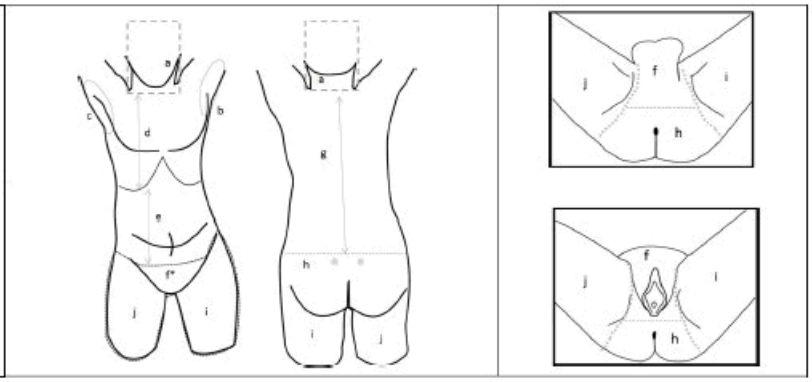
☐ 2= mild pain and/or tenderness with palpation

☐ 3= moderate pain and/or tenderness with palpation, participant winces

☐ 4= severe pain and/or tenderness with palpation, participant winces and attempts to withdraw

10.10. Appendix 10: Hidradenitis Suppurativa Activity and Severity Index (HASI)

Hidradenitis suppurativa Area and Severity Index (HASI)



Body Site	Reference BSA	Extent of BSA involved by Active HS		Percentage BSA Involved by Active HS						
				0	1-9%	10-29%	30-49%	50-69%	70-89%	90-100%
a. Head & Neck	10%									
b. Left Axilla	2%									
c. Right Axilla	2%									
d. Chest	9%									
e. Abdomen	9%		AND							
f. Pubis & Genitals	2%									
g. Back	15%									
h. Buttocks including Intergluteal Cleft	9%									
i. Left Thigh	9%									
j. Right thigh	9%									

Body Site	Inflammatory Color Change (AVERAGE red, purple, or other color depending on skin color)				Inflammatory Induration (AVERAGE inflammatory swelling of skin, NOT skin elevation due to scarring)				Open Skin Surface (Extent of exuberant granulation tissue, erosions & ulceration, single or multiple)				Tunnels (Extent of tunneling lesions, single or multiple, draining and non-draining)			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None, Closed	Mild, Limited	Moderate	Extensive	None, Closed	Mild, Limited	Moderate	Extensive
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3
a. Head & Neck																
b. Left Axilla																
c. Right Axilla																
d. Chest																
e. Abdomen																
f. Pubis & Genitals																
g. Back																
h. Buttocks including Intergluteal Cleft																
i. Left Thigh																
j. Right thigh																

10.11. Appendix 11: Hidradenitis Suppurativa Symptom Diary (HSSD) (7-Day Version)

Hidradenitis Suppurativa Symptoms Diary (7-Day Version)

Individuals with Hidradenitis Suppurativa (HS) may have lesions in several different parts of their body and may experience a range of symptoms. When answering the questions below, please consider your HS lesions in **all** of your affected areas.

Please indicate the severity of each symptom **at its WORST** during the **past 7 days** using a scale of 0 to 10 (0=None and 10=Worst Possible).

1. How severe was the **pain** from your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10
None Possible										Worst

2. How severe was the **tenderness (sensitive to touch)** from your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

3. How severe was the **swelling** from your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

4. How severe was the **heat** coming from your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

5. How severe was the **pressure** under your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

6. How severe was the **itch** from your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

7. How severe was the **odor** from your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

8. How severe was the **drainage** coming out from your HS lesions **at its WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

In this next section, please indicate the severity of any flu-like symptoms due to your HS during the **past 7 days.**

How severe were the **flu-like symptoms (e.g., having body aches, feeling very tired, etc.)** due to your HS **at their WORST** in the **past 7 days**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

10.12. Appendix 12: Hidradenitis Suppurativa Symptom Diary (HSSD) (24-hour Version)

Hidradenitis Suppurativa Symptoms Diary (24-hour Version)

Individuals with Hidradenitis Suppurativa (HS) may have lesions in several different parts of their body and may experience a range of symptoms. When answering the questions below, please consider your HS lesions in **all** of your affected areas.

Please indicate the severity of each symptom **at its WORST** during the **past 24 hours** using a scale of 0 to 10 (0=None and 10=Worst Possible).

1. How severe was the **pain** from your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10
None Possible										Worst

2. How severe was the **tenderness (sensitive to touch)** from your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

3. How severe was the **swelling** from your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

4. How severe was the **heat** coming from your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

5. How severe was the **pressure** under your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10
None										Worst Possible

6. How severe was the **itch** from your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

7. How severe was the **odor** from your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

8. How severe was the **drainage** coming out from your HS lesions **at its WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

In this next section, please indicate the severity of any flu-like symptoms due to your HS during the **past 24 hours.**

How severe were the **flu-like symptoms (e.g., having body aches, feeling very tired, etc.)** due to your HS **at their WORST** in the **past 24 hours**?

0	1	2	3	4	5	6	7	8	9	10

None Worst Possible

10.13. Appendix 13: Dermatology Life Quality Index

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score:

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you

10.14. Appendix 14: Patient Global Impression of Change (PGIC) of Hidradenitis Suppurativa Severity

Patient's Global Impression of Change (PGIC) of Hidradenitis Suppurativa Severity

Compared to when you received the first treatment in this study, how has your Hidradenitis Suppurativa changed? (Please select one response)

- ☐ 1. A lot better now
- ☐ 2. Moderately better now
- ☐ 3. A little better now
- ☐ 4. Neither better, nor worse (no change)
- ☐ 5. A little worse now
- ☐ 6. Moderately worse now
- ☐ 7. A lot worse now

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

Patient's Global Impression of Severity (PGIS) of Hidradenitis Suppurativa

Overall, how would you rate the severity of your Hidradenitis Suppurativa currently? (Please select one response)

- ☐ 1. None
- ☐ 2. Mild
- ☐ 3. Moderate
- ☐ 4. Severe
- ☐ 5. Very Severe

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

PROMIS–29 Profile v2.1

Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.1

	Fatigue In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep118	My sleep was refreshing	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CAPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CAPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CAPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER45_CAPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ21	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ24	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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PROMIS–29 Profile v2.1

Pain Intensity
In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

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10.17. Appendix 17: HS Lesion Monitoring Using Imaging (Visible Light Photography and Medical Infrared Thermography

Medical imaging can be used in the clinical assessment of HS to complement manual palpation (Elkin, 2020). As part of the 77474462HDS2001 study, visible light photography and medical infrared thermography (MIT) will be used to acquire images of lesions in HS patient. In the 77474462HDS2001 study, the SWIFT medical solution will be used to perform the lesion imaging.

The SWIFT medical solution, which consists of the SWIFT app (installed on iPhone study phones provided to the sites), the SWIFT HEALX scientific calibrant stickers which allow for color and size calibration across images acquired at different time points and the SWIFT VISION thermal camera (which clips onto the study iPhones). Both visible light and MIT images will be acquired using the SWIFT solution.

At baseline and throughout the study, sites will collect images from both axillae (left and right), regardless of presence of HS lesions. Images will be analyzed by computer vision based algorithms to understand if the images can be used to identify lesion features and lesion heat distribution, which may be indicative of the levels of inflammation in lesions. Finally, imaging derived metrics will be compared to clinical evaluations of HS axilla lesions to determine the suitability of imaging for objective clinical assessment of HS. Imaging will be conducted in a limited number of participants who consent to this optional substudy at some clinical sites. Instructions for acquiring photographs and completing assessments are provided in the imaging manual. At visits when images are collected, imaging should be completed prior to clinical disease assessment by the investigator. The results of these analyses will be presented in a separate report.

References

Elkin, K., Daveluy, S., & Avanaki, K. (2020). Review of imaging technologies used in Hidradenitis Suppurativa. Skin Research and Technology, 26(1), 3–10. https://doi.org/10.1111/srt.12772

10.18. Appendix 18: Guidance on Study Conduct during the COVID-19 Pandemic

It is recognized that the Coronavirus Disease 2019 (COVID-19) pandemic may have an impact on the conduct of this clinical study due to, for example, self-isolation/quarantine by participants and study-site personnel; travel restrictions/limited access to public places, including hospitals; study site personnel being reassigned to critical tasks.

In alignment with recent health authority guidance, the sponsor is providing options for study-related participant management in the event of disruption to the conduct of the study. This guidance does not supersede any local or government requirements or the clinical judgment of the investigator to protect the health and well-being of participants and site staff. If, at any time, a participant's safety is considered to be at risk, study intervention will be discontinued, and study follow-up will be conducted.

Scheduled visits that cannot be conducted in-person at the study site will be performed to the extent possible remotely/virtually or delayed until such time that on-site visits can be resumed. At each contact, participants will be interviewed to collect safety data. Key efficacy endpoint assessments should be performed if required and as feasible. Participants will also be questioned regarding general health status to fulfill any physical examination requirement.

Every effort should be made to adhere to protocol-specified assessments for participants on study intervention, including follow up. Modifications to protocol-required assessments may be permitted via COVID-19 Appendix after consultation with the participant, investigator, and the sponsor. Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.

The sponsor will continue to monitor the conduct and progress of the clinical study, and any changes will be communicated to the sites and to the health authorities according to local guidance. If a participant has tested positive for COVID 19, the investigator should contact the sponsor's responsible medical officer to discuss plans for study intervention and follow-up. Modifications made to the study conduct as a result of the COVID-19 pandemic should be summarized in the clinical study report.

ADDITIONAL ELEMENTS, WHERE APPLICABLE:

- Certain protocol-mandated visits to the study site may not be possible during the COVID-19 outbreak. Therefore, temporary measures may be implemented if considered appropriate by the sponsor and investigator to maintain continuity of patient care and study integrity. Certain measures, such as those listed below, may be necessary and should be instituted in accordance with applicable (including local) laws, regulations, guidelines, and procedures:
  - remote (eg, by phone / telemedicine) or in-person, off-site (e.g. in-home) interactions between site staff (or designees) and patients for study procedures e.g. those related to safety monitoring / efficacy evaluation / study drug storage and administration (including training where pertinent)

  - procurement of study drug by patients (or designee) or shipment of study drug from the study site directly to patients for at-home administration (including the potential for patient self-administration of study drug)
  - laboratory assessments using a suitably accredited local laboratory; for selected measures (e.g. urine pregnancy), home testing may be employed
  - other procedures, eg, imaging, may be conducted at an appropriate facility

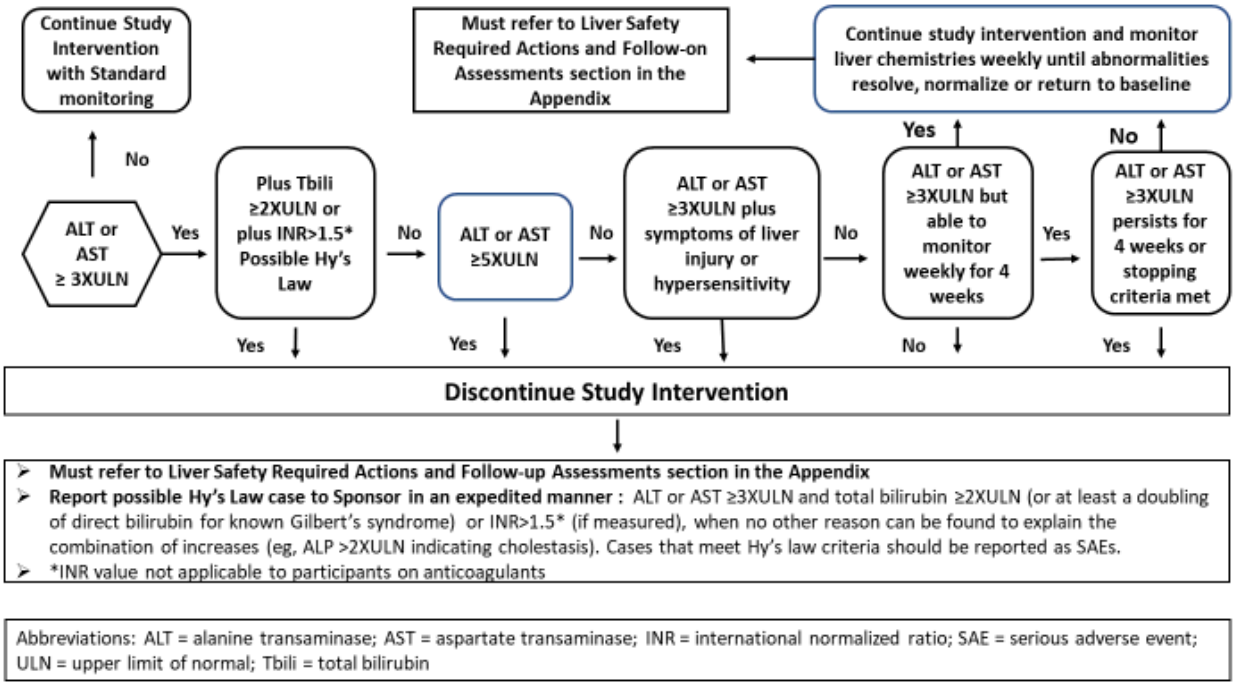
- Missed assessments/visits will be captured in the clinical trial management system for protocol deviations. Discontinuations of study interventions and withdrawal from the study should be documented with the prefix "COVID-19-related" in the CRF.
  - other relevant study data elements impacted by the pandemic should also be documented / labeled as "COVID-19-related" in CRFs and / or other study systems, as directed by detailed sponsor guidance. These may include missed / delayed / modified study visits / assessments / dosing, and instances where temporary measures such as those above are implemented.
- The sponsor will evaluate the totality of impact of COVID-19 on collection of key study data and additional data analyses will be outlined in study SAP(s).
- Precaution: for those who may carry a higher risk for severe COVID-19 illness (e.g. those aged over 65 years), follow guidance from local health authorities when weighing the potential benefits and risks of enrolling in the study, and during participation in the study.

10.19. Appendix 19: Liver Safety: Suggested Actions and Follow-up Assessments

10.19.1. Stopping Algorithm

Study intervention will be discontinued for a participant if liver chemistry stopping criteria are met.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm (no preexisting liver disease)



10.19.2. Follow up Assessments

Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure participant safety and to evaluate liver event etiology. In patients with alternative clinical reasons for elevated liver enzymes (for example, patients experiencing exercise induced CPK elevation or cholelithiasis), rechallenge with investigational product may be possible after discussion with medical monitor.

Liver Chemistry Stopping Criteria	
ALT/AST-absolute	ALT **or AST-** ≥5xULN
ALT/AST-Increase	**If cannot monitor:** ALT **or AST-** ≥3 x ULN and cannot be monitored weekly for 4 weeks **Or if able to monitor:** ALT **or AST-** ≥3xULN persists for ≥4 weeks
Total bilirubin[1, 2]	ALT **or AST-** ≥3xULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome)
INR[2]	ALT **or AST-** ≥3xULN **and** international normalized ratio (INR) >1.5, if INR measured
Symptomatic[3]	ALT **or AST-** ≥3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions, Monitoring and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** stop study intervention • Report the event to the sponsor **within 24 hours** • Complete an SAE form[2] • Perform follow-up assessments as described in the Follow Up Assessment column • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **MONITORING**) **MONITORING:** **If ALP <2 x ULN ,ALT or AST- ≥3xULN AND total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or INR >1.5 (if measured):** • Repeat liver chemistry tests (include ALT, aspartate transaminase [AST], alkaline phosphatase, total and direct bilirubin and INR) and perform liver event follow-up assessments within **24 hours** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline • A specialist or hepatology consultation is recommended **If ALT or AST- ≥3xULN AND total bilirubin <2xULN and INR ≤1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total and direct	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Obtain blood sample for pharmacokinetic (PK) within 1 week of the event of ALT or AST ≥3xULN[5] • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin • Fractionate bilirubin • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF as per CRF completion guidelines • Record use of concomitant medications (including acetaminophen, herbal remedies, recreational drugs and other over-the-counter medications) • Record alcohol use on the CRF as per CRF completion guidelines

bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline **RESTART/RECHALLENGE** • **If liver event causality is determined to be "not related", restart may be permitted upon written approval of the sponsor**. See restart guidelines	**If ALT or AST ≥3xULN AND total bilirubin ≥2xULN or INR >1.5 (if measured)** obtain the following in addition to the assessments listed above**:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete CRF as per CRF completion guidelines • Liver biopsy may be considered and discussed with local specialist if available: – In participants when serology raises the possibility of autoimmune hepatitis (AIH) – In participants when suspected DILI progresses or fails to resolve on withdrawal of study intervention – In participants with acute or chronic atypical presentation • If liver biopsy conducted complete CRF as per CRF completion guidelines

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study intervention if ALT ≥3xULN **and** total bilirubin ≥2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALP <2 x ULN, ALT **or AST-** ≥3 x ULN **and** total bilirubin ≥2xULN (or at least a doubling of direct bilirubin in known Gilbert's syndrome) or ALP <2 x ULN , ALT **or AST-** ≥3 x ULN **and** INR >1.5 (if measured) may indicate severe liver injury **(possible 'Hy's Law') and must be reported to sponsor in an expedited manner and as an SAE if SAE criteria are met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).

4. Includes: hepatitis A immunoglobulin M (IgM) antibody; HBsAgG and HBcAB; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.
5. PK sample may not be required for participants known to be receiving placebo or non-comparator interventions. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention prior to the blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the laboratory manual.

10.20. Appendix 20: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 1 (08 July 2021)

Overall Rationale for the Amendment: The overall rationale for the amendment is to make the FibroTx Patch assessment optional due to the potential unavailability of the FibroTx Patch kits.

Section number and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Subheaders were added for each SoA as follows: Section 1.3.1. Period 1 and Period 2 (Screening Through Week 16), and Section 1.3.2. Period 3 and Period 4 (Week 17 Though Week 36).	To clarify that the study periods are in 2 SoAs and to align with protocol terminology.
1.3.1 Period 1 and Period 2 (Screening through Week 16) 1.3.2 Period 3 and Period 4 (Week 17 through Week 36) 8.6 Biomarkers 8.6.1 Skin Biomarkers	Footnote m was added to the FibroTx Patch assessment to indicate that participation is optional. Footnote j was added to the FibroTx Patch assessment to indicate that participation is optional. It was clarified that the FibroTx Patch assessment is to be collected for participants who consent to this optional part of the study and when kits are available.	The FibroTx Patch assessment is optional due to the potential unavailability of the FibroTx Patch kits.
8.6 Biomarkers 8.6.1 Skin Biomarkers	The wound exudate assessment is to be collected only for those participants who have wound exudate.	To clarify that the wound exudate assessment can only be collected for those participants who have wound exudate.
1.3.1 Period 1 and Period 2 (Screening through Week 16)	A vital signs assessment was added to the screening period.	The assessment was inadvertently omitted.
1.3.1 Period 1 and Period 2 (Screening through Week 16)	The Hidradenitis Suppurativa Investigator's Global Assessment was removed from the screening period.	To clarify that this assessment is not needed at screening.
1.3.1 Period 1 and Period 2 (Screening through Week 16)	Serum, plasma, and whole blood sample assessments for biomarkers were added at Week 6. An Exudate Swab assessment was removed at Week 4 and added at Week 6. A FibroTx Patch assessment was removed at Week 4 and added at Week 6 in the SoA and in footnote t.	The time points of selected biomarker assessments were updated to support dosing decisions.
1.3.1 Period 1 and Period 2 (Screening through Week 16) 8.2.3 Electrocardiograms	An electrocardiogram was added at Week 16.	To monitor any changes after participants have received study intervention.
1.1 Synopsis 3 Objectives and Endpoints	The endpoints in the Synopsis, and Objectives and Endpoints were updated.	To align on consistent terminology.

Section number and Name	Description of Change	Brief Rationale
2.2 Background	The bermekimab no observed adverse effect level dose exposures maximum concentration and area under the curve for intravenous administration and subcutaneous administration were updated.	To align with the bermekimab Investigator's Brochure (IB).
4.2.1 Study-Specific Ethical Design Considerations 8 Study Assessments and Procedures	The expected total blood volume to be collected from each participant was removed. A statement was added that the maximum amount of blood drawn per participant will not exceed 500 mL. Table 1: Volume of Blood to be Collected from Each Participant was removed.	To reduce the site-level operational burden.
5.1 Inclusion Criteria	Inclusion criterion 12 was modified to increase the interval during which the participant agrees not to receive a live virus or live bacterial vaccination after the last administration of study intervention from 5 weeks to 90 days.	To align with the bermekimab IB guidance on the use of live virus or live bacterial vaccination.
5.2 Exclusion Criteria 5.3 Lifestyle Considerations	Exclusion criterion 11 was modified to remove the recommendation on vaccinations in the NOTES on COVID-related exclusion, which was moved to lifestyle considerations.	To clarify that the vaccination recommendations are not intended to be eligibility criteria.
6.7.4 Analgesic Therapy	A statement that participants will not be permitted to use any analgesics related to hidradenitis suppurative pain within 24 hours of a scheduled study visit was removed.	The statement was not applicable because pain is recorded in the participant's diary entries and not assessed at scheduled study visits.
7.1 Discontinuation of Study Intervention 8.2.6 Allergic Reactions	Detailed clinical specifications regarding hypersensitivity reactions were removed. Revised clinical recommendations for assessing hypersensitivity reactions were consolidated in Section 7.1.	To provide flexibility for clinicians in assessing the severity of hypersensitivity reactions and consolidate clinical recommendations in a single section of the protocol.
8.2.7 Injection-site Reactions	It was specified that participants should be monitored for the occurrence of injection-site reactions for 30 minutes after the study intervention administration.	To clarify the length of time of observation for injection-site reactions.
8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information 10.3 Appendix 3: Clinical Laboratory Tests	The parameters and reporting requirements for a possible/potential Hy's Law case were added.	To clarify reporting requirements.
10.6 Appendix 6: Contraceptive Guidance	Bilateral tubal occlusion was updated as an example of tubal closure.	To clarify that other types of tubal closure are considered highly effective, user independent methods of contraception.
10.7 Appendix 7: Hepatitis B Virus (HBV) Screening	Guidelines for hepatitis B screening specific to participants from sites in Japan were added.	To provide guidance and the evaluations to be obtained in the setting of specific patterns of

Section number and Name	Description of Change	Brief Rationale
with HBV DNA Testing		hepatitis B virus test abnormalities in Japan.
10.10 Appendix 10: Hidradenitis Suppurativa Activity and Severity Index (HASI)	The 2018 version of the HASI was replaced with the 2019/2020 version of the HASI.	A new version of the index was received from the developer.
10.17 Appendix 17: Hidradenitis Suppurativa Lesion Monitoring Using Imaging (Visible Light Photography and Medical Infrared Thermography	The Spectron IR system was removed as an option to perform the lesion imaging.	The Spectron IR system is not available.
10.19 Appendix 19: Liver Safety: Suggested Actions and Follow-up Assessments	An appendix with the liver safety stopping algorithm and follow-up assessments was added.	The sponsor's template was updated to provide guidance and evaluations to be obtained in the setting of specific patterns of liver enzymes abnormalities.
1.3.1 Period 1 and Period 2 (Screening through Week 16) 1.3.2 Period 3 and Period 4 (Week 17 through Week 36)	Acronym definitions were added to the SoA.	The definitions were inadvertently omitted.
Throughout the protocol	Minor grammatical, formatting, or spelling changes were made.	Minor errors were noted.

11. REFERENCES

Abdel-Razzak Z, Loyer P, Fautrel A, et al. Cytokines down-regulate expression of major cytochrome P-450 enzymes in adult human hepatocytes in primary culture. Mol Pharmacol. 1993;44(4):707–715.

Elkin, K., Daveluy, S., & Avanaki, K. (2020). Review of imaging technologies used in Hidradenitis Suppurativa. *Skin Research and Technology*, *26*(1), 3–10.

FDA Guidance for Industry: Drug-Drug Interaction Assessment for Therapeutic Proteins (Draft Aug 2020). Available at: https://www.fda.gov/media/140909/download. Assessed 18 July 2022.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Experi Dermatol. 1994;19(3):210-216.

Gottlieb A, Natsis NE, Kerdel F, et al. A Phase II Open-Label Study of Bermekimab in Patients with Hidradenitis Suppurativa Shows Resolution of Inflammatory Lesions and Pain. J Invest Dermatol. 2020;140(8):1538-1545.e2.

Humira SmPC - https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf, Accessed 23 Apr 2021.

Ingram JR, Hadjieconomou S, Piguet V. Development of core outcome sets in hidradenitis suppurativa: systematic review of outcome measure instruments to inform the process. Br J Dermatol. 2016; 175:263-272. J Eur Acad Dermatol Venereol. 2016; 30:989-994.

Jemec GBE. Hidradenitis suppurativa. N Engl J Med 2012; 366:158-164.

Kanni T, Argyropoulou M, Spyridopoulos T, et al. MABp1 Targeting IL-1α for Moderate to Severe Hidradenitis Suppurativa Not Eligible for Adalimumab: A Randomized Study. J Invest Dermatol. 2018;138(4):795-801.

Kimball AB, Jemec GB, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurative Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol. 2014;171:1434-1442.

Kimball AB, Okun MM, Williams DA, et al. Two Phase 3 trials of adalimumab for hidradenitis suppurativa. N Engl J Med. 2016; 375:422-434.

Kimball AB, Sobell JM, Zouboulis CC, et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. J Eur Acad Dermatol Venereol. 2016; 30(6):989-994.

Margesson LJ. Hidradenitis suppurativa. Best Pract Res Clin Obstet Gynaecol. 2014; 28(7):1013-1027.

Murphy JE, Robert C, Kupper TS. Interleukin-1 and cutaneous inflammation: a crucial link between innate and acquired immunity. J Invest Dermatol. 2000;114(3):602-608.

Okun M, Yang M, Sundaram M, Gu Y. Validation of the hidradenitis suppurative clinical response as a clinical endpoint for hidradenitis suppurative treatment evaluation. Journal of the American Academy of Dermatology. 2013;68(4): suppl. 1, AB68.

Renton KW. Regulation of drug metabolism and disposition during inflammation and infection. Expert Opin Drug Metab Toxicol. 2005;1(4):629-640.

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-397.

Vekic DA (2018a), Cains GD. Hidradenitis suppurativa, a review of pathogenesis, associations and management. Part 2. Australas J Dermatol. 2018;59(4):261-266.

Vekic DA (2018b), Frew J, Cains GD. Hidradenitis suppurativa, a review of pathogenesis, associations and management. Part 1. Australas J Dermatol. 2018;59(4):267-277.

Zouboulis CC, Desai N, Emtestam L, et al. European Dermatology Forum Guideline on Hidradenitis Suppurativa/Acne Inversa (HS)-S1 Guideline. Available at: http://www.euroderm.org/edf/index.php/edf-guidelines/category/5-guidelines-miscellanous. Accessed 03 Apr 2018.

INVESTIGATOR AGREEMENT

JNJ-77474462 (bermekimab) Clinical Protocol 77474462HDS2001 Amendment 2

INVESTIGATOR AGREEMENT

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study intervention, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Sponsor's Responsible Medical Officer:

Name (typed or printed): PPD

Institution: Janssen Research & Development

Signature: PPD Date: PPD

(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

CONFIDENTIAL – FOIA Exemptions Apply in U.S. 144

Status: Approved, Date: 12 August 2022