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Statistical Analysis Plan

A Phase 2b Pivotal Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Moderate to Severe Hidradenitis Suppurativa

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Glossary of Abbreviations

Abbreviation	Term
ADA	Anti-Drug Antibody
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AN	Abscess and Inflammatory Nodules
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\infty}$	Area under the plasma concentration time curve from time zero to infinity
$AUC_{0-\tau}$	Area under the plasma concentration time curve over a dosing interval
BID	Twice Daily
BLQ	Below Limit of Quantification
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CFR	Code of Federal Regulations
C_{max}	Maximum Plasma Concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease of 2019
CRF	Case Report Form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	Percent Coefficient of Variation
DBP	Diastolic Blood Pressure
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
FAS	Full Analysis Set
FC	Functional Class
HADS	Hospital Anxiety and Depression scale
HBV	Hepatitis B virus
HBcAb	Hepatitis B core antibodies
HBsAb	Hepatitis B surface antibodies
HBsAg	Hepatitis B surface antigen
HiSCR	Hidradenitis Suppurativa Clinical Response
HIV	Human Immunodeficiency Virus
HS	Hidradenitis Suppurativa
HS-PGA	Hidradenitis Suppurativa-Physician's Global Assessment
IBD	Inflammatory Bowel Disease
ICE	Intercurrent Event
ICH	International Council for Harmonization

Abbreviation	Term
ICF	Informed Consent Form
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	Interleukin
ISR	Injection site reaction
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IXRS	Interactive Voice/Web Response System
IV	Intravenous(ly)
JAK	Janus-Kinase
LLN	Lower Limit of Normal
MCAR	Missing Complete at Random
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple Imputation
mmHg	Millimeters of Mercury
MMRM	Nonlinear Mixed Effects Model with Repeated Measures
NC	Not Calculated
NRI	Non-response Imputation
NRS	Numeric Rating Scale
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PPD	Purified Protein Derivative
PT	Preferred Term
QW	Every Week
Q2W	Every Other Week
SAE	Serious AE
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus
SC	subcutaneous(ly)
SD	Standard Deviation
SE	Standard Error
SI	International System of Units
SoA	Schedule of Activities
SOC	System Organ Class
$t_{1/2}$	Half-life
TEAE	Treatment-emergent Adverse Events
TFLs	Tables, Figures and Listings
t_{max}	Time to Maximum Observed Concentration
TNF-α	Tumor Necrosis Factor-α
ULN	Upper Limit of Normal
US	United States
WHO DD	World Health Organization Drug Dictionary
WOCBP	Women of Childbearing Potential

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	04NOV2021	1.0
Protocol	28JUL2022	2.0
Protocol	26APR2023	3.0
Protocol	13DEC2023	4.0
CRF	15FEB2023	Initial Version

2. Protocol Details

2.1. Overall Study Design

This is a phase 2b pivotal, multi-center, dose-finding study to evaluate the efficacy, safety, and immunogenicity of izokibep in subjects with moderate to severe Hidradenitis Suppurativa (HS).

This study consists of 2 parts, Part A and Part B as described below.

Part A: Single Arm, Open Label

Part A is a single-arm, open-label, proof-of-concept investigation to explore preliminary efficacy and safety of izokibep in adult subjects with moderate to severe HS. Part A consists of up to a 28-day screening period, a 31-week treatment period, and a follow-up period that includes 2 visits to be completed by all subjects at Week 39 and Week 45. For subjects that early terminate the follow-up visits should be completed 8-weeks (± 5 days) and 14 weeks (± 5 days) after the last dose of study drug. A minimum of 20 subjects and up to 30 subjects will be enrolled in Part A (Group 0: izokibep SC 160 mg QW from Day 1/week 0 to Week 31).

Subjects will complete study assessments according to the study visits outlined in the Schedule of Activities (SoA) in the protocol. The primary endpoint will be assessed at Week 16.

After enrollment and through the end of the study if the subject's abscess and inflammatory nodule (AN) count is ≥ 150% of Day 1 AN count, antibiotic rescue medication is permitted. Subjects who qualify may initiate treatment with minocycline or doxycycline up to 100 mg BID. The dosing regimen must remain stable throughout study participation. In the case that a subject was previously intolerant or has a contraindication to both minocycline and doxycycline for the treatment of HS, the medical monitor should review to determine whether another rescue medication would be more appropriate. Rescue antibiotic therapy should be captured in the source and on the Prior and Concomitant Medications form of the CRF.

Once enrollment in Part A has finished, enrollment will begin into Part B.

Part B: Randomized, Double-blind, Dose-finding

Part B is a randomized, double-blind, placebo-controlled, parallel group, dose-finding investigation to evaluate the efficacy, safety, and immunogenicity of izokibep in subjects with moderate to severe HS. Subjects will complete up to a 28-day screening period, followed by a 16-week double-blind treatment period. At completion of the Week 16 visit procedures, subjects randomized to placebo will be switched to active treatment in a blinded manner for the Week 16 dose through Week 30 (Q2W dose group) or Week 31 (QW dose group). Subjects randomized to izokibep will remain on the same dose through Week 30 (Q2W dose

group) or Week 31 (QW dose group). After their respective treatment periods, all subjects will enter a follow-up period that includes 2 visits to be completed at Week 39 and Week 45. For subjects that early terminate the follow-up visits should be completed 8-weeks (± 5 days) and 14 weeks (± 5 days) after the last dose of study drug.

Approximately 170 subjects will be randomized into 1 of 4 groups in a 1:1:2:2 ratio as follows:

- Group 1 (n = 28-29): placebo SC QW from Day 1 (Week 0) to Week 15, then izokibep SC 160 mg QW from Week 16 to Week 31.
- Group 2 (n = 28-29): placebo SC Q2W from Day 1 (Week 0) to Week 14, then izokibep SC 160 mg Q2W from Week 16 to Week 30.
- Group 3 (n = 56-57): izokibep SC 160 mg QW from Day 1 (Week 0) to Week 31.
- Group 4 (n = 56-57): izokibep SC 160 mg Q2W from Day 1 (Week 0) to Week 30.

Randomization will be stratified by any prior biologic/Janus Kinase (JAK) inhibitor used for HS (Yes/No) and Hurley Stage (II or III).

Subjects will complete study assessments according to the study visits outlined in the SoA in the protocol. Day 1 corresponds to the first dose of study drug. All subsequent visits will be scheduled based on the Day 1 visit.

Subjects in the QW dosing groups (Group 0 [Part A], Groups 1 and 3 [Part B]) will have study visits at screening, Day 1 (Week 0), and at Weeks 1, 2, 3, 4, 8, 12, 13, 14, 15, 16, 17, 20, 24, 28, and 32 as well as at the follow-up visits.

Subjects in the Q2W dosing regimens (Groups 2 and 4 in Part B) will have study visits at screening, Day 1 (Week 0), and at Weeks 2, 4, 8, 12, 14, 16, 18, 20, 24, 28, and 32 as well as at the follow-up visits.

Subjects assigned to placebo SC QW and placebo SC Q2W will be grouped into a single placebo group for comparison to each dosing regimen of izokibep for Part B. The primary endpoint will be assessed at Week 16.

After randomization and through the end of the study if the AN count is ≥ 150% of Day 1 AN count, antibiotic rescue medication will be permitted, similar to what is allowable in Part A.

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective for Part A is to explore the efficacy of izokibep as measured by HiSCR75 at Week 12.

The primary objective for Part B is to demonstrate that one or both treatment regimens of izokibep is efficacious compared to placebo, as measured by HiSCR75 at Week 16.

2.2.2. Secondary Objectives

The secondary objectives for Part A are:

- To explore the safety and tolerability of izokibep
- To explore the immunogenicity of izokibep as measured by the presence of Anti-Drug Antibodies (ADAs)

The secondary objectives for Part B are:

- To demonstrate that one or both regimens of izokibep is efficacious, as measured by:
  - Percentage of subjects achieving HiSCR90 at Week 16;
  - Percentage of subjects achieving HiSCR100 at Week 16;
  - Percentage of subjects achieving HiSCR50 at Week 16;
  - Percentage of subjects who experience ≥ 1 disease flare through 16 weeks of treatment;
  - Percentage of subjects with baseline Hurley Stage II who achieve AN count of 0, 1, or 2 at Week 16;
  - Percentage of subjects achieving at least 3 points reduction from baseline in Numeric Rating Scale (NRS) in Patient Global Assessment of Skin Pain at its worst at Week 16 among participants with baseline NRS ≥ 4.
- To assess the safety and tolerability of izokibep as measured by the incidence of Treatment-emergent Adverse Events (TEAEs), events of interest, Serious Adverse Events (SAEs), and clinically significant laboratory values and vital signs.
- To assess the immunogenicity of izokibep as measured by the presence of ADAs.

2.2.3. Exploratory Objectives

The exploratory objectives for Part B are:

- To explore if one or both regimens of izokibep is efficacious, as measured by:
  - Percentage of subjects who achieve HiSCR75 at Weeks 4, 8, 12, and 32;
  - Percentage of subjects who achieve HiSCR90 at Weeks 4, 8, 12 and 32;
  - Percentage of subjects who achieve HiSCR100 at Weeks 4, 8, 12, and 32;
  - Percentage of subjects who achieve HiSCR50 at Weeks 4, 8, 12, and 32;
  - Percentage of subjects with baseline Hurley Stage II who achieved AN count of 0, 1, or 2 at Weeks 4, 8, 12, 24, and 32;
  - NRS Patient Global Assessment of Skin Pain from baseline after 4, 8, 12, 16, 24, and 32 weeks of treatment;
  - Modified Sartorius Score after 4, 8, 12, 16, 24, and 32 weeks of treatment;
  - HS flare rates through 4 and 32 weeks of treatment;

  - International Hidradenitis Suppurativa Severity Score System (IHS4), after 4, 8, 12, 16, 24, and 32 weeks of treatment;
  - Hidradenitis Suppurativa-Physician's Global Assessment (HS-PGA).
- To explore the effect of izokibep on PROs as measured by change from baseline over time in:
  - European Quality of Life-5 Dimensions (EQ-5D);
  - Dermatology Life Quality Index (DLQI);
  - Hospital Anxiety and Depression Scale (HADS).
- To evaluate the pharmacokinetics of izokibep in subjects with HS.

2.3. Sample Size and Power

In Part A, a minimum of 20 subjects and up to 30 subjects will be enrolled. With the minimum of 20 subjects enrolled if the true HiSCR response rate is 50%, an observed rate of 30% to 70% will be observed with 95% probability. Conversely, an observed response rate of 25% or lower suggests that the true rate is < 50% and an observed rate of 75% or higher suggests that the true rate is > 50%, based on limits of a two-sided 95% CI.

For Part B, power calculations were reported in protocol 21102 version 3.0, dated 26 April 2023, for the original primary endpoint of HiSCR50 and not for the updated primary endpoint of HiSCR75. Using the updated primary endpoint of HiSCR75, the comparisons of a regimen of izokibep to placebo will have approximately 55 subjects in each izokibep regimen compared to approximately 55 subjects on placebo (QW and Q2W combined). In prior studies of adalimumab in a similar patient population, a HiSCR75 response rates of 10% to 15% was observed with placebo compared with response rates of 25% to 35% with adalimumab. If true response rates with placebo and izokibep are 15% and 40%, respectively, this study will have approximately 80% power to reject the null hypothesis of equal response rates. This calculation was made in SAS® using the POWER procedure on an unstratified test of binomial proportions.

2.4. Primary Efficacy Variable

The primary efficacy variable for Part A and Part B is HiSCR75, the proportion of subjects who achieve at least a 75% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count. The primary timepoint for analysis is Week 12 for Part A and Week 16 for Part B.

HiSCR50/75/90/100 is defined as meeting all three criteria below:

- (AN count at baseline - AN count at current visit) / AN count at baseline × 100% ≥ 50/75/90/100%
- Abscess count at baseline ≥ abscess count at the current visit
- Draining fistula count at baseline ≥ draining fistula count at the current visit

where AN count is abscess count + inflammatory nodule count, and abscess count and fistula count are summed across all regions and are inclusive of all abscesses, inflammatory nodules and fistula that have previously undergone localized surgical or medical intervention and are no longer present. The baseline value for lesion count (including draining fistula count) and Hurley stage is the latest value on or before the randomization day (Day 1).

2.5. Secondary Efficacy Variables

The secondary efficacy variables for Part B are:

- HiSCR90 at Week 16
- HiSCR100 at Week 16
- HiSCR50 at Week 16
- HS flare through Week 16, where HS flare is defined as proportion meeting the following two criteria at any assessment after baseline and at or before Week 16:
    - (AN count at current visit- AN count at baseline) / AN count at baseline ×100% ≥ 25%
    - AN count at current visit- AN count at baseline ≥ 2
- Achieving AN count of 0, 1, or 2 at Week 16 among subjects with baseline Hurley Stage II
- NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among subjects with baseline NRS ≥ 4. NRS in Patient Global Assessment of Skin Pain at its worst is the answer from Question: In the last 24 hours, which number best describes your skin pain at its WORST due to your HS? The answer is in the range of 0 (No skin pain) to 10 (Skin pain bad as you can imagine). The skin pain score at each visit will be calculated using average of daily scores among the 7 days up to and including the day of visit, with a minimum of 4 days (consecutive or non-consecutive) with scores required. The skin pain at baseline will be calculated using average of daily scores among the 7 days up to and including the first study drug administration day, with a minimum of 4 days with scores required. For any visit, if Patient Global Assessment of Skin Pain at its worst is available for 3 or few of the 7 days up to and including the day of visit, the pain score will be missing for analysis.

2.6. Exploratory Efficacy Variables

The exploratory efficacy variables for Part B are:

- HiSCR75 at Weeks 2, 4, 8, 12, and 32
- HiSCR90 at Weeks 2, 4, 8, 12, and 32
- HiSCR100 at Weeks 2, 4, 8, 12, and 32
- HiSCR50 at Weeks 2, 4, 8, 12 and 32

- Achieving AN count of 0, 1, or 2 at Weeks 4, 8, 12, 24, and 32 among subjects with baseline Hurley Stage II
- Change in PGA of Skin Pain (at its worst and average respectively) from baseline at Weeks 4, 8, 12, 16, 24, and 32
- Modified Sartorius Score after Weeks 4, 8, 12, 16, 24, and 32 (see Appendix for scoring method)
- HS flares through Weeks 4 and 32
- IHS4 scores at Weeks 4, 8, 12, 16, 24, and 32, where IHS4 is defined as:
  IHS4 score (points) = (number of inflammatory nodules × 1) + (number of abscesses × 2) + (number of draining tunnels [fistulae/sinuses] × 4)
- IHS4-55 response rates at Weeks 4, 8, 12, 16, 24 and 32, where IHS4-55 is defined as a decrease in IHS4 of 55% or more from baseline
- Change from baseline to Week 16 in HS-PGA
- Change from baseline to Week 16 in EQ-5D (see Appendix for scoring method)
- Change from baseline to Week 16 in DLQI (see Appendix for scoring method)
- Change from baseline to Week 16 in HADS, HADS-anxiety, and HADS-depression (see Appendix for scoring method)
- Trough plasma concentrations of izokibep at collected timepoints (baseline, Week 4, 8, 12, 16, 24, 32, 39, and 45)

2.7. Safety Variables

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

Adverse events will be reported by the subject (or when appropriate, by a caregiver, a surrogate, or the subject's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an Adverse Event (AE) or SAE. The investigator is responsible for following up on all AEs that are serious, considered related to the study drug or study procedures, or that caused the subject to discontinue the study drug.

2.7.1.1. Events of Special Interest

Based on the class effects or potential risks with IL-17 inhibitors, the following events of special interest will be monitored:

- Candida infection
- Inflammatory bowel disease

In addition, based on the potential risk with an IL-17 receptor inhibitor the following event of special interest will also be monitored:

- Suicidal ideation
- Malignancies
- Major cardiovascular and cerebrovascular events
- Tuberculosis
- Infections (including opportunistic infections and serious infections)
- Cytopenias
- Hypersensitivity reactions

2.7.2. Clinical Safety Laboratory Tests

- See SAP

- Table 1 Laboratory *Tests* for the list of clinical laboratory tests to be performed and the SoA in the protocol for the timing and frequency.

2.7.3. Vital Signs

Vital signs will be measured in a sitting position after 5 minutes of rest and will include temperature, systolic and diastolic blood pressure, pulse, (collected as "Heart rate" in the CRF) and respiratory rate.

2.7.4. Physical Examination

A complete physical examination will include, at a minimum, assessments of the dermatological, cardiovascular, respiratory, gastrointestinal, and neurological systems.

Clinically significant findings observed prior to the first dose of study drug should be listed as medical history in the CRF and reported as AEs if observed after the first dose of the study drug.

2.7.5. Suicidal Ideation and Behavior Risk Monitoring

Suicidal ideation and behavior will be assessed during the study by trained study personnel using the Columbia–Suicide Severity Rating Scale (C-SSRS). The visits at which the C-SSRS assessments will be performed are specified in the SoA in the protocol. The C-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent.

2.7.6. Pharmacokinetics Variable(s)

Blood samples will be collected for measurement of plasma concentrations of izokibep as specified in the SoA in the protocol.

2.8. Immunogenicity

Antibodies to izokibep will be evaluated in serum samples collected from all subjects according to the SoA in the protocol. These samples will be tested by the sponsor or sponsor's designee.

Samples may be further tested for IL-17A binding domain and albumin binding domain (positive vs negative) and/or in a neutralizing antibody assay.

3. Estimands

The ICH[1] E9 (R1) addendum on estimands[2] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary, secondary, and exploratory objectives. Each estimand is defined according to the following five attributes:

- The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
- The **population** of subjects targeted by the clinical question.
- The **variable** (or endpoint) to be obtained for each subject that is required to address the clinical question.
- The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
- A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

3.1. Estimand for the Primary Objective

The main estimand is defined through the following five attributes:

3.1.1. Treatment Condition of Interest

The primary treatment condition of interest is izokibep 160 mg QW and izokibep 160 mg Q2W. The reference treatment condition is the combined placebo, administered either QW or Q2W. Izokibep 160 mg QW and izokibep 160 mg Q2W will each be compared to the combined placebo. Subjects will be analyzed according to their randomized treatment regardless of treatment compliance, use of rescue medications except as noted below, or any other protocol deviations.

3.1.2. Population of Subjects Targeted by the Clinical Question

The population of subjects is males and females ≥ 18 years and ≤ 75 years with moderate to severe HS (AN count of ≥ 5) as further defined by the inclusion criteria and exclusion criteria. The population being studied represents a population normally seen in clinical practice. This ensures the activity of izokibep can be evaluated across a distribution of disease severity in the study.

3.1.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variable to address the clinical question is HiSCR75 at Week 16.

3.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The treatment policy strategy approach for the estimand will be used in general, so subjects will be included using observed data at Week 16 regardless of treatment compliance, use of rescue medications except as noted below, or any other protocol deviation. Subjects with missing HiSCR75 assessments at Week 16 will be imputed as non-responders (non-response imputation or NRI). A composite strategy will be used for intercurrent events of receiving oral antibiotic therapy that could affect HS: a list of all subjects who received oral antibiotic therapy that results in such imputation will be finalized after review of all oral antibiotic therapy received by any subject and before unblinding of the study, and will include any subject who initiated a new regimen of tetracycline, clindamycin, and possibly other products, and any subject who was on a stable dose of minocycline or doxycycline at randomization but received a higher dose during the study. The endpoint for such subjects will be imputed using NRI.

3.1.5. Population-level Summary for Comparison Between Treatment Conditions

The population level summary is the response rate, or proportion of subjects who meet HiSCR75 at Week 16 and did not use oral antibiotic therapy that could affect HS before Week 16. The null hypothesis of equal response rates will compare each dosing regimen of izokibep to the combined placebo group respectively. A stratified test of response rates will be implemented in the analysis. If a subject was incorrectly classified during the randomization process, the analysis will use the correct classification, not the classification used during randomization. Within each of the four strata, any prior biologic/Janus Kinase (JAK) inhibitor use for HS (Yes/No) and Hurley Stage (II or III), the response rate for each treatment group and corresponding standard error will be calculated. The difference in response rates (risk difference) will be calculated for each stratum. The common risk difference among the four strata and associated standard error will be estimated by combining the observed risk differences using Cochran-Mantel-Haenszel weighting. The estimated risk difference divided by the standard error will be used as the test statistic and a p-value calculated assuming that the test statistic follows a standard normal distribution under the null hypothesis. Analyses at earlier timepoints when data to calculate the HiSCR75 are collected will also be presented using the same methodology.

The treatment effect will be quantified by the response rate difference of HiSCR75 at Week 16 between placebo and each dosing regimen of izokibep at Week 16.

3.2. Estimands for the secondary objectives

The main estimands for each of the secondary objectives are defined through the same five attributes as listed in the beginning of Section 3.

3.2.1. Treatment Condition of Interest

The primary treatment condition of interest is izokibep 160 mg QW and izokibep 160 mg Q2W. The reference treatment condition is the combined placebo, administered either QW or Q2W. Izokibep 160 mg QW and izokibep 160 mg Q2W will each be compared to the combined placebo. Subjects will be analyzed according to their randomized treatment regardless of treatment compliance, use of rescue medications except as noted below, or any other protocol deviations.

3.2.2. Population of Subjects Targeted by the Clinical Question

The population of subjects is all randomized males and females ≥ 18 years and ≤ 75 years with moderate to severe HS (AN count of ≥ 5) as further defined by the inclusion and exclusion criteria. The population being studied represents a population normally seen in clinical practice. This ensures the activity of izokibep can be evaluated across a distribution of disease severity in the study. Additional restrictions for some endpoints are specified in Section 3.2.3 respectively.

3.2.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each subject in the study, the variables to address the clinical questions are:

- HS flares through Week 16
- Achieve AN count of 0, 1, or 2 at Week 16. The population will be restricted to the subject with baseline Hurley Stage II
- Achieve at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16. The population will also be restricted to the subject with baseline NRS ≥ 4

3.2.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The secondary efficacy variables of the percentage of subjects who experience HS flare and percentage of subjects who achieved AN count of 0, 1, or 2 among participants with baseline Hurley Stage II will be analyzed analogously to the primary efficacy variable, using a treatment policy strategy approach. Subjects will be analyzed as randomized treatment using observed data regardless of treatment compliance, use of rescue medications, or any other protocol deviation, except for receiving an oral antibiotic that could impact HS. Subjects who received an oral antibiotic that could impact HS will be included in the analysis with NRI in line with a composite strategy.

The secondary efficacy variable of the percentage who achieve at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 will be analyzed as a binary variable. The treatment policy strategy approach for the estimand will

be used in general, whereby subjects will be included using observed data regardless of treatment compliance, use of rescue medications (except prohibited pain medications), or any other protocol deviation. Using prohibited pain medications at Week 16 will be handled by the composite strategy. Subjects using prohibited pain medications within 28 days of Week 16 will be treated as non-responder with NRI.

3.2.5. Population-level Summary for Comparison between Treatment Conditions

- Percentage of subjects that experience ≥ 1 HS flare through 16 weeks of treatment
- Percentage of subjects who achieved AN count of 0, 1, or 2 at Week 16 among participants with baseline Hurley Stage II
- Percentage of subjects achieving at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among participants with baseline NRS ≥ 4. Those who receive prohibited pain medications will be imputed as non-responders.

For each of these endpoints, the difference in proportions will be summarized.

3.2.6. Sensitivity Estimators for the Secondary Estimand

No sensitivity estimators are specified.

3.3. Estimands for the exploratory objectives

Analyses of exploratory objectives will be consistent with analogous primary and secondary objectives.

4. Analysis Sets

In accordance with ICH E3 and E9[3], the following analysis sets will be used for the analyses.

4.1. All Screened Set

The All Screened Set will include every subject who has signed the informed consent form. The All Screened Set will be used for summaries of disposition and the associated listing.

4.2. Full Analysis Set

Part A

For assessing efficacy in Part A, the full analysis set (FAS) will include all subjects who receive at least one administration of study drug.

Part B

For assessing the primary and secondary efficacy objectives, all subjects randomized in Part B will be included in the analyses as FAS. Intercurrent events (ICEs) such as missed assessments, missed or discontinued treatment, and protocol deviations, will be addressed as described in the definition of the estimands in Section 17. Subjects will be included according to randomized treatment.

4.3. Safety Analysis Set

Part A

The safety analysis set for subjects in Part A will include all subjects who received at least one administration of test.

Part B

For assessing the safety objectives, all subjects randomized who receive at least one administration of test material will be included in the summaries and analyses. The subject will be grouped according to the actual treatment received; if a subject receives both, the subject will be grouped according to the first actual treatment received.

4.4. Pharmacokinetics Analysis Set

The Pharmacokinetics analysis set for subjects in Part A and Part B will include all subjects who received at least one administration of test material (izokibep or placebo) and have at least 1 quantifiable PK concentration.

4.5. ADA Analysis Set

The ADA analysis set for subjects in Part A and Part B will include all subjects who received at least 1 administration of test material (izokibep or placebo) and have both baseline ADA and at least 1 post-dose ADA measurement.

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

All assessment days will be related to the first day of the first dose of the study drug.

Day 1 is defined as the date of the first dose of the study drug. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. There is no Day 0.

The date of the first dose of study drug for each subject will be taken from the Study Drug Administration CRF page. If the date in this CRF page is missing, alternatively the date of enrollment/randomization will be used.

The date of the last dose of study drug for each subject will be taken from the Study Drug Administration form, with the last study drug administration date from any visit used as the date of last study drug.

5.1.2. Screening Period

For all subjects, the screening period starts when the subject signs and dates the informed consent form (ICF) and ends when the subject is enrolled/randomized, or screen failed. The screening period is up to 28 days. Certain initial screening period procedures may be repeated during the original initial screening period. This is not considered "rescreening," which may occur in this study. These procedures include laboratory assessments due to value(s) out of range due to potential sampling error or that could be within range with repeat sampling.

The baseline value for a variable is therefore defined as the last non-missing value collected before enrollment/randomization.

5.1.3. Treatment Period

Data collected on Day 1 will be assigned to the Treatment Period unless the time (HH:MM) of data collection and time (HH:MM) of the first dose of study drug are both recorded and the data collection time is before the time of the first dose of study drug. In this case, the assessment will be assigned to the screening period. If the time (HH:MM) of data collection is not recorded but the protocol and/or CRF includes an instruction to the effect that all Day 1 assessments are to be performed prior to the first dose of study drug, the data collected at Day 1 will be assigned to the screening period. However, adverse events and concomitant medications starting on Day 1, will be assigned to the Treatment Period, unless the time (HH:MM) demonstrates otherwise.

The Treatment Period is defined as the period from the date/time of the first dose of study drug to Week 32 (four weeks after the last dose) or early termination/end of treatment visit (within two weeks from the last dose).

Treatment will be divided into two periods, Period 1 and Period 2. In Part B, Period 1 will start at the first dose of study drug and end at Week 16 when Week 16 assessments are completed and before administration of study drug. Period 2 will start at the time of first administration of study drug at or after Week 16 and end at Week 32 or early termination/end of treatment visit.

5.1.4. Visit Windows

All data will be analyzed using the nominal study visit as defined in the SoA in the protocol and CRF.

In the event that a subject discontinues the study early, the subject will have an early termination visit which includes efficacy assessments. If the early termination visit occurs in a timeframe that corresponds to a scheduled efficacy assessment (week 4, 8, 12, 16, 24 or 32), and if the subject does not have an actual visit at or after the corresponding scheduled efficacy assessment, the following day ranges will be used to map the early termination visit to a scheduled efficacy assessment for use in all efficacy summaries at that timepoint.

Table 1 Definition of Time Point Windows for Analyses

Time Point	Time Point Window [a]
Baseline	Day 1
Week 4	Days 21 to 42
Week 8	Days 43 to 70
Week 12	Days 71 to 98
Week 16	Days 99 to 112
Week 24	Days 113 to 196
Week 32	Days 197 or later

[a] relative to the date of first dose of study drug during the Treatment Period/date of Baseline Visit (Day 1)

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Efficacy Data

Subjects with missing HiSCR75 assessments at Week 16 will be imputed as non-responders (non-response imputation or NRI). A composite strategy will be used for intercurrent events of receiving oral antibiotic therapy that could affect HS. A list of all oral antibiotic therapy that results in such imputation will be finalized after review of all oral antibiotic therapy received by any subject and before unblinding of the study, and will include tetracycline,

clindamycin, and possibly other products. Such subjects will be imputed using NRI. The number of subjects imputed with NRI will be tabulated with reasons for imputation at Week 16.

To assess the sensitivity of the results, additional analyses will be performed where the response for HiSCR75 for all subjects will be used for sensitivity analysis, regardless of receipt of oral antibiotic therapy. Another sensitivity analysis will impute non-response for any subject who received any new oral antibiotic or an increased dose of oral antibiotic before Week 16.

For continuous efficacy endpoints, inference will be done using mixed-effects models repeated-measures[4], which is robust to missing outcomes that are missing at random (MAR) or missing complete at random (MCAR).

The secondary endpoints of the percentage of subjects who experience HS flare and the percentage of subjects who achieved AN count of 0, 1, or 2 among participants with baseline Hurley Stage II will be analyzed analogously to the primary endpoint. Subjects who have missing data at Week 16 or who received an oral antibiotic that could impact HS will be included in the analysis as non-responders with NRI (did experience HS flare, or did not achieve AN count of 0, 1, or 2).

5.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and ECG data will not be imputed. Adverse event imputations for missing severity or relationship are given in Section 6.7.2. Unknown or partial medication and AE date imputations are given below and are to be used only for the assessment of prior/concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Dates for Date of Birth, Adverse Events, Prior/ Concomitant Medications

Partial and Missing Dates of Birth

Where the Date of Birth is missing the following convention will be used:

Where the day is missing and month and year are available the day will be completed as the 15th. For example, Date of Birth specified as --JAN1980 will be completed as 15JAN1980.

If the day and month are missing and the year is available, the day and month will be completed as 02JUL (the 183rd day of the year). For example, Date of Birth specified as ----1980 will be completed as 02JUL1980.

Missing or Partial Adverse Event and Prior/Concomitant Medication Start/Stop Dates

Missing and/or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date. The stop date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing/incomplete start date/time the earliest date/time of the following will be imputed:

- The later date of: the earliest possible start date/time, and the date/time of the first dose of treatment.
- The latest possible start date/time.
- The latest possible stop date/time.

For a missing/incomplete stop date/time the later date/time of the following will be imputed:

- The earlier date/time of the latest possible stop date/time and the date/time of last dose of treatment.
- The earliest possible stop date/time.
- The earliest possible start date/time.

Here, the earliest possible date/time is defined as:

- The date/time itself if available.
- The date/time of the first day of the month at 00:00hrs, if month and year are available but the day/time is missing.
- The date/time of the first day of the year at 00:00hrs, if year is available but day/time and month are missing.
- 00:00hrs on the day of informed consent, if the date/time is completely missing.

The latest possible date/time is defined as:

- The date/time itself if available.
- The date/time of the last day of the month at 23:59hrs, if month and year are available but the day/time is missing.
- The date/time of the last day of the year at 23:59hrs, if year is available but day/time and month are missing.
- 23:59hrs on the date of last known date on the study for the subject plus one year, if the date/time is completely missing.

5.2.4. Handling of Plasma Concentrations that are Below the Lower Limit of Quantification

Plasma concentrations that are below the limit of quantification (BLQ) will be handled as follows for descriptive statistics:

- Pre-dose concentrations that are BLQ will be treated as zero.
- Post-dose concentrations that are BLQ will be treated as missing elsewhere.
- Values below the limit of quantification (BLQ) that are set to 0 in the source dataset will be treated as 0 in the calculation of summary statistics.
- Missing values will be excluded from the calculation of means, and n will reflect the actual number of values used in the calculation.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any pre-dose BLQ results (treated as 0) are in a series of summarized data, geometric mean and coefficient of variation (CV) % of geometric mean will be reported as not calculated (NC).

6. Statistical Methods

6.1. General Principles

All data processing, summarization, and analyses will be performed using [redacted]'s SAS Environment/Version 9.4 (or later) of the SAS® statistical software package. When data are collected both in IRT and EDC, all data for summaries and analyses will come from the EDC unless it is specifically stated that a particular data point will come from IRT.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min), and maximum (max), for those subjects with data.

For qualitative variables, the number (n) and percentage (%) of subjects with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. The number of subjects in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFLs mock shell(s).

The treatment group labels and presentation order are given below:

Part A

Full treatment group label:	**Short treatment group label:**	**Treatment group ordering:**
Open label izokibep 160 mg QW from Day 1/week 0 to Week 31	Open label Izokibep 160 mg QW	1

Part B

Full treatment group label:	**Short treatment group label:**	**Treatment group ordering:**
Placebo SC Q2W Week 0 to Week 14; Izokibep SC 160 mg Q2W Week 16 to Week 30	Placebo Q2W-Izokibep Q2W	1
Placebo SC QW Week 0 to Week 15; Izokibep SC 160 mg QW Week 16 to Week 31	Placebo QW-Izokibep QW	2

Placebo SC QW Week 0 to Week 15; Izokibep SC 160 mg QW Week 16 to Week 31 or Placebo SC Q2W Week 0 to Week 14; Izokibep SC 160 mg Q2W Week 16 to Week 30	Combined Placebo - Izokibep QW or Q2W	3
Izokibep SC 160 mg Q2W Week 0 to Week 30	Izokibep SC 160 mg Q2W	4
Izokibep SC 160 mg QW Week 0 to Week 31	Izokibep SC 160 mg QW	5

All statistical comparisons will be made using two-sided tests at the $\alpha = 0.05$ significance level unless specifically stated otherwise. All null hypotheses will be of no treatment difference. All alternative hypotheses will be two-sided.

All laboratory test results will be received from the central/local laboratories, and the results will be provided in either standard internal (SI) or conventional units, or both. For the TFLs, the results will be summarized or presented in International System of Units (SI) units. Refer to Appendix of the TLFs mock shells for the SI unit corresponding to each laboratory test. Refer to Appendix of the TLF shells for the precision level in which each laboratory test is reported by the central laboratories.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

Data from Parts A and B will be summarized separately. Objectives and statistical hypotheses will be addressed using data from Part B only. The treatment policy estimand will be used in general for efficacy data, with all treated subjects contributing to Part A and all randomized subjects contributing to Part B. All treated subjects will contribute to safety analyses in both Parts A and B.

For comparisons of izokibep to placebo in Part B, the two dosing regimens of izokibep (QW and Q2W) will be compared separately to placebo. The 2 placebo dosing regimens (QW and Q2W) will be combined for comparison to each izokibep dosing regimen. Binary endpoints including the primary endpoint of HiSCR75 will be compared with a stratified test of risk difference. Continuous endpoints will be compared with a repeated measures mixed model.

Safety data will be summarized separately for Part A and Part B. Adverse events, serious adverse events, and laboratory data will be summarized.

6.2. Subject Disposition and Data Sets Analyzed

Subject disposition will be summarized by treatment group and overall for the All Screened Set. The following information will be reported:

- Number of subjects for the following categories:
  - Screened
- Number and percentage of subjects for the following categories:
  - Enrolled (Part A)/Randomized (Part B)
  - Treated
  - Not Treated
  - Completed the study
  - Ongoing in the study
  - Discontinued the Study
  - Reasons for study discontinuation
- Number and percentage of subjects included in, and excluded from, each study population together with the reasons for exclusion from the analysis set
- Number and percentage of subjects who completed/discontinued treatment by period, including the reasons for treatment discontinuation
- Number and percentage of subjects who met/did not meet all eligibility criteria, together with the criteria not met
- Number and percentage of subjects who failed screening prior to enrollment (Part A)/randomization (Part B), including the primary reason for screen failure
- Number and percentage of subjects at each region (and each country within region)
  - Regions are defined using the following countries:
    - North America (US or Canada)
    - Europe (Spain, Hungary, Poland, or Germany)
    - Non-US (Spain, Hungary, Poland, Germany, or Canada)
- Number and percentage of subjects by stratification factors (Part B only). Each stratification variable will be presented by the stratum collected in Interactive Voice/Web Response System (IXRS)

A subject will be regarded as having completed the study if the status recorded on the End of Study CRF form is Complete, or assessments at Week 45 have been completed. A subject will be considered as having discontinued the study if they have an CRF status of premature study discontinuation. Otherwise, the subject will be considered as ongoing study.

A listing of all subjects with their treatment and study completion status, including the respective reasons for treatment discontinuation will be presented for all subjects enrolled (Part A) and randomized (Part B) in the FAS.

A listing of all screen failed subjects with their reasons for screen failure will be presented for the All Screen Set. A separate listing of subjects who failed at least one inclusion/exclusion criteria including a text description of the criterion failed will be presented for the All Screen Set. Subjects who screen failed will be assigned to Part A if the subject was screened at a site in the United States and the date of screen fail is before 27-Jul-2022 and assigned to Part B if the screen fail date is on or after 27-Jul-2022 or the subject was screened at a site outside of the United States.

A listing of all randomized subjects from Part B with their randomization details, including first dose date and time, and actual treatment received will be presented for the FAS.

A listing of all enrolled (Part A) and randomized (Part B) subjects excluded from the FAS will be presented.

6.3. Protocol Deviations

All important protocol deviations will be summarized for the FAS for Part A (overall) and Part B by treatment group and overall as described below:

- The number of unique subjects with at least one important protocol deviation as well as the number of subjects in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all subjects with one or more protocol deviations will be presented for the FAS.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the FAS for Part A (overall) and Part B by treatment group and overall as described below. All missing data will be presented as part of a missing category. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)

Total counts and percentages of subjects will be presented for the categorical variables of:

- Age group (years):
  - < 65
  - ≥ 65
- Sex
- Ethnicity
- Race

Demographic characteristics will be listed for the FAS for Part A (overall) and Part B by treatment group.

6.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the FAS for Part A (overall) and Part B by treatment group and overall as described below. All missing data will be presented as part of a missing category.

Standard descriptive statistics will be presented for the continuous variables of:

- Disease duration (years)
- Number of previous systemic treatments
- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)
    - calculated as (body weight / $height^2$) where weight is in kg and height is in m, and presented to one decimal precision
- Body Temperature (degrees Celsius)
- Respiration Rate (breaths per minute)
- Systolic Blood Pressure (SBP [mmHg])
- Diastolic Blood Pressure (DBP [mmHg])
- Heart Rate (beats per minute [bpm])
- Time Since Diagnosis with HS (calculated as year IC signed minus year of diagnosis, plus 1)
- AN Count - Total Number of abscesses plus inflammatory nodules
- Number of Abscesses
- Number of Inflammatory Nodules
- Number of Draining Fistulae
- Number of Non-draining Fistulae
- Number of total Fistulae (Draining plus Non-draining)
- HADS total score
- HADS-Anxiety
- HADS-Depression
- HS-PGA
- Erythema Score
- DLQI total score
- IHS4
- EQ-5D-3L (Domain Scores, Index Score, and VAS Score)

- SF-12 (Physical Component Score and Mental Component Score) (see Appendix 2 for scoring method)

Total counts and percentages of subjects will be presented for the categorical variables of:

- Hurley Stage (II, III)
- Prior Biologic/Janus Kinase (JAK) Inhibitor Use for HS (yes/no)
- Alcohol (Never, Former, Current)
- Nicotine (Never, Former, Current)
- Presence of draining fistulae at baseline (yes/no)

The subject's Hurley Stage and erythema score (see Appendix 2 for scoring method) will be the worst reported for any anatomical region for that subject. Baseline characteristics will be listed for the FAS.

6.4.3. Medical History

Medical history is defined as any condition, with the exception of the study indication, that the subject may have prior to enrollment in the study, including any chronic conditions diagnosed prior to entry into the study. Non-serious AEs with onset after signing ICF but before the first dose (Part A) or randomization (Part B) will be included as medical history.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) using the latest MedDRA dictionary around the time of Database Lock and will be presented by System Organ Class (SOC) and Preferred Term (PT) and total. The SOCs and PTs are to be sorted by Internationally Agreed order SOCs and descending PTs in the total column.

Medical history records will be summarized for the FAS for Part A (overall) and for Part B by treatment group and overall as follows:

- The number and percentage of subjects with at least one medical history record will be presented.
- The number and percentage of subjects with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-subject and within-subject by medical history start date for the FAS.

6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, Format B3 using the latest version around time of database lock, Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken with a stop date prior to the start of the Treatment Period.
- Concomitant medications are those with a start date and time on or before the end of the Treatment Period and a stop date on or after the start of the treatment period, including prior medications that are ongoing at the start of the treatment period.

See Section 5.2.3 for imputation of missing or partial dates for medication.

Prior and concomitant medications will be summarized separately for the FAS for Part A (overall) and Part B by treatment group and overall as follows:

- The number and percentage of subjects with at least one prior/concomitant medication will be presented.
- The number and percentage of subjects with at least one prior/concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior medications and concomitant medications will be listed separately for the FAS. In the listings the relative start and stop day of prior/concomitant medication use will be calculated relative to the first dose date and time of study drug and will be presented for those subjects who received at least one dose of study drug. If the concomitant medication is “Ongoing” it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.5. Measurements of Study Drug Compliance

Study Drug compliance is defined as the number of doses that were actually taken relative to the number of doses that should have been taken as per the protocol for the planned duration of treatment exposure. A partial dose in CRF will be treated as a half dose. Study drug compliance in Part B will be summarized for period 1 and period 2 separately.

In general, the percentage of overall compliance, assessed by dose count, will be calculated as follows:

For Part A

$$Compliance\ (\%) = \frac{(Total\ doses\ administered\ from\ Week\ 0\ to\ Week\ 31)}{Total\ doses\ expected\ to\ be\ administered\ from\ Week\ 0\ to\ Week\ 31} \times 100\%$$

For Part B Period 1

$$Compliance\ (\%) = \frac{(Total\ doses\ administered\ from\ Week\ 0\ up\ to\ before\ Week\ 16)}{Total\ doses\ expected\ to\ be\ administered\ from\ Week\ 0\ to\ before\ Week\ 16} \times 100\%$$

For Part B Period 2

$$Compliance\ (\%) = \frac{(Total\ doses\ administered\ from\ Week\ 16\ to\ EOT)}{Total\ doses\ expected\ to\ be\ administered\ from\ Week\ 16\ to\ EOT} \times 100\%$$

For Part A, the total number of doses expected to be administered from Week 0 to Week 31 is 32 for all subjects. For Part B, the total doses expected to be administered differs by treatment assignment: for QW dosing, the total doses expected to be administered is 16 for Period 1 and 16 for Part 2; for Q2W dosing, the total doses expected to be administered is 8 for Period 1 and 8 for Part 2.

The calculated percentage compliance will be categorized as:

- $< 80\%$ compliance
- $\geq 80\%$ compliance

Compliance will be summarized for the Safety Analysis Set for Part A (overall) and for Part B by treatment group and Period as follows:

- Number of doses will be presented by default summary statistics.
- Percent compliance will be presented by default summary statistics.
- Number and percentage of subjects within each of the compliance categories will be presented. Treatment compliance will be listed for the Safety Analysis Set. Missing data will not be imputed and only original data for those fields (for example, date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

6.6. Efficacy

Primary, secondary and exploratory endpoints will be presented by study part, timepoint and, for Part B, randomized treatment group. Observed data for binary endpoints, with NRI, will be presented with 2-sided 95% confidence intervals calculated using asymptotic Wald method. Observed data for continuous endpoints, with no imputation for missing values, will be presented with 2-sided confidence intervals calculated using normal approximations.

No statistical hypotheses will be tested in Part A of this study.

Hypotheses tested using data from Part B will be adjusted to control the family-wise error rate in the strong sense at $\alpha = 0.050$, two-sided. An adjustment of 0.0001 will be made to account for the unblinded data summaries reviewed by the DMC. The hypotheses will therefore be tested at $\alpha = 0.0499$.

The statistical comparisons in Part B for the primary efficacy endpoint and the secondary endpoints, all at Week 16, will be carried out in sequential order. The primary endpoint, comparing izokibep dosed QW to placebo dosed QW or Q2W, will be tested first, with significance concluded if $p < 0.0499$. If significant, the primary endpoint, comparing izokibep dosed Q2W to placebo dosed QW or Q2W will be tested next, with significance concluded if $p < 0.0499$. Testing of secondary endpoints will only be carried out if all prior tests, including both tests of the primary endpoint, first show significance with $p < 0.0499$. As long as all prior tests are significant, testing will proceed in the following order:

- The first secondary endpoint, proportion of subjects who experience ≥ 1 disease flare through 16 weeks of treatment, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The first secondary endpoint, proportion of subjects who experience ≥ 1 disease flare through 16 weeks of treatment, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.
- The second secondary endpoint, achieving AN count of 0, 1, or 2 at Week 16 among subjects with baseline Hurley Stage II, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The second secondary endpoint, achieving AN count of 0, 1 or 2 at Week 16 among subjects with baseline Hurley Stage II, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.
- The third secondary endpoint, proportion of subjects who achieve at least 3 points reduction from baseline in NRS at Week 16 among participants with baseline NRS ≥4, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The third secondary endpoint, proportion of subjects who achieve at least 3 points reduction from baseline in NRS at Week 16 among participants with baseline NRS ≥4, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.

If a null hypothesis is not rejected, p-values for subsequent hypotheses in the sequence will be reported as nominal, and will not be used to assess objectives or make determinations of efficacy.

For Part B, efficacy endpoints will be summarized by Period 1 and Period 2 separately. For Period 2, in general, no hypothesis test will be performed and p-value will not be reported. For binary endpoints, stratified tests will use the four strata from the randomization process. If a subject was incorrectly classified during the randomization process, the analysis will use the correct classification as recorded in EDC, not the classification used during randomization as recorded in IRT.

For each primary and secondary efficacy endpoint, the number and proportion of subjects achieving the endpoint in each treatment group will be reported by stratum and overall. Confidence intervals will be present with stratification (CMH weighting) and without stratification (Wald method). P-values will be reported for the stratified analysis. A bar graph showing the proportion of subjects achieving the endpoint for each treatment group along with the associated p-value will be produced. Results will also be listed.

6.6.1. Primary Efficacy Analysis

The primary efficacy variable is defined as HiSCR75, the proportion of subjects who achieve at least a 75% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count at Week 16 (comparing to baseline).

For Part B, the statistical null and alternative hypotheses to be used to assess the primary objective are:

$$H_0: \pi_{ABY} - \pi_{PBO} = 0$$

$$H_A: \pi_{ABY} - \pi_{PBO} \neq 0$$

where π_{ABY} and π_{PBO} are the proportion of subjects achieving HiSCR75 at Week 16 among subjects randomly assigned to receive izokibep and placebo, respectively. One set of hypotheses will be tested for each dosing frequency of izokibep.

The treatment policy strategy approach for the estimand will be used in general, so subjects will be included using observed data at Week 16 regardless of treatment compliance, use of rescue medications or procedures except as noted below, or any other protocol deviations. Subjects with missing HiSCR75 assessments at Week 16 will be imputed as non-responders (non-response imputation or NRI). A composite strategy will be used for intercurrent events of receiving oral antibiotic therapy that could affect HS. A list of all oral antibiotic therapy that results in such imputation will be finalized after review of all oral antibiotic therapy received by any subject and before unblinding of the study and will include tetracycline, clindamycin, and possibly other products. Such subjects will be imputed using NRI. The

number of subjects imputed with NRI will be tabulated with reasons for imputation at Week 16. Additionally, any lesions that received lesional incision and drainage or intralesional steroid injection will be counted as continuing to exist in the AN count, even if fully healed, at all later timepoints.

The null hypothesis of equal response rates will compare each dosing regimen of izokibep to the combined placebo group.

A stratified test of response rates will be used for the primary analysis. Within each of the four strata used for randomization, the response rate for each treatment group and corresponding standard error will be calculated. The difference in response rates (risk difference) will be calculated for each stratum. The common risk difference among the four strata and associated standard error will be estimated by combining the observed risk differences using Cochran-Mantel-Haenszel weighting. The estimated risk difference divided by the standard error will be used as the test statistic and a p-value calculated assuming that the test statistic follows a standard normal distribution under the null hypothesis. Analyses at earlier timepoints when data to calculate the HiSCR75 are collected will also be presented using the same methodology. P-values from earlier timepoints will be presented for descriptive purposes, not part of the alpha-preserving multiple testing strategy. No P-values after Week 16 will be presented.

Sample SAS code with stratification factors of comparing each dosing regimen of izokibep to the combined placebo group is given as following:

```
ods output commonpdiff = ;
proc freq data= ;
  tables stratum * treatment * response / cmh commonriskdiff (test=mh cl=mh);
  weight count / zeros;
run;
```

6.6.2. Supplementary Analyses for the Primary Efficacy Analysis

As a supplementary analysis, Clopper-Pearson 95% CI for the difference between 2 proportions will be calculated using the asymptotic Wald method. Sample SAS codes of comparing each dosing regimen of izokibep to the combined placebo group is given as following are:

```
ods output RiskDiffCol2= ;
proc freq ;
  tables treatment*response / riskdiff(cl=wald);
  weight count / zeros;
run;
```

This analysis will assess whether stratification impacted the conclusions.

For Part B, supplementary analyses using other assumptions about ICEs and other ways to address missing data will also be reported. These will be defined before the database is locked and treatment assignments are unblinded.

Worst Case Scenario Imputation: All subjects with prohibited medication will be imputed as NR in active arms, and as Responder in the placebo arm. A stratified test will be used with the actual randomization factors as strata.

Lesional incision and intralesional steroid: An analysis imputing subjects as non-responders if any lesion received lesional incision and drainage or intralesional steroid injection will be reported. This analysis will match the primary analysis, except that subjects who received any (one or more) such treatments will be imputed as non-responders in this analysis (instead of only continuing to count the lesion as present, as in the primary analysis).

Tipping point analysis: A tipping point analysis will be performed in order to evaluate the robustness of the results of the primary analysis. This analysis will use simulations to assess the impact of different response rates in subjects with missing primary endpoint data, and how different the response rates must be to change the conclusions of the study. The tipping point analysis will impute mean response rates in the two groups. Imputed response rates will be based on the response rates among subjects with observed primary endpoint data at week 16. Sets of imputed mean response rates will include the observed response rates ($\hat{\pi}_{ABY}$, $\hat{\pi}_{PBO}$), and rates that differ in increments of ±0.02, adjusted independently in each arm. For each set of imputed mean response rates, 1000 simulations will be reported. Within each simulation, a random number mechanism will be used to assign each subject who is missing the primary endpoint at week 16 to either response or non-response, with response probability of the mean response rate for that treatment arm in that simulation. The primary stratified analysis will be reported on each simulated study, and the probability that the null hypothesis of equal response rates is rejected will be reported for each set of 1000 imputed response rates. A graphical output will summarize the rejection probability for various sets of response, with different shadings representing probabilities of >95%, 80-95%, 50-80%, 20-50% and ≤20%.

Multiple Imputation: Multiple imputation[5] will be implemented to replace missing endpoint data using multiple draws from a posterior predictive distribution estimated from the placebo group only. First, a monotone missingness pattern will be enforced using Markov Chain Monte Carlo (MCMC). The MCMC process will use predictor variables of baseline abscess count (continuous), baseline inflammatory nodule count (continuous), baseline draining fistula count (continuous), age (continuous), baseline BMI (continuous) for nonmonotone missingness at Week 4 (missing at Week 4 but available at a later timepoint). MCMC predictors in the regression model for missing values after Week 4 will be all of these variables, plus counts of abscess (continuous), inflammatory nodule (continuous), and

draining fistula (continuous) at prior scheduled assessments. After monotone missingness is enforced, missing HiSCR75 at Week 4, 8, 12, and 16 will be imputed, assuming monotone missingness pattern. Any missing HiSCR75 will be imputed by first imputing components of the AN count (abscess and inflammatory nodules) and draining fistula count, then assigning HiSCR75 status from the imputed values. Predictors in the regression model for missing values at Week 4 will be baseline Hurley stage (II/III), baseline abscess count (continuous), baseline inflammatory nodule count (continuous), baseline draining fistula count (continuous), sex (male/female), race (white/non-white), age (continuous), BMI (continuous) and Prior Biologic/Janus Kinase (JAK) Inhibitor Use for HS (yes/no). Predictors in the regression model for missing values after Week 4 will be all of these variables, plus counts of abscess (continuous), inflammatory nodule (continuous), and draining fistula (continuous) at prior scheduled assessments. Missing HiSCR75 values in both the placebo group and two izokibep groups will be imputed using observed data from the placebo group only. Data will be processed sequentially by repeatedly calling SAS® PROC MI to impute missing outcomes at Week 4, 8, 12, and 16. A total of 100 imputations will be imputed to form the complete data set with a pre-specified seed (3617627) to ensure reproducibility. These multiple imputed data sets are then analyzed by using the same method for the primary analysis for complete data as specified in Section 6.6.1. The final inference on treatment difference is conducted from the multiple datasets using Rubin's combining rules[6]. Other imputation, fully conditional specification method may be implemented if the multiple imputation model does not converge. If imputation is not possible due to sparseness of data for certain predictor variables, that predictor variable will be collapsed. If the predictor variable is race, race will be first collapsed into three categories (Black, White and Other) and, if further collapsing is necessary, into two categories (Black and Other). If the predictor variable is other than race, that predictor variable will be collapsed into a single category, in essence removing that predictor from the predictor model.

6.6.3. Secondary Efficacy Analysis

The secondary efficacy variables are HiSCR50, HiSCR90 and HiSCR100 at Week 16. The same primary efficacy analysis approach will be applied on the secondary efficacy variables.

Other secondary efficacy variables are percentage of subjects who experience HS flare through Week 16, percentage of subjects who achieved AN count of 0, 1, or 2 at Week 16 among participants with baseline Hurley Stage II, and percentage of subjects achieving at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among participants with baseline NRS ≥ 4.

Analogous statistical hypotheses to the primary objective will be used for the secondary objectives.

6.6.3.1. Subjects Experiencing HS flare through Week 16

The secondary endpoints of percentage of subjects who experience HS flare through Week 16 will be analyzed analogously to the primary endpoint. HS flare will be determined programmatically at each assessment of AN count. To be counted as a HS flare, the AN count must increase from baseline by at least 25% and by at least 2 compared to baseline. A subject will be counted as having HS flare if they have a HS flare at any assessment after baseline, up to and including the assessment at Week 16 (including scheduled and unscheduled visits and early termination visits). The statistical null and alternative hypotheses to be used to assess these objectives are:

$$H_0: \pi_{ABY} - \pi_{PBO} = 0$$

$$H_A: \pi_{ABY} - \pi_{PBO} \neq 0$$

where π_{ABY} and π_{PBO} are the proportion experiencing HS flares through Week 16 among subjects randomly assigned to receive izokibep and placebo, respectively. One set of hypotheses will be tested for each dosing frequency of izokibep.

Subjects who received an oral antibiotic that could impact HS at any point before the Week 16 assessment will be included in the analysis with NRI (did experience HS flare). Subjects who have missing assessments will be included with multiple imputation, as described below.

The number and proportion of subjects for subjects who experience a HS flare in each treatment group will be reported, along with p-values, 95% CI without strata calculated using asymptotic Wald method will be reported as well. A bar plot showing the proportion of subjects experiencing HS flare for each treatment will be produced. Results will also be listed.

Multiple imputation will be used to impute data for subjects with missing data. The multiple imputation process will be the same the supplementary analysis defined in section 6.6.2 for HiSCR75, except that draining fistula counts do not play a role in flare and will therefore not be imputed when missing. Subjects with missing AN counts at any scheduled visit (week 4, week 8, week 12 and/or week 16) will have their abscess and inflammatory nodules counts imputed (separately) for each visit with missing data. The imputed counts will be summed and compared to criteria for flare. If the observed or imputed value at any visit meets the definition of flare, the subject will be counted as having a flare; otherwise, the subject will be counted as not having a flare. A total of 100 imputations will be imputed to form the complete data set with a pre-specified seed (3617627) to ensure reproducibility. These multiple imputed data sets are then analyzed by using the same method for the primary analysis for complete data as specified in Section 6.6.1. The final inference on treatment difference is conducted from the multiple datasets using Rubin's combining rules[7]. Other imputation, fully conditional specification method may be implemented if the multiple imputation model does not converge.

Note that NRI will not be used for the primary analysis of flare. The number of subjects with missing data may be larger than the number of subjects who experience a flare, so using NRI may result in an analysis dominated by missing data. A supportive analysis, described below, will be reported using NRI.

6.6.3.2. Hurley Stage II Subjects Achieving AN Count of 0, 1, or 2 at Week 16

The secondary endpoints of percentage of subjects with baseline actual Hurley Stage II who achieved AN count (including those lesions that had interventions before Week 16 and were no longer present at Week 16) of 0, 1, or 2 at Week 16 will be analyzed analogously to the primary endpoint. The statistical null and alternative hypotheses to be used to assess these objectives are:

$$H_0: \pi_{ABY} - \pi_{PBO} = 0$$

$$H_A: \pi_{ABY} - \pi_{PBO} \neq 0$$

where π_{ABY} and π_{PBO} are the proportion achieving AN count of 0, 1, or 2 at Week 16 among subjects randomly assigned to receive izokibep and placebo, respectively. One set of hypotheses will be tested for each dosing frequency of izokibep.

Subjects who have missing data at Week 16 or who received an oral antibiotic that could impact HS will be included in the analysis with NRI (did not achieve AN count of 0, 1, or 2). Only subjects with Hurley Stage II at baseline will be included in the hypothesis test for AN count, while other subjects will be summarized, and a p-value reported for descriptive use only. Methodology will be identical to that used for the primary endpoint with the exception of stratification factors. For the secondary endpoint, achieve AN count of 0, 1, or 2 at Week 16, which uses only subjects with Hurley Stage II at baseline, the stratification factor of baseline Hurley Stage will be omitted from the analysis. For the analysis using all subjects, the stratification factor of baseline Hurley Stage will be used, as in the primary endpoint analysis.

The number and proportion of subjects who achieved AN count of 0, 1, or 2 among participants with baseline Hurley Stage II in each treatment group will be reported, along with p-values, 95% CI without strata calculated using asymptotic Wald method will be reported as well. A bar plot showing the proportion of subjects who achieved AN count of 0, 1, or 2 among participants with baseline Hurley Stage II for each treatment will be produced. Secondary endpoint results will also be listed.

6.6.3.3. NRS of Skin Pain at Week 16

The secondary endpoint of percentage of subjects achieving at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among participants with baseline NRS ≥ 4 will be analyzed analogously to the primary endpoint.

Hypotheses to assess percentage of subjects achieving at least 3 points reduction from baseline in NRS:

H_0: $\pi_{ABY} - \pi_{PBO} = 0$

H_A: $\pi_{ABY} - \pi_{PBO} \neq 0$

where π_{ABY} and π_{PBO} are the proportion of subject achieve NRS Week 16.

The number and proportion of subjects achieving at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among participants with baseline NRS ≥ 4 in each treatment group will be reported, along with a bar plot showing the proportion of subjects with baseline NRS ≥ 4 who achieved NRS each treatment will be produced. Results will also be listed.

If a subject received certain prohibited analgesic therapy within 28 days of the visit (including the day of the visit), the subject will be imputed as a non-responder due to the ICE. A list of all subjects who took prohibited analgesic therapy which results in NRI will be created after the data is final and before unblinding, and will include justification for choosing the subjects based on specific analgesic, timing relative to Week 16, and other factors considered.

Since the NRS in Patient Global Assessment of Skin Pain is collected as a daily diary, the score used for analysis will be the average of the scores recorded 6 days prior to and including the Week 16 visit (7 days total for the average).

6.6.4. Supplementary Analyses for the Secondary Efficacy Analysis

For Part B, supplemental analyses of NRS pain will use MMRM among subjects with baseline NRS ≥ 4, using observed change in NRS Patient Global Assessment of Skin Pain (average in the last 24 hours) at all scheduled post-baseline assessments up to Week 16. The model will include baseline NRS Patient Global Assessment of Skin Pain, visit week, treatment, and treatment by visit week interaction as covariates and will use an unstructured variance-covariance matrix. Other variance-covariance matrices, such as autoregressive, and compound-symmetric will be considered if the model does not converge. Sample SAS code is given as following:

```
proc mixed ;
class week subjectid treatment(ref = "placebo")
model change_y = baseline_y week treatment * week treatment
repeated week / subject = subjected (treatment) TYPE = UN;
lsmeans treatment * week /slice = week cl;
slice treatment * week/ sliceby = week pdiff cl;
run;
```

Another supplemental analysis of pain will be analogous but will use all subjects, including those with baseline NRS < 4.

Two supplemental analyses of flare will be reported. The first will impute any subject with missing AN count at any time after baseline as having a flare (missing = yes). The analysis will be analogous to that of the primary endpoint. The second will impute any subject with missing AN count at any time after baseline as not having a flare at that timepoint (but as having a flare if other observed data meet the definition of flare). This is equivalent to using only observed data for assessing flare. The analysis will again be analogous to that of the primary endpoint.

A supplementary analysis of HiSCR75 at week 16 will impute as non-responder any subject who received a new antibiotic or increased dose of antibiotic at any time after randomization and before week 16.

6.6.5. Exploratory Analysis

Exploratory endpoints will be analyzed analogously to primary and secondary endpoints with the same strategies for ICEs. Binary endpoints will be analyzed with a stratified test of risk difference and continuous endpoints will be analyzed with an MMRM model in general. Continuous data at timepoints before and including the primary timepoint will use all data from planned assessments up to and including the primary timepoint; continuous data after the primary timepoint will use all data from all planned assessments. Visit week, treatment group and interaction will be included in the MMRM model.

The number and proportion of subjects for binary endpoints in each treatment group will be reported, along with p-values, 95% CI without strata calculated using asymptotic Wald method will be reported as well. Results for continuous endpoints will presented as LS mean changes and associated SEs with associated 95% CI and p-values. For binary endpoints, a line plot showing the proportion of subjects experiencing such endpoints will be produced. For continuous endpoints, a line plot showing the LS mean and SE for each treatment group will be produced. Exploratory endpoint results will also be listed.

The following binary endpoints before or on Week 16 will be analyzed analogously to the primary endpoints of HiSCR75 at Week 16. The number and proportion of subjects for binary endpoints in each treatment group, p-values, 95% CI without strata calculated using asymptotic Wald method will be reported as well. The binary endpoints after week 16 will include number and proportion along with Clopper-Pearson 95% CI without strata according to the four randomized treatment groups. No p-value will be reported.

- HiSCR50, HiSCR75, HiSCR90 and HiSCR100 at Weeks 2, 4, 8, 12, 24 and 32;
- AN count of 0, 1, or 2 at Weeks 4, 8, 12, 24, and 32 among subjects with baseline Hurley Stage II;

- HS flares through Weeks 4 and 32;
- IHS4-55 response rates at Weeks 4, 8, 12, 16, 24 and 32;
- Draining fistula count of 0 at weeks 4, 8, 12, 16, 24 and 32
- Draining fistula count of 0 at weeks 4, 8, 12, 16, 24 and 32, among subjects with baseline draining fistula count of at least 1
- Draining fistula count of 0 at weeks 4, 8, 12, 16, 24 and 32, among subjects with baseline draining fistula count of at least 2
- Proportion with at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst, among subjects with baseline NRS ≥ 4, at weeks 4, 8 12, 24 and 32. NRI will be handled analogously to the corresponding secondary endpoint analysis.
- $\geq 50\%$ reduction from baseline in total inflammatory lesion count (abscesses + inflammatory nodules + draining fistula) at Weeks 4, 8, 12, 16, 24 and 32
- $\geq 50\%$ reduction from baseline in draining fistula count (draining fistula alone)
- No increase in abscesses from baseline at Weeks 4, 8, 12, 16, 24 and 32

The following continuous endpoints before or on Week 16 will be analyzed with an MMRM model as specified in sec 6.6.4. LS mean changes and associated SEs with associated 95% CI and p-values will be presented. Model will include all data up to Week 16. The following continuous endpoints after Week 16 will be reported at all collected timepoints and be summarized according to the four randomized treatment groups. Mean values, mean changes and associated descriptive statistics along with 95% CI (for change from baseline) according to the four randomized treatment groups will be presented.

- Change of Modified Sartorius Score from baseline, Weeks 4, 8, 12, 16, 24, and 32;
- Change in PGA of Skin Pain (at its worst and average respectively) from baseline to Weeks 4, 8, 12, 16, 24, and 32;
    - If a subject received certain prohibited analgesic therapy within 28 days of the visit (including the day of the visit), the subject will be imputed as a non-responder (PGA of Skin Pain = 10) due to the ICE at the visit.
- Change in draining fistula count at Weeks 4, 8, 12, 16, 24 and 32;
- Change from baseline to Week 16 in EQ-5D;
- Change from baseline to Week 16 in DLQI;
- Change from baseline to Week 16 in HADS, HADS-anxiety, and HADS-depression;
- Change from baseline in IHS4 scores at Weeks 4, 8, 12, 16, 24, and 32

HS-PGA is an ordinal scale, as defined as below,

- Clear: No inflammatory or non-inflammatory nodules
- Minimal: Only the presence of non-inflammatory nodules

- Mild: < 5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules
- Moderate: < 5 inflammatory nodules or 1 abscess or draining fistula and ≥ 1 inflammatory nodules or 2 to 5 abscesses or draining fistulas and < 10 inflammatory nodules
- Severe: 2 to 5 abscesses or draining fistulas and ≥ 10 or more inflammatory nodules
- Very severe: > 5 abscesses or draining fistulas

A shift table will be present by treatment to display the numbers of subjects change from baseline to Week 16. Data at Week 16 will be presented as observed data, and separately with missing data imputed using the last observed value before Week 16.

The HAD questionnaire comprises seven questions for anxiety and seven questions for depression. HADS will be summarized as HADS (total), HADS-anxiety, and HADS-depression respectively.

The EQ-5D (3L) comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. EQ-5D will be summarized as one utility score.

DLQI comprises 10 items arranged in six categories: symptoms and feelings (questions 1 and 2), daily activity (3 and 4), leisure (5 and 6), work or study (7), interpersonal relationships (8 and 9), and treatment (10). The total score can vary from 0 (no impact) to 30 (maximum impact).

SF-12 v2 questionnaire is an abbreviated version of the 36-Item Short Form Health Survey with 12 items in eight domains. Physical Component Score and Mental Component Score derived from the SF-12 v2 questionnaire will be summarized by treatment groups at baseline and each timepoint (Week 8, 16, and 32) with mean values and changes from baseline and associated 95% CI without further divided into Period 1 and 2.

The Patient Global Assessment of Skin Pain is collected as a daily diary, so the score used for analysis at visits prior to Week 16 will be the average of the scores recorded 6 days prior to and including the visit (7 days total for the average). For Patient Global Assessment of Skin Pain collected after Week 16, the value collected on the visit day will be used for analysis. No averaging will be done. If more than one value is collected at the visit, the first value collected will be used.

Erythema score at each visit will be listed.

6.6.6. Subgroup Analysis

Various subgroup analyses of the efficacy data will be reported. These analyses will investigate the treatment response within specific subgroups of interest, and assess whether the treatment response is consistent across different subgroup levels. All analyses will be

performed on the FAS data set using methods analogous to those used for the primary analysis of that endpoint, defined above.

Summaries of these variables will be presented by subgroup:

- HiSCR50/75/90/100 at Week 16
- NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among subjects with baseline NRS ≥ 4
- HS flare through Week 16
- Achieved AN count of 0, 1, or 2 at Week 16

The following subgroups are of interest:

- Race (White, Black or African American, other)
- Sex (male, female)
- Age (< 65, ≥ 65)
- Hurley stage at baseline (II, III)

The following subgroups are also of interest for HiSCR50/75/90/100 at Week 16:

- Geographic region
  - North America (US or Canada)
  - Europe (Spain, Hungary, Poland or Germany)
  - Non-US (Spain, Hungary, Poland, Germany or Canada)
- Country
  - United States
  - Canada
  - Poland
  - Hungary
  - Spain
  - Germany
- BMI (≤ 18, > 18 - ≤ 25, > 25 - ≤ 30, > 30 - ≤ 35, > 35)
- Smoking status (never, former, current)
- Prior biologic or JAK inhibitor (Any prior biologic or JAK inhibitor, any prior biologic, and prior TNF inhibitor, no prior biologic or JAK inhibitor)

Difference in response rate and 2-sided Mantel-Haenszel 95% CI will be reported for subgroup analyses for each endpoint similar to Section 6.6.1 and 6.6.3 using stratified tests. A forest plot for the difference in response rate and 2-sided 95% CI will also be presented No p-values will be reported for the subgroup analyses.

6.6.7. Post-Week 16 (Part B, Period 2) Additional Analyses

The following analyses will be done for all four randomized treatment groups in the FAS:

- Proportion with at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst, among subjects with baseline NRS ≥ 4, at weeks 24 and 32 will be summarized by number and proportion along with Clopper-Pearson 95% CI without strata according to the four randomized treatment groups.
    - NRI will be handled analogously to the corresponding secondary endpoint analysis, except subjects who took Tramadol as allowed per-protocol (at a dose of up to 100 mg po every 4 hours, not to exceed 400 mg per 24 hours) during the 28 days prior to the visit will not be counted as a non-responder.
- Descriptive MMRM analyses will be performed by randomized treatment group, for the continuous endpoints described below. The measured value at the visit will be used as the response variable, with visit week, treatment, and treatment * visit week interaction included as predictors. The model will include all visits from Day 1 through Week 32. Unstructured covariance matrix will be used. Other variance-covariance matrices, such as autoregressive, and compound-symmetric will be considered if the model does not converge. Estimated LSMean, corresponding SE values, and 95% confidence intervals will be summarized at the timepoints defined below.
    - Modified Sartorius Score at Weeks 24 and 32;
    - NRS PGA of Skin Pain (at its worst and average respectively) at Weeks 24 and 32. To maintain consistency between all visits, only the score collected on the visit day will be used for this analysis.
    - Draining fistula count at Weeks 24 and 32;
    - EQ-5D at Weeks 24 and 32;
    - DLQI at Weeks 24 and 32;
    - HADS, HADS-anxiety, and HADS-depression at Weeks 24 and 32;
    - IHS4 scores at Weeks 24, and 32

  These summaries will address the question of expected results if a subject is assigned to either 32 weeks of izokibep or 16 weeks of placebo followed by 16 weeks of izokibep.

- A time-to-event analysis using Kaplan-Meier (KM) curves by randomized treatment group will be created for the events listed below.). If estimable, quartiles of the time to each event will be summarized by randomized treatment group. Product limit estimate at Week 32 (Day 224) will be provided. Participants will be censored at the time of last recorded assessment on study:
    - First achievement of HiSCR75
    - First achievement of HiSCR100
    - First achievement of HiSCR90
    - First achievement of HiSCR50

- First achievement of AN count of 0, 1, or 2 for subjects with baseline Hurley Score II
- First achievement of >= 3 point reduction in NRS in Patient Global Assessment of Skin Pain at its worst among subjects with baseline NRS ≥ 4
  - To maintain consistency between all visits, only the score collected on the visit day will be used for this analysis.

These graphics will address the question of whether subjects originally randomized to placebo catch up in efficacy to the subjects who were randomized to izokibep by week 32.

The following analyses will be done by all four randomized treatment groups for the FAS subjects who had at least one dose of izokibep on or after Week 16. The analyses in subjects who received izokibep for the first 16 weeks will be done to address the question of whether responders/non-responders in the first 16 weeks of treatment experience subsequent sustained or added benefit in the following 16 weeks of treatment. The analyses in subjects who received placebo for the first 16 weeks will be done to evaluate if there is additional benefit after initial placebo response, or if placebo non-responders catch up to the subjects receiving 32 weeks of izokibep.

- The subgroup of subjects who were responders by HiSCR75 at Week 16 will be further evaluated by randomized treatment group at Week 24 and Week 32:
  - Response rate for HiSCR75, HiSCR100, HiSCR90, HiSCR50 will be summarized by randomized treatment group at Week 24 and Week 32. The responder proportions and Clopper-Pearson 95% CI without strata will be presented. The NRI approach to missing data will be the same as for the primary analysis.

  - Response rate for AN count of 0, 1, or 2 among those with Hurley stage II at baseline will be summarized by randomized treatment group at Week 24 and Week 32. The responder proportions and Clopper-Pearson 95% CI without strata will be presented. NRI approach will be the same as for the primary analysis.

  - Descriptive MMRM analyses will be performed by randomized treatment group, for change from baseline of IHS4 score and draining fistula count at Week 24 and Week 32. The change from baseline value will be used as the response variable, with baseline value, visit week, treatment, and treatment * visit week interaction included as predictors in the model. Estimated LSMean change from baseline, corresponding SE values, and 95% confidence intervals will be presented in the table summaries.

- The subgroup of subjects who were responders at Week 16 by AN count of 0, 1, or 2 (among those with Hurley stage II at baseline) will also be evaluated at Week 24 and Week 32 in the same manner as described for HiSCR75 responders.

- The subgroup of subjects who were non-responders at Week 16 by HiSCR75 will also be evaluated at Week 24 and Week 32 in the same manner as described for HiSCR75 responders.

- The subgroup of subjects who were non-responders at Week 16 by AN count of 0, 1, or 2 among those with Hurley stage II at baseline will also be evaluated at Week 24 and Week 32 in the same manner as described for the HiSCR75 responders.

- McNemar test will be used to evaluate the relationship between HiSCR75 response at Week 16 vs various response criteria at Week 32. P-values will be provided for descriptive purposes. The following response criteria at Week 32 will be used for this analysis:
    - HiSCR75
    - HiSCR90
    - HiSCR100
    - HiSCR50
    - AN count of 0, 1, or 2

- McNemar test will be used to evaluate the relationship between "AN count of 0, 1, or 2" response at Week 16 vs various response criteria at Week 32. P-values will be provided for descriptive purposes. The following response criteria at Week 32 will be used for this analysis:
    - HiSCR75
    - HiSCR90
    - HiSCR100
    - HiSCR50
    - AN count of 0, 1, or 2

The following analyses will be done (by randomized treatment groups) for only the FAS subjects randomized to placebo who had least one dose of izokibep in Period 2 of the study AND who had a total AN count of ≥ 5 at Week 16 and HS lesions present in at least 2 distinct anatomic areas (to correspond to the inclusion criteria), to address the question of how subjects respond to izokibep after 16 weeks of placebo, when they still meet original eligibility criteria:

- The baseline characteristics summary described in section 6.4.2 will be repeated for this analysis set at Week 16.

- The following binary endpoints will be analyzed analogously to the primary endpoint by randomized treatment group. The number and proportion of subjects for binary endpoints in each treatment group, 95% CI without strata calculated using asymptotic Wald method will be reported as well.
    - HiSCR50, HiSCR75, HiSCR90 and HiSCR100 calculated with respect to Day 1 at weeks 24 and 32;

      HiSCR50, HiSCR75, HiSCR90 and HiSCR100 calculated with respect to Week 16 at weeks 24 and 32

      HiSCR50/75/90/100 with respect to Week 16 is defined as meeting all three criteria below:

        - (AN count at Week 16 - AN count at current visit) / AN count at Week 16 × 100% ≥ 50/75/90/100%
        - Abscess count at Week 16 ≥ abscess count at the current visit
        - Draining fistula count at Week 16 ≥ draining fistula count at the current visit
    - AN count of 0, 1, or 2 at weeks 24 and 32 among subjects with baseline Hurley Stage II;
    - AN count of 0, 1, or 2 at weeks 24 and 32 among subjects with Week 16 Hurley Stage II;
    - HS flares from week 16 through 32, where HS flare is defined as proportion meeting the following two criteria at any assessment after Week 16 and at or before Week 32:
        - (AN count at current visit- AN count at Week 16) / AN count at Week 16 ×100% ≥ 25%
        - AN count at current visit- AN count at baseline ≥ 2
    - IHS4-55 response rates at weeks 24 and 32;
    - Draining fistula count of 0 at weeks 24 and 32
    - Proportion with at least 3 points reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst, among subjects with Week 16 NRS ≥ 4, at weeks 24 and 32

- Descriptive MMRM analyses will be performed by randomized treatment group, for the continuous endpoints described below. The measured value at the visit will be used as the response variable, with visit week, treatment, and treatment * visit week interaction included as predictors. The model will include all visits from Day 1

through Week 32. Estimated LSMean, corresponding SE values, and 95% confidence intervals will be summarized. Line plots by treatment group will be produced:

- NRS Patient Global Assessment of Skin Pain (WORST). To maintain consistency between all visits, only the score collected on the visit day will be used for this analysis.
- Draining fistula count, Modified Sartorius Score, IHS4 Score, HS-PGA score, all HADS scores (Total, Anxiety, Depression), EQ-5D Utility Score and DLQI Total Score.

6.7. Safety

For all Safety Tables, data in Part A and Part B will be summarized as follows, unless otherwise specified:

- Part A summarized with all subjects for the entire time (Week 0 to Week 32)
- Part B, for Period 1, will include the first 16 weeks until the first dose of treatment administered in Period 2 at or after Week 16, summarized by the randomized treatment arms and the combined placebo group (Placebo QW/ Placebo Q2W; Izokibep QW; Izokibep Q2W), and includes all subjects who received at least one dose of study treatment. AEs will be included if date of onset is on or after the day of the first dose received in Period 1 and before the date of the first dose received in Period 2. If a subject did not receive any dose of study treatment in Period 2, all AEs with onset on or after the day of first dose received in Period 1 through 4 weeks (28 days) after the last dose received will be included.
- Part B, Period 2, will include data collected on and after the first dose of study treatment administered at Week 16 visit (or after Week 16 visit, if Week 16 visit is missing), summarized by the randomized treatment groups (Placebo - Izokibep QW; Placebo - Izokibep Q2W; Izokibep QW; Izokibep Q2W), and includes all subjects who took at least one dose of study treatment in Period 2. AEs will be included if date of onset is on or after the day of first dose received in Period 2 through 4 weeks (28 days) after the last dose received.

6.7.1. Extent of Exposure

Exposure will be reported for Period 1, Period 2, and for the entire study for the Safety Analysis Set. Exposure duration will also be summarized and will be calculated as (last dose [in the period of interest] – first dose [in the period of interest] + 1). The total number of doses taken and the total number of active doses of izokibep taken in each period (and overall for the study) as well as the total study will be reported.

Descriptive statistics will be presented for duration of exposure. The summary will include exposure duration, and number of doses administered, and number of doses of active izokibep administered (for the full study period summary only).

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented together with compliance for the Safety Analysis Set. Further, study treatment administration data will be listed for the Safety Analysis Set.

6.7.2. Adverse Events

All SAEs will be collected from the signing of the ICF until the 8-week follow-up visit. All AEs will be collected from the first dose of study drug until 4 weeks after the last dose of study drug. All AEs recorded on the CRF will be coded using the latest MedDRA dictionary around the time of Database Lock and classified as either AEs or TEAEs as follows:

- TEAEs for Part A and Period 1 in Part B are either events with start date and time after the start of the Treatment Period and up to 4 weeks after the end of the Treatment Period (for subjects in Part A or those who don't enter Part B Period 2), or events with start date and time prior to the start of the Period 1 whose severity worsens on or after the start of Period 1 and up to 4 weeks after the end of the Treatment Period (for subjects in Part A or those who don't enter Part B Period 2).
- TEAEs for period 2 in Part B are either events with start date and time after the start of administration of Week 16 treatment and up to 4 weeks after the end of the Treatment Period, or events with start date and time prior to the start of administration of Week 16 treatment whose severity worsens on or after the start of administration of Week 16 treatment through 4 weeks after the end of the treatment period. For subjects who receive treatment in period 2, TEAEs with start date after the start of period 2 will be assigned to period 2 only, not to period 1.
- Treatment-Emergent Serious AEs (TESAEs) will be defined as TEAEs which meet the criteria as Serious = "Yes".
- The relationship between a TEAE and treatment is assessed as related or not related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as related to treatment or with unknown/missing relationship to treatment.
- Assessment of AE intensity will be based on CRF AEs form. Severe TEAEs are defined as TEAEs assessed as being "Severe" in intensity and include those events where the intensity is missing.
- TEAEs leading to discontinuation of treatment are defined as TEAEs where "Action Taken with Study Treatment" is indicated as "Drug Withdrawn".
- Injection site reactions (ISRs) will be defined as any adverse event where the preferred term contains the words "injection site".

In addition to the aforementioned AE types, the following TEAEs of special interest will be summarized:

- Candida infection,
- Inflammatory bowel disease,
- Suicidal ideation.
- Malignancies
- Major adverse cardiovascular and cerebrovascular events (cerebrovascular accident and transient ischemic attack, non-fatal myocardial infarction or unstable angina, and cardiovascular death)
- Tuberculosis
- Infections (opportunistic, serious, or fungal only)
- Cytopenias
- Systemic hypersensitivity reaction

Adverse events of special interest will be identified manually. After all data are entered into the database and before database unblinding, a list of all unique PTs will be generated. ACELYRIN pharmacovigilance and clinical development representatives will review the list and determine which are TEAEs of special interest in each category listed above. This determination will be documented in a memo, signed and dated after database lock and prior to unblinding for the primary analysis (and after final database lock for the final analysis), and stored in the study trial master file. The memo will specify the subjects and preferred terms to be included as TEAEs of special interest, including justification for including or excluding events as appropriate. The database will not be unblinded until the memo is finalized and signed.

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the Safety Analysis Set as follows:

- An overview of TEAEs including the number and percentage of subjects with at least one of each mentioned TEAE type:
    - Any TEAE
        - Leading to discontinuation of study drug
        - Mild
        - Moderate
        - Severe
        - Any moderate or severe AE
    - Any study treatment related TEAE
        - Leading to discontinuation of study treatment
    - Any serious TEAE
        - Leading to discontinuation of study treatment

        - Leading to death
    - Any serious study treatment related TEAE
        - Leading to discontinuation of study treatment
        - Leading to death
- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by SOC and PT for the following types of TEAEs.
    - TEAEs of Special Interest
    - TEAEs Leading to Discontinuation of Study Treatment
    - TEAEs by Maximum Severity
    - TEAEs by Relationship to Treatment
    - TEAEs by Relationship and Maximum Severity
    - Study Treatment related TEAEs
    - Study Treatment Related TEAEs Leading to Discontinuation of Study Treatment
    - Serious TEAEs
    - Serious TEAEs Leading to Discontinuation of Study Treatment
    - Serious TEAEs Leading to Death
    - Study Treatment Related Serious TEAEs
    - Study Treatment Related Serious TEAEs Leading to Discontinuation of Study Treatment
    - Study Treatment Related Serious TEAEs Leading to Death
- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by SOC and PT for two subgroups:
    - Subjects < 65 years of age at baseline
    - Subjects ≥ 65 years of age at baseline
- The number and percentage of subjects who died will be summarized
- The number and percentage of subjects reporting each TEAE and the count of number of events will be summarized by descending incidence PT (by total group) for the following types of TEAEs.
- All TEAEs
- TEAEs of Special Interest

In the above summaries, subjects with more than one TEAE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one TEAE within a particular PT are counted only once for that PT.

For summaries by maximum severity, subjects with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included in the counts as severe.

Summaries by SOCs and PTs will be sorted by SOCs by their Internationally Agreed Order (MedDRA) and PTs within SOC by descending order of total incidence. Where PTs tie, PTs will be sorted alphabetically. Summaries by PTs only will be sorted by descending order of total incidence.

All AE data will be listed and AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and stop day of the AE calculated relative to the first dose of treatment and will be presented for those subjects who received at least one dose of treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

AESIs and ISRs will be summarized for by treatment group, SOC, and PT. A similar summary will be provided by PT only for ISRs. These tables will be presented for the whole study period as well as by period (Period 1 and Period 2, separately, for Part B). Only subjects who have at least one dose of study drug in Period 2 are included in the summaries during Period 2.

To assess the pattern of initial onset, AESIs and ISRs will also be presented by Kaplan-Meier plot. This summary will be done for the full study period and, separately, only for Period 2. For the Period 2 summary, the day of onset will be calculated with respect to the Week 16 date of dosing (Date of AE – Date of Week 16 dose + 1).

Separate Kaplan Meier (KM) plots will be created for the study duration and Period 2 for time to:

- First onset of an event in each AESI category
    - If an AESI category has < 3 events in a treatment arm, then this analysis will not be done.
    - Subjects who do not experience an event will be censored at their date of last contact.
- First ISR
    - Subjects who do not experience an event will be censored at the date of their last injection.

The date/time of onset of the first instance of the event of interest (AESIs or ISRs) will be used as the date/time of the event in the analysis.

The product limit estimator will be presented by treatment group for Week 4 (Day 28), Week 8 (Day 56), Week 12 (Day 84), Week 16 (Day 112), Week 20 (Day 140) , Week 24 (Day 168), Week 28 (Day 196), and Week 32 (Day 224) for each AESI category and for ISRs.

Incidence of ISRs will be summarized for the whole study period by treatment group, and injection visit week (Day 1, Week 1, Week 2, etc). If a subject didn't have an injection at the visit week, they will not be counted in the denominator for the incidence calculation.

A similar presentation of ISRs by treatment group and injection visit week will also be done, but the cumulative number of ISRs up to the injection visit week will be summarized at the visit week. This summary will be done for the full study period as well as by treatment period.

An overall summary of ISRs will be produced by treatment group, Period 1, Period 2, and for the full 32 week treatment period. The summary will include the number of subjects with:

- ISRs leading to discontinuation
- ISR at each maximum intensity/severity
- Related ISRs
- Serious ISRs
- Serious related ISRs

An ISR is considered to correspond to a particular visit week if it occurs on or after the indicated injection visit date/time, and prior to the next inject visit date/time. If no subsequent injection visit date/time is available, then the ISR will correspond to the closest injection visit date occurring prior to it.

To evaluate the pattern of subjects experiencing multiple ISRs in Period 1 of the study (or the full treatment period in Part A), the number and percent of subjects with ISRs on or after Day 29 (through the end of the period) will be presented by the four treatment groups and by the following subgroups:

- Subjects who had at least one ISR on Days 1-28
- Subjects who had no ISRs on Days 1-28

A similar analysis by the four treatment groups will be presented for Period 2 Part B, where the two subgroups of interest are:

- Subjects who had at least one ISR up to Week 16
- Subjects who had no ISRs up to Week 16

ISRs will also be graphically presented by treatment group using a lasagna plot. The y-axis will be each injection visit week, the x-axis will represent each subject, and each 'square' on the plot will be color coded into the following categories: missing injection, no ISR at the visit, mild, moderate, and severe ISRs. The lasagna plot will be presented by treatment group, and sorted by ISR first onset and severity (earliest and most severe will be sorted at the top).

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of TEAEs
- Listing of Serious TEAEs
- Listing of AEs Leading to Interruption of Study Treatment
- Listing of AEs Leading to Discontinuation of Study Treatment
- Listing of AEs of Special Interest

6.7.3. Laboratory Evaluations

Data for the following hematology, clinical chemistry, routine urinalysis, pregnancy testing, other screening tests, and other tests analytes received from the central laboratory are to be measured at the scheduled timepoints (Baseline, Week 4, 8, 12, 16, 24, 32, and 39).

Table 1 Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase[2]	Fasting lipid (total cholesterol, triglycerides & HDL)
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) at screening			
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Serology hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody • Tuberculosis testing: QuantiFERON® test or purified protein derivative (PPD) test • Note: T-SPOT® tuberculosis test may be acceptable if agreed upon with the medical monitor			

In accordance with the baseline value definition in Section 5.1.2, the change from baseline will be derived as follows:

Change (unit) = (post-baseline value – baseline value)

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed timepoints (Baseline, Week 4, 8, 12, 16, 24, 32, and 39) will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For summaries which present the worst value with respect to the reference range at the subject level, low and high are each chosen in preference to normal values. For parameters with both low and high reference ranges, subjects who have assessments within both low and high ranges will be counted within each category for worst value summary tables.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the Safety Analysis Set:

- Observed values and change from baseline at each assessed timepoint (Week 4, 8, 12, 16, 24, 32, and 39) for each standard continuous laboratory parameter
- Number and percentage of subjects with categorized shift (low, normal, and high) values relative to the reference range at baseline compared to each post-baseline timepoint (Week 4, 8, 12, 16, 24, 32, and 39) for hematology and clinical chemistry
- Number and percentage of subjects with worst categorized (low, normal, and high) values relative to the reference range

Listings of all clinical laboratory data including derived change from baseline will be provided for the Safety Analysis Set. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low.

6.7.3.1. Liver toxicity review

Potential liver toxicity will be assessed by listing subjects who met potential drug induced liver injury (DILI) criteria as described in the protocol and by summarizing subjects who met Hy's Law.

Subjects who met any (one or more) of the following criteria will be included in a listing for consideration of DILI:

- ALT or AST ≥5 x ULN at any time
- ALT or AST ≥3 x ULN at all (2 or more) assessments in a span of ≥4 weeks
- ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN (>35% direct bilirubin) simultaneously at any time
- ALT or AST ≥3 x ULN and international normalized ratio (INR) ≥1.5 simultaneously at any time

- ALT or AST ≥3 x ULN at any time during the study and weekly assessments after this finding are not available for at least 4 weeks
- ALT or AST ≥3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity at any time

To determine subjects who meet the last criterion, a listing of all subjects who have at least one ALT or AST ≥3 x ULN at any time, and who do not meet any of the first five criteria, will be reviewed by qualified medical professionals along with a listing of all AEs reported by such subjects. In coordination with the investigator, the medical professionals will assess whether any AE is believed to be related to liver injury or hypersensitivity and, if so, whether the elevated ALT or AST is in temporal association with the AE. Any subjects who meet these criteria will be included on a memo that will be filed in the TMF prior to database lock and unblinding, and included in the listings. For subjects who meet any of the six criteria, all LFT results at any time during the study will be listed, sorted by subject and date. Listing will include subject, treatment assignment, ALT, AST, bilirubin and INR, along with specific criterion met.

Subjects who meet the criteria for Hy's Law will be displayed in shift tables. Hy's Law is met when ALT or AST is ≥3 x ULN, total bilirubin ≥2 x ULN and ALP is <2 x ULN, with all occurring simultaneously (at the same draw). At each assessment, subjects will be classified as meeting Hy's Law or not meeting Hy's Law. The shift tables will be presented as follows:

- Treatment period 1
  - Baseline (meet Hy's Law / not meet Hy's Law)
  - Any time during period 1 (meet Hy's Law at least one time / not meet Hy's Law at any time)
  - One table presented for each treatment arm (160 mg QW / 160 mg Q2W / combined placebo)
- Treatment period 2
  - Baseline prior to treatment period 1 (meet Hy's Law / not meet Hy's Law)
  - Any time during period 2 (meet Hy's Law at least one time / not meet Hy's Law at any time)
  - One table presented for each treatment arm (160 mg QW / 160 mg Q2W / placebo – 160 mg QW / placebo – 160 mg Q2W)

Separate Kaplan Meier (KM) analyses plots will be created for time to:

- First instance of meeting Hy's Law
- First instance of ALT or AST ≥5 x ULN
- First instance of ALT or AST ≥3 x ULN and total bilirubin ≥2 x ULN (>35% direct bilirubin) simultaneously

- First instance of ALT or AST ≥3 x ULN and international normalized ratio (INR) ≥1.5 simultaneously
- First instance of ALT or AST ≥3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity at any time

for the study duration (Day 1 through Week 32). In each plot, the subjects taking any treatment with Q2W frequency will be indicated by a solid line. The subjects taking any treatment with QW frequency will be indicated by a dashed line. Separate colors will be used to distinguish subjects randomized to izokibep and those randomized to placebo.

Subjects who do not experience an event will be censored at their last attended assessment. The date/time of onset of the first instance of the event of interest will be used as the date/time of the event in the analysis.

The product-limit estimator at Week 16 and Week 32 will be summarized by treatment group.

If there are < 3 events in a treatment arm for an event, then the KM analysis will not be done.

A listing of all LFT results from all subjects who meet Hy's Law at least one time during the study will be produced, sorted by subject and date. This listing will show subject, treatment assignment, period, ALT, AST, ALP, bilirubin and INR.

6.7.4. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- SBP (mmHg)
- DBP (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (breaths/min)
- Body Temperature (°C)

In accordance with the baseline value definition in Section 5.1.2, the change from baseline will be derived as follows:

Change (unit) = (post-baseline value – baseline value)

The following will be summarized for the Safety Analysis Set:

- Observed values and change from baseline at each assessed timepoint (Week 1, 2, 3, 4, 8, 12, 13,14, 15,16, 17 18, 20, 24, 28, 32, and 39) for each standard vital sign parameter using default summary statistics for continuous variables.

A listing of all vital signs data including derived change from baseline will be provided for the Safety Analysis Set.

6.7.5. Electrocardiograms

The following electrocardiogram (ECG) assessments will be taken at baseline, Weeks 16, 32 and 39:

- An overall assessment classified as normal or abnormal
- Abnormal assessments will be further classified as clinically significant or not clinically significant

At baseline assessment, the subject will be classified as abnormal if any (one or more) of the replicate assessments are classified as abnormal. Similarly, the abnormal assessment will be classified as clinically significant if any (one or more) abnormal assessments are classified as clinically significant. The subject will be classified based on the worst finding of triplicate 12-Lead ECG. A list of ECG assessments will be presented.

6.7.6. Physical Examination

Clinically significant findings observed prior to the first dose of study drug will be entered on the CRF in medical history in the CRF and reported as medical history. Clinically significant findings observed after the first dose of study drug will be reported as AEs in the CRF and reported as AEs.

For each physical examination body system, the number and percentage of subjects with abnormalities at baseline and at each assessed timepoint (Screen and Week 32) will be summarized for the Safety Analysis Set.

Physical examination findings (normal/abnormal/clinically significant) and details of abnormalities will be listed for each subject at each assessment timepoint (Screen and Week 32).

6.7.7. C-SSRS

Suicidal ideation and behavior will be assessed during the study (Screen, Week 0, 4, 8, 12, 16, 20, 24, 28, 32, and 39) by trained study personnel using the C-SSRS. C-SSRS evaluates suicidal ideation (Category 1 - Category 5) and behavior (Category 6 - Category 10). The following outcomes are C-SSRS categories and have binary responses (yes/no).

- Category 1 – Wish to be Dead
- Category 2 – Non-specific Active Suicidal Thoughts
- Category 3 – Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
- Category 4 – Active Suicidal Ideation with Some Intent to Act, without Specific Plan

- Category 5 – Active Suicidal Ideation with Specific Plan and Intent
- Category 6 – Preparatory Acts or Behavior
- Category 7 – Aborted Attempt
- Category 8 – Interrupted Attempt
- Category 9 – Actual Attempt (non-fatal)
- Category 10 – Completed Suicide

At the screen visit, the C-SSRS will be listed by lifetime and past 6 months from suicidal ideation, and lifetime and past two years from suicidal behavior for each category. At the post-screen visit, the C-SSRS will be listed as since the last visit for each category.

6.7.8. Interim Analysis and Data Monitoring

An independent Data Monitoring Committee (DMC) will be established to monitor data on an ongoing basis to ensure the continuing safety of the subjects enrolled in this study.

The DMC will consist of at least one medical expert with the relevant therapeutic area and at least one statistician. The DMC will also have a minimum of three members, one of whom will serve as the Chair. The DMC responsibilities, authorities, and procedures will be documented in the DMC charter. The committee will meet approximately every 6 months to review interim data. After each review, the DMC will make recommendations regarding the continuation of the study based on safety. In addition, the DMC will meet as indicated below to review data from Part A and Part B.

Part A

The DMC will review data in Part A after all subjects have had the opportunity to complete the Week 8 visit (or discontinued the study early). Based on this review, the DMC may recommend continuing, stopping, or altering Part B.

Part B

In Part B, no formal interim analysis is planned for purposes of stopping or altering this study. The DMC will review unblinded data when the first approximately 105 subjects randomized into Part B have had the opportunity to complete the Week 8 visit to make a recommendation on further development activities for izokibep. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The type I error rate for hypothesis tests at the end of the study will be decreased by 0.0001 to account for this interim summary of unblinded data. The study team and the investigators will remain blinded to these interim results until after the study is completed.

After all subjects have had an opportunity to complete the Week 16 visit (complete the visit, or complete a subsequent visit, or permanently discontinue the study), the primary endpoint analyses may be conducted. These will be the final analyses for the primary endpoint, so no

adjustment of the type I error will be applied. Site staff, and all Sponsor staff who interact with site staff, will remain blinded to individual subject treatment assignment until the final subject has completed the final visit.

6.8. Pharmacokinetic Assessments

Pharmacokinetic data will be summarized by treatment group and scheduled visit, including N (number of non-missing data), N BLQ (for concentrations only), arithmetic mean, standard deviation (SD), arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, median, minimum, and maximum. Only trough collections are planned, so no calculations of PK parameters (maximum concentration, area under the concentration curve, etc.) will be provided.

For the calculation of summary statistics, pre-dose concentrations that are below the limit of quantification (BLQ) will be treated as zero and post-dose concentrations that are BLQ will be treated as missing.

Pharmacokinetic data may be combined with data from other studies of izokibep for modeling. If this is done, details will be described in a separate document.

6.9. Anti-Drug Antibodies

Samples tested for ADAs will be reported as positive or negative based on a non-specific screening assay. Samples that are positive, and are further tested, will be reported as positive or negative for the IL-17A binding domain, positive or negative for the albumin binding domain, and/or positive or negative as a neutralizing ADA. Any continuous values of concentration (titers) will be summarized using observed data.

Subjects will be summarized at each scheduled visit according to the screening test, with number (%) positive. Positive samples on the screening test, that are further tested, will be reported according to each specific binding domain, with number (%) positive for the IL-17A binding domain, number (%) positive for the albumin binding domain, and number (%) positive for either (one or both) binding domain. Samples that are further tested on a neutralizing antibody assay will be reported as number (%) positive for neutralizing activity, with percentage calculated using the number that were positive according to the screening test as the denominator.

7. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 10FEB2023	Not applicable; the first version
Version 2, Final, 19JUN2023	Updated according to Protocol V3, 26APR2023
Version 3, Final, 03APR2024	Updated to include additional details on post-Week 16 efficacy and safety analyses; updated handling of BLQ for PK to align with other studies in the program; added clarity to definitions of Period 1 and Period 2; updated Appendix 2 scoring rules and added clarity to align with verified approach

Appendix 2: End Points Definitions and Scoring Method

Modified Sartorius Score[8]

The modified Sartorius score includes an assessment of the anatomical regions involved, the numbers and scores of lesions for each region, the longest distance between 2 relevant regions (or size of a single lesion), and whether all lesions are separated by normal skin (yes or no). The detailed scoring is as following:

Each region will score as:

Item No	Items	Scoring Rules	Points	Score:
1	Anatomical region	If the region is affected	3	
		If the region is not affected, the score for that region is 0, and no further calculations are needed for the region. If the region is affected, the following are added in addition to the 3 points for the region in line 1 above.		
	For each affected region:			
2	Nodules (Inflammatory)	Count from this region	1	1 × count
3	Fistulae (Draining only)	Count from this region	6	6 × count

4	Longest distance between two relevant lesions within a region or size of the lesion if single	< 5 cm	1	
		5 - 10 cm	3	
		> 10 cm	9	
5	Lesions separated by normal skin?*	Yes	0	
		No	9	
	Score for the region			Sum of above

* If Lesions separated by normal skin = "No" and/or Hurley Stage = "STAGE III" then 9 points is added for the region.

Score for each region is (if the region involved) = 3 + (number of inflammatory nodule) × 1 + {(number of draining fistula) × 6 +{0 < (The longest distance between two relevant lesions [or size of lesion if single]) <5} × 1+ {5≤(The longest distance between two relevant lesions [or size of lesion if single]) ≤ 10} × 3 + {(The longest distance between two relevant lesions [or size of lesion if single]) > 10 } × 9 + (all lesions separated by normal skin = Yes or Hurley Stage = "STAGE III") × 9

Modified Sartorius score is the sum of the score of each region. Any region with no involvement will have a score of zero for purposes of calculating the modified Sartorius score.

A region is considered "affected" if any of the following conditions are true:

- Abscess Count > 0 OR
- Any "Interventions needed" questions response = YES
- Any "Interventions needed DATE" question is not missing.
- Any "How many lesions had intervention" question > 0
- Any "How many lesions had intervention AND are no longer present" > 0
- Non-draining fistula count > 0
- Draining fistula count > 0
- Non-inflammatory nodule count > 0

- Inflammatory nodule count > 0
- Hypertrophic scar > 0
- Longest distance > 0
- Normal appearance tissue = NO
  Hurley Stage contains "STAGE"

EQ-5D[9]

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, and extreme problems. A unique health state is defined by combining 1 level from each of the 5 dimensions. There are 243 possible health states defined in this way. Each state is referred to in terms of a 5-digit code. No health state value will be calculated if any of the dimensions are missing.

Domain Scores of EQ-5D-3L Descriptive System

Response Category	Score
No problems	1
Moderate problems	2
Severe problems	3

Note: Missing values are coded as '.'. Ambiguous values (e.g., 2 boxes are ticked for a single dimension) should be treated as missing values.

EQ-5D-3L = sum(non-missing question score)/(number of non-missing questions) × 5. If the number of questions with a missing answer is ≥ 3 (≥ 50%) then EQ-5D-3L is missing.

For example, if a patient provides the following responses: Mobility = No problems, Self-care = No problems, Usual Activities = Moderate problems, Pain/Discomfort = Moderate problems, Anxiety/Depression = Extreme problems, his response sequence is 11223. The 243 theoretical possible sequences can then be mapped to an index value to provide a summary across all dimensions. For the calculation of the index value, the UK value set based on Time Trade-Off method will be used. The scoring algorithm is as follows:

Full health (11111) =	1.000
At least one domain at 2 or 3 (N2):	-0.081
At least one domain at 3 (N3):	-0.269
Mobility level 1:	0

Mobility level 2:	-0.069
Mobility level 3:	-0.314
Self-care level 1:	0
Self-care level 2:	-0.104
Self-care level 3:	-0.214
Usual activities 1:	0
Usual activities 2:	-0.036
Usual activities 3:	-0.094
Pain/discomfort 1:	0
Pain/discomfort 2:	-0.123
Pain/discomfort 3:	-0.386
Anxiety/depression 1:	0
Anxiety/depression 2:	-0.071
Anxiety depression 3:	-0.236

The index for the patient with example sequence 11223 = 0.255, calculated as follows:

Full health = 1

Minus N2: -0.081

Minus N3: -0.269

Minus mobility level 1: 0

Minus self-care level 1: 0

Minus usual activities level 2: -0.036

Minus pain/discomfort level 2: -0.123

Minus anxiety/depression level 3: -0.236

where level 1 corresponds to no problems, level 2 to some problems and level 3 to extreme problems.

DLQI[10]

DLQI measures the health-related quality of life of adult patients suffering from a skin disease. It comprises 10 items arranged in six categories: symptoms and feelings (questions 1 and 2), daily activity (3 and 4), leisure (5 and 6), work or study (7), interpersonal relationships (8 and 9), and treatment (10). The total score can vary from 0 (no impact) to 30 (maximum impact). The DLQI score is calculated by summing the score of each question resulting in a maximum of 30 and a minimum of 0. The highest score represents the highest impairment of the health-related quality of life.

The scoring of each question is as follows:

• Very much	Scored 3
• A lot	Scored 2
• A little	Scored 1
• Not at all	Scored 0
• Not relevant	Scored 0
• Question unanswered or missing	Scored 0
• If leading Question 7 response is Yes*	Scored 3
• If leading Question 7 response is not Yes*	Scored as above using follow-up Question 7

* Questions 7 and 7a substitute each other. Only 1 of them may contribute to overall DLQI both in terms of score and number of questions. I.e. if Q7 = "Yes" and Q7a = "A little" – only Q7 is scored as "3" and +1 non missing-question, while Q7a is completely ignored.

DLQI = sum(non-missing question score) / (number of non-missing questions) × 10. If the number of questions with a missing answer is ≥ 5 (≥ 50%) then DLQI is missing.

HADS[11]

The HADS is a self-report rating scale of 14 items on a 4-point Likert scale (range 0–3, with 0 least severe and 3 most severe). It is designed to measure anxiety and depression (7 items for each subscale). The total score is the sum of the 14 items, and for each subscale, the score is the sum of the respective seven items (ranging from 0–21). HADS-Anxiety includes questions 1, 3, 5, 7, 9, 11, and 13. HADS-Depression includes questions 2, 4, 6, 8, 10, 12, and 14.

HADS will be present as anxiety, depression, and overall respectively. If the number of questions with a missing answer is ≥ 4, ≥ 4, and ≥ 7 (≥ 50%) for anxiety, depression, and overall respectively, then the score is missing.

Erythema Score

At every visit, for each anatomic region affected by HS, the investigator will assess the overall degree of erythema using a four-point ordinal scale ranging between 0 and 3.

- Left axilla
- Right axilla
- Left sub/inframammary area
- Right sub/inframammary area
- Intermammary area
- Left buttock

- Right buttock
- Left inguino-crural fold
- Right inguino-crural fold
- Perianal
- Perineal
- Upper Back and Neck
- Other

The scoring rule as following:

- 0 = no redness
- 1 = faint but discernible pink coloration
- 2 = moderate red coloration
- 3 = very red or bright red coloration

Erythema score = 12 × {sum (non-missing score of each region [total 12 regions + Other regions])/ (number of non-missing region)}. The multiplier of 12 will not change even if the number of non-missing + Other regions changes. If the number of questions with a missing answer is ≥ 6 (≥ 50%) then the Erythema score is missing.

A region is considered "affected" if it has a > 0 abscess/nodule/fistula count or a non-zero response to any of the other quantitative questions on the Lesion Count/Hurley Stage eCRF form for the region or "intervening normal appearance tissue" = "No" or Hurley Stage not equal to "Not Applicable".

SF-12v2

The SF-12v2[12] is a self-reported outcome measure assessing the impact of health on an individual's everyday life. Two component scores are derived from the SF-12 including the SF-12 Physical Component Score and the SF-12 Mental Component Score. SF-12 summary score can be calculated only when all components are non-missing (i.e. all answers provided), otherwise should be set to missing. If all answers are available then calculate as per following steps.

The instructions for computing the component scores are as follows:

1. Compute raw scale scores based on the table from precoded item value to final item value.
2. Transform raw scale scores to 0-100 scale.
3. Standardization of SF-12v2 scales (Z-scores), Standard Form
4. Norm-Based Transformation of SF-12v2 scales Z-scores, Standard Form
5. Norm-Based Scoring SF-12v2 Physical and Mental Summary Measures

1. Precoded and final values by items:

Item: 1

Response choices	Precoded Item Value	Final Item Value
Excellent	1	5.0
Very good	2	4.4
Good	3	3.4
Fair	4	2.0
Poor	5	1.0

Items: 2a, 2b

Response choices	Precoded Item Value	Final Item Value
Yes, limited a lot	1	1
Yes, limited a little	2	2
No, not limited at all	3	3

Items: 3a, 3b, 4a, 4b, 7

Response choices	Precoded Item Value	Final Item Value
All of the time	1	1
Most of the time	2	2
Some of the time	3	3
A little of the time	4	4
None of the time	5	5

Item: 5

Response choices	Precoded Item Value	Final Item Value
Not at all	1	5
A little bit	2	4
Moderately	3	3
Quite a bit	4	2
Extremely	5	1

Items: 6a, 6b

Response choices	Precoded Item Value	Final Item Value
All of the time	1	5
Most of the time	2	4
Some of the time	3	3
A little of the time	4	2
None of the time	5	1

Items: 6c

Response choices	Precoded Item Value	Final Item Value
All of the time	1	1
Most of the time	2	2

Some of the time	3	3
A little of the time	4	4
None of the time	5	5

2. Transformation of scale scores:

The next step involves transforming each raw score to 0-100 scale using the formula shown below:

$$Transformed\ scale = \left[\frac{(Actual\ raw\ score - lowest\ possible\ raw\ score)Possible\ raw\ score\ range}{}\right] \times 100$$

This transformation converts the lowest and highest possible scores to zero and 100, respectively. Scores between these values represent the percentage of the total possible score achieved.

Scale items aggregated and range of possible scores:

SF-12v2 scale	**Sum final Item Values (after recoding items)**	**Lowest and highest possible raw scores**	**Possible raw score range**
Physical Functioning (PF)	Items 2a + 2b	2, 6	4
Role Physical (RP)	Items 3a + 3b	2, 10	8
Bodily Pain (BP)	Item 5	1, 5	4
General Health (GH)	Item 1	1, 5	4
Vitality (VT)	Item 6b	1, 5	4
Social Functioning (SF)	Item 7	1, 5	4
Role Emotional (RE)	Items 4a + 4b	2, 10	8
Mental Health (MH)	Items 6a + 6c	2, 10	8

1. Standardization of SF-12v2 scales (Z-scores), Standard Form:

Formulas for z-score standardization of SF-12v2 scales, Standard Form:

SF-12v2	**Z-scores**
Physical Functioning (PF_Z)	PF_Z = (PF – 81.18122) / 29.10558
Role Physical (RP_Z)	RP_Z = (RP – 80.52856) / 27.13526
Bodily Pain (BP_Z)	BP_Z = (BP – 81.74015) / 24.53019
General Health (GH_Z)	GH_Z = (GH – 72.19795) / 23.19041
Vitality (VT_Z)	VT_Z = (VT – 55.59090) / 24.84380
Social Functioning (SF_Z)	SF_Z = (SF – 83.73973) / 24.75775
Role Emotional (RE_Z)	RE_Z = (RE – 86.41051) / 22.35543

Mental Health (MH_Z)	MH_Z = (MH – 70.18217) / 20.50597

Norm-Based Transformation of SF-12v2 scales Z-scores, Standard Form:

SF-12v2	**Norm-Based scores**
Physical Functioning (Norm-Based PF)	Norm-Based PF = 50 + (PF_Z * 10)
Role Physical (Norm-Based RP)	Norm-Based RP = 50 + (RP_Z * 10)
Bodily Pain (Norm-Based BP)	Norm-Based BP = 50 + (BP_Z * 10)
General Health (Norm-Based GH)	Norm-Based GH = 50 + (GH_Z * 10)
Vitality (Norm-Based VT)	Norm-Based VT = 50 + (VT_Z * 10)
Social Functioning (Norm-Based SF)	Norm-Based SF = 50 + (SF_Z * 10)
Role Emotional (Norm-Based RE)	Norm-Based RE = 50 + (RE_Z * 10)
Mental Health (Norm-Based MH)	Norm-Based MH = 50 + (MH_Z * 10)

3. Norm-Based Scoring SF-12v2 Physical and Mental Summary Measures (Standard 4-week recall)

SF-12v2	**Aggregated scores**
Aggregate Physical Summary Score (AGG_PHYS)	AGG_PHYS = (PF_Z * 0.42402) + (RP_Z * 0.35119) + (BP_Z * 0.31754) + (GH_Z * 0.24954) + (VT_Z * 0.02877) + (SF_Z * -0.00753) + (RE_Z * -0.19206) + (MH_Z * -0.22069)
Aggregate Mental Summary Score (AGG_MENT)	AGG_MENT = (PF_Z * -0.22999) + (RP_Z * -0.12329) + (BP_Z * -0.09731) + (GH_Z * -0.01571) + (VT_Z * 0.23534) + (SF_Z * 0.26876) + (RE_Z * 0.43407) + (MH_Z * 0.48581)

4. Transformation of Summary Scores (Standard Form)

SF-12v2	**Z-scores**
Transformed Physical Component Score (PCS)	50 + (AGG_PHYS * 10)
Transformed Mental Component Score (MCS)	50 + (AGG_MENT * 10)

8. References

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