Protocol Number: 22107

Official Title: A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Moderate to Severe Hidradenitis Suppurativa

NCT Number: NCT05905783

Document Date: 14 May 2024

Title Page

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A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Moderate to Severe Hidradenitis Suppurativa

Protocol Number: 22107

Protocol Version: 2.0

Protocol Date: 10 May 2024

Compound: Izokibep

Brief Title: Hidradenitis Suppurativa Phase 3 Study of Izokibep

Study Phase: 3

Sponsor Name: ACELYRIN, INC.

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Regulatory Agency Identifier Number(s):

Registry	**ID**
EU Clinical Trial Number	2022-503160-33-00

Previous version	Date
1.0	24 March 2023

Amendment 1 (10 May 2024)
This amendment is substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:
The main purpose of this amendment is to update the timepoint for the primary and secondary endpoints, and improve the method of handling missing data for the primary and secondary endpoints.

Summary of Changes

Section #	Description of Change	Brief Rationale
Title page	Removed sponsor signatory.	Sponsor approval is provided and maintained within the regulatory information management system.
1.1	Removed exploratory endpoints from the synopsis.	To streamline the synopsis to include only critical information.
1.1, 4.1, 4.1.3	Revised description on the number of subjects to be enrolled for the study from approximate to planned.	Change incorporated from country-specific protocol (CSP) Europe v.1.2 made in response to request from European Medicines Agency (EMA).
1.1, 3, 4.1, 4.2, 8.1.12, 9.1, 9.1.1, 9.2, 9.3.2, 9.3.3, 9.4, 9.5	Updated the timepoint for the primary and secondary objectives and endpoints from Week 16 to Week 12.	This change was made to account for the unanticipated and historically high placebo response rates between weeks 12 and 16 and a high rate of dropouts among responders that was largely unrelated to safety observed in Phase 2b Study 21102.
1.1, 4.1.1	Updated frequency of data monitoring committee (DMC) meetings every 6 months to more flexible language.	Added flexibility to the frequency of DMC meetings, to allow for meetings less frequent than every 6 months.
1.3	Added visit windows to the table and made changes to the footnotes to reduce redundancy between footnotes and between the main body of the document.	Clarity and readability.
1.3, 8	Updated maximum allowed window between dose from 10 days to 13 days.	To correct a potential inconsistency for cases where +3-day windows are utilized on both sides of the weekly dose, resulting in 13 days between doses, rather than the previous 10 day maximum.
1.3	Added assessments to Week 12, including Hurley staging, electrocardiogram, optional photography, 12 Item Short Form Survey, urinalysis, fasting lipids, and hemoglobin A1C.	To align with change of primary endpoint timepoint to Week 12.
1.3	Removed the Week 18 visit.	To correct an error that was a carryover from the Phase 2 Study 21102 protocol.
1.3	Added collections of Hidradenitis Suppurativa -Patient Global Impression of Change (PGIC) at Week 24.	Collection of PGIC at Week 24 is included in the exploratory endpoints but was inadvertently left out of the schedule of assessments.

Section #	Description of Change	Brief Rationale
2.2.3.3	Added high-level safety data from Study 21102.	New data became available after the primary analysis of Study 21102.
2.2.3.2	Added high-level efficacy data from Study 21102.	New data became available after the primary analysis of Study 21102.
2.3.2	The benefit/risk assessment was updated to reflect the allowance of the use of a stable dose of oral antibiotics in up to 30% of subjects enrolled and the rationale for the cap was added.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
3	Updated the timepoint for the exploratory objectives and endpoints from Week 12 to Week 16.	To align with primary and secondary endpoints and avoid duplication.
3	Added a Week 24 timepoint for the exploratory endpoints of the hidradenitis suppurativa clinical response (HiSCR) values (HiSCR50, HiSCR75, HiSCR90, and HiSCR100).	Consistency with other exploratory endpoints.
3	Corrected exploratory endpoints for Numeric Rating Scale (NRS) Patient Global Assessment of Skin Pain.	To capture the intended objectives/endpoints for assessment of change from baseline in both NRS Patient Global Assessment of Skin Pain questions: “In the last 24 hours, which number best describes your skin pain at its worst due to your HS?” and “In the last 24 hours, which number best describes your skin pain on average due to your HS?”
3	Updated estimands for the primary and secondary objectives.	To clarify and align with the new missing data handling approach.
Inclusion criterion 2 of Section 5.1	Removed cap of ≤ 75 years of age by deleting inclusion criterion 2 and adding inclusion criterion 12.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
Inclusion criterion 7 of Section 5.1	Added flexibility for the requirement of daily use of topical antiseptic to allow a minimum use of 3 days a week.	Change incorporated from CSP Europe v.1.2 made in response to a request from EMA for consistency with Section 6.8.2.1.
Inclusion criterion 9 of Section 5.1	Added allowance of subjects with a known history of active tuberculosis (TB) if adequately treated according to World Health Organization/Center for Disease Control and Prevention therapeutic guidance and determined to be fully recovered by a TB specialist.	To add flexibility to include subjects that had active TB in the past but were treated and no longer have active TB.

Section #	Description of Change	Brief Rationale
Inclusion criterion 10 of Section 5.1 and Section 8.2.8	Clarified that for interferon-gamma release assay (IGRA) TB test (QuantiFERON recommended) indeterminate results, subjects are permitted to retest once. If the retest results are negative, the subject is eligible for the study. If the retest results are positive or remain indeterminate, the subject may not be randomized without further evaluation by a TB specialist and for positive IGRA TB test results, subjects may not be randomized without further evaluation by a TB specialist.	To reduce confusion and provide clear instructions on how to handle various TB testing results.
Exclusion criterion 13 of Section 5.2	Updated timing of the chest x-ray requirement within 3 months of the first dose of study drug or screening to within 3 months prior to screening.	Previous language was ambiguous and could cause confusion if a subject's chest x-ray was more than 3 months prior to the first dose but less than 3 months prior to screening.
Exclusion criterion 26 of Section 5.2	Reorganized for readability, content was maintained.	Clarity.
1.3, 3, 8.6, Table 5 of Section 10.2	Specified that exploratory biomarker sampling and analysis applies to the United States only.	Operational feasibility.
6.1.1, 6.4, 8.2.1.2	Moved instructions for home dosing of study drug from 6.4 and 8.2.1.2 to 6.1.1.	To include relevant information in the correct section.
6.3.4	Added clarification to allow investigator unblinding in response to urgent therapeutic intervention without notifying the medical monitor before the unblinding event, as long as the unblinding event is reported to the medical monitor within 1 business day.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
6.8.2.3	Wording reorganized but content was maintained.	To clarify how to manage subjects on non-opioid analgesic that is used for hidradenitis suppurativa (HS) pain (but not listed as one of the allowed HS pain medications) on a stable dose prior to enrollment.
6.8.3	Added exception that prescription topical corticosteroids can be used to treat localized erythema, edema, or pruritis at the injection site without medical monitor approval.	To mitigate the symptoms of injection site reactions
7.1	Consolidated reasons for discontinuation of study drug.	To reduce redundancy and better align with electronic data capture and clinical data interchange standards consortium allowable terms.

Section #	Description of Change	Brief Rationale
7.3	Removed redundancy that if the subject continues to be unreachable, they will be considered withdrawn from the study and added that where permitted by local regulations and approved by Institutional Review Board/Independent Ethics Committee, third-party vendors may be employed by the site (funded by the sponsor) to assist the site in re-establishing contact.	To reduce redundancy and improve discontinuation rates in the study.
8.28	Defined TB terms and clarified how to handle various IGRA TB test results.	Clarity.
8.3.6	Clarified that major adverse cardiovascular and cerebrovascular events includes cerebrovascular accident and transient ischemic attack, non-fatal myocardial infarction or unstable angina, and cardiovascular death. Clarified that for infections, only those that are serious, opportunistic, or fungal are included as adverse events of interest.	Improved the clarity of the definitions for events that qualify as adverse events of special interest.
8.6	Language updated to align with the informed consent form (ICF) regarding storing samples for future use and removed reference to a future use consent form.	There is only a single ICF for this study, not a separate ICF for future use.
9.2	Added clarification to the analyses for the full analysis set and safety analysis set for timepoints after Week 16.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
9.3.1	Added a statement that all hypothesis tests will use a type I error rate of 5%.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
9.3.1	Clarified how safety and efficacy data after Week 16 will be summarized.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
9.3.2, 9.3.3	Updated statistical analyses to use a multiple imputation method for the primary analysis of the primary and secondary endpoints in place of the non-response imputation analysis method for handling of dropouts and missing data.	Following the primary analysis of Study 21102, ACELRYIN believes that the single imputation procedure of non-response imputation is potentially misleading and is not an appropriate approach for the primary analysis of Study 22107 and that multiple imputation methods better represent missing data and can be appropriately used for the primary analysis of Study 22107.
9.3.3	Clarified that the imputation model for analyzing the secondary endpoint of experiencing flare will use baseline lesion counts, demographics (age, sex, race, stratification factors), and counts at prior post-randomization visits.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.

Section #	Description of Change	Brief Rationale
9.4	Added details for a potential futility assessment.	To allow for a futility assessment and limit exposure to new subjects in the event that the efficacy results of izokibep are not positive.
10.1.1	Clarified that the study will be conducted in accordance with 21 Code of Federal Regulations and European Regulation 536/2014 for clinical studies.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
10.1.3	Clarified that the ICF will meet the requirements of European Regulation 536/20141.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
10.1.4	Added data protection information.	Change incorporated from CSP Europe v.1.2 made in response to request from EMA.
10.3.5	Added new section to provide a list of adverse events and laboratory abnormalities that could lead to discontinuation of study drug, including the addition of serious adverse event and common terminology criteria for adverse events version 5.0 grade 3 adverse event.	Clarity and readability. New reasons for discontinuation of study drug incorporated from CSP Europe v.1.2 made in response to request from EMA.
11	Added references: Ali et al, 2020; Deckers and Prens, 2016; and Gulliver et al, 2016.	New data were added to the clinical overview and benefit/risk sections, requiring additional references.
Global	Minor editorial and document formatting revisions.	Administrative change.
Global	Version and date were revised on the title page and in the header throughout the document.	Administrative change.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Randomized, Double-blind, Placebo-controlled, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Izokibep in Subjects with Moderate to Severe Hidradenitis Suppurativa

Brief Title:

Hidradenitis Suppurativa Phase 3 Study of Izokibep

Rationale:
Izokibep is a small protein molecule that acts as a selective, potent inhibitor of interleukin-17A, to which it binds with high affinity. Izokibep has been investigated in non-clinical and clinical studies in healthy subjects and subjects with hidradenitis suppurativa (HS). The clinical development plan also includes axial spondyloarthritis, uveitis, psoriasis, and psoriatic arthritis. This study investigates izokibep in subjects with active HS, including tumor necrosis factor-alpha inhibitor (TNFi) naïve subjects, and those who had an inadequate response or intolerance to TNFi, or for whom TNFi is contraindicated. The study is intended to be 1 of 2 adequate and well-controlled studies to support a claim of efficacy of izokibep in subjects with HS.

Objectives and Endpoints:

Objectives	**Endpoints**
Primary	
To demonstrate the efficacy of izokibep compared with placebo, as measured by percentage of subjects achieving HiSCR75[1] at Week 12	• HiSCR75[a] at Week 12
Secondary (Efficacy)	
To demonstrate that izokibep is efficacious compared with placebo as measured by: • Percentage of subjects achieving HiSCR90 at Week 12 • Percentage of subjects achieving HiSCR100 at Week 12 • Percentage of subjects achieving HiSCR50 at Week 12	• HiSCR90[b] at Week 12 • HiSCR100[c] at Week 12 • HiSCR50[d] at Week 12

• Percentage of subjects who experience ≥ 1 disease flare through 12 weeks of treatment[e]	• HS flares through Week 12
• Dermatology Life Quality Index (DLQI)	• Change from baseline to Week 12
• Percentage of subjects with baseline Hurley Stage II who achieve AN count of 0, 1, or 2 at Week 12	• AN count of 0, 1, or 2 at Week 12
• Percentage of subjects achieving at least 3-point reduction from baseline in NRS Patient Global Assessment of Skin Pain at its worst among subjects with baseline NRS ≥ 4	• NRS in Patient Global Assessment of Skin Pain at its worst at Week 12
Secondary (Other)	
To assess the safety and tolerability of izokibep as measured by the incidence of TEAEs, events of interest, SAEs, and clinically significant laboratory values and vital signs	• TEAEs and SAEs • Laboratory values and vital signs at collected timepoints

ADA = anti-drug antibody; AN = abscess and inflammatory nodule; HiSCR = hidradenitis suppurativa clinical response; HS = hidradenitis suppurativa; IHS4 = International Hidradenitis Suppurativa Severity Score; NRS = numeric rating scale; SAE = Serious Adverse Event; SF-12v2 = Short Form-12v2; TEAE = treatment-emergent adverse event
[a] The HiSCR75 is defined as at least a 75% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[b] The HiSCR90 is defined as at least a 90% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[c] The HiSCR100 is defined as 100% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[d] The HiSCR50 is defined as at least a 50% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[e] Flare defined as ≥ 25% increase in AN count with a minimum increase of 2 AN relative to baseline.

Overall Design:

This is a Phase 3, pivotal, confirmatory, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of izokibep in subjects with moderate to severe HS. Subjects must have HS lesions present in ≥ 2 distinct anatomic areas, one of which must be Hurley Stage II or Hurley Stage III, and a total abscess and inflammatory nodule (AN) count of ≥ 5. Subjects with draining fistula count of > 20 at screening will be excluded.

This study will be conducted at sites globally in North America, Europe, and Asia Pacific. Additional sites and regions may be added during the study.

Brief Summary

The number of subjects planned to be enrolled is 250 (125 subjects per treatment group).

Subjects will be screened within 28 days of study drug administration. Subjects meeting eligibility criteria will be randomized 1:1 to 1 of 2 treatment groups on Day 1, and will receive the following via subcutaneous injection:

- Group 1 (n = 125): placebo every week (QW) from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Week 16 to Week 51.
- Group 2 (n = 125): izokibep 160 mg QW from Day 1/Week 0 to Week 51.

Randomization will be stratified by prior TNFi use for HS (Yes/No) and Hurley Stage (II or III). The AN count is the sum of abscesses and inflammatory nodules. Subjects enrolled with stable concomitant antibiotic use (dosing regimen has been stable for ≥ 4 weeks prior to first dose of study drug) will be capped at approximately 30%.

Subjects will complete study assessments according to the study visits outlined in the schedule of activities (Section 1.3). The primary endpoint will be assessed at Week 12. The last dose of study drug will be administered on Week 51.

An end of treatment visit will be conducted at Week 52 (± 5 days). A safety follow-up visit will be conducted at Week 59 (± 5 days). For subjects who early terminate, the end of treatment visit should be completed 1 week after last dose of study drug, and the safety follow-up visit should be completed 8 weeks after last dose of study drug (± 5 days), where possible.

The final analysis of primary and secondary endpoints will be conducted after the last subject has had the opportunity to complete Week 12 assessments or early terminates from the study.

Number of Subjects:

The number of subjects planned to be enrolled is 250 (125 subjects per treatment group).

Intervention Groups and Duration:

- Group 1 (n = 125): placebo QW from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Week 16 to Week 51
- Group 2 (n = 125): izokibep 160 mg QW from Day 1/Week 0 to Week 51

Izokibep and matching placebo (collectively referred to as study drug) will be visually indistinguishable to prevent unblinding during preparation or administration of study material.

Study drug doses are fixed and will not be adjusted for individual subjects during the study.

Eligibility Criteria:

Refer to Section 5 in Protocol.

Data Monitoring/Other Committee:

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 and to make recommendations on further development activities for izokibep.

The DMC will consist of at least 1 medical expert with expertise in the relevant therapeutic area and at least 1 statistician and will have a minimum of 3 members, 1 of whom will serve as the Chair. The DMC responsibilities, members (including their qualifications and possible conflicts of interest), authorities, meeting frequency to review unblinded interim data, and procedures will be documented in the DMC charter. The committee will meet as needed to review significant safety findings. After each review, the DMC will make recommendations regarding the continuation of the study based on safety. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The study team operationalizing the day-to-day of the study, the subjects, and the investigators will remain blinded to these interim results until after the study is completed.

Statistical Considerations

Summaries of continuous variables will include mean, median, standard deviation, minimum, and maximum; change from baseline will additionally include standard error. Summaries of dichotomous, categorical, and ordinal variables will include counts and percentages.

Baseline characteristics and demographics will be summarized by randomized treatment group using the last value obtained before randomization. Efficacy and safety data will be summarized by randomized treatment group during the first 16 weeks of treatment; these data will also be summarized by randomized treatment group over 52 weeks, and additionally over the last 36 weeks for only the subjects who received placebo in the first 16 weeks and received at least 1 dose of izokibep. Efficacy variables (primary, secondary, and exploratory) will be summarized at each planned collection timepoint. Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs; percent of subjects reporting each TEAE and each SAE) will be summarized. Anti-drug antibodies (ADAs) will be summarized at each planned collection timepoint.

Comparisons of efficacy will test izokibep versus placebo in a single analysis. Response rates will be compared with a stratified test for differences: the strata used for randomization (prior TNFi use for HS [Yes/No] and Hurley Stage [II or III]), using Cochran-Mantel-Haenszel weights. The p-values for comparing izokibep versus placebo will be reported, with a 2-sided 95% confidence interval on the difference in response rates. Continuous endpoints will be analyzed with a longitudinal model using values at each post-randomization timepoint.

The primary efficacy comparison will be of hidradenitis suppurativa clinical response (HiSCR75), which is a 75% reduction in AN count with no increase in the number of abscesses or the number of draining fistulae. The AN count is the sum of the number of abscesses and the number of inflammatory nodules. Testing will be reported at $\alpha = 0.05$, 2-sided.

Secondary endpoints will be tested analogously. The sequence will consider the secondary endpoints in a pre-specified order, comparing izokibep to placebo. If all prior tests showed statistically significant differences compared with placebo, testing will proceed using $\alpha = 0.05$. If

any comparison (primary or secondary) results in $p > 0.05$, p-values for subsequent comparisons will be reported but not considered conclusive.

Exploratory endpoints will be compared analogously, with the exception of a pre-specified alpha-controlling testing strategy. The p-values for exploratory endpoints will be considered descriptive and not considered conclusive. The primary efficacy analyses will use the treatment policy estimands except as noted, using all available data from all randomized subjects regardless of treatment compliance. Subjects will be analyzed in the group to which they are randomized. Subjects who do not have an evaluation for a dichotomous endpoint at a given timepoint will be imputed as non-responders or imputed with multiple imputation. Subjects who do not have a continuous measure at a given timepoint will have available data at other timepoints included in the longitudinal model, resulting in an analysis that is robust to data that are missing at random or missing completely at random. Sensitivity and supplementary analyses will be used to assess the impact of missing data assumptions.

Incidence of TEAEs over the first 12 weeks will be summarized by treatment group. No p-values will be reported. Incidence will also be summarized over all 52 weeks for subjects who received izokibep in the first 16 weeks and summarized over the last 40 weeks for subjects who received placebo for the first 16 weeks (and received at least 1 dose of izokibep after 16 weeks of placebo). Serious adverse events will be summarized analogously. Subjects will be summarized for safety according to the treatment they actually received.

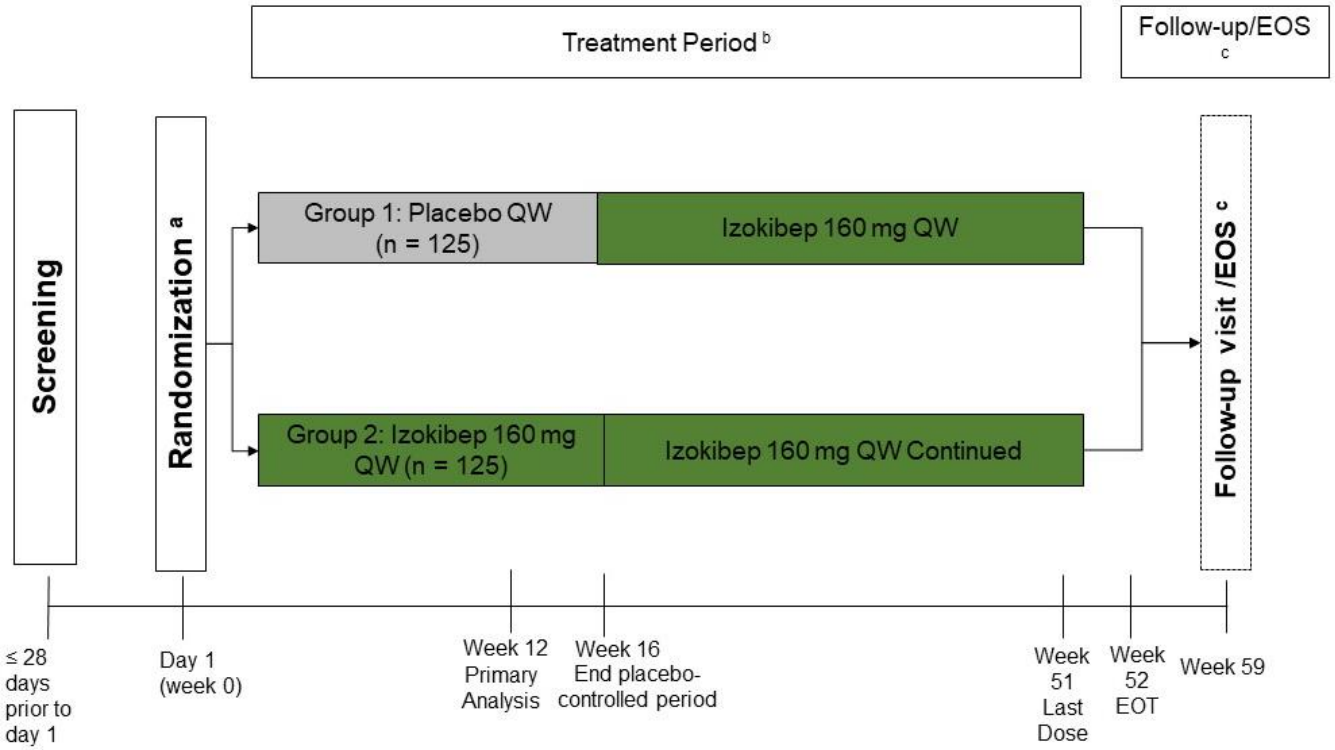
Available pharmacokinetic data will be summarized by dose group of izokibep.

Incidence of ADAs at any time will be summarized by treatment group and overall.

At Week 12, HiSCR75 response rates are expected to be 15% for placebo and 35% for izokibep. With 125 subjects receiving placebo and 125 subjects receiving izokibep, this study will have 95% power for the true difference in HiSCR75 response rates of 20 percentage points.

1.2. Schema

Figure 1. Study Design



EOS = end of study; EOT = end of treatment; QW = every week

[a] Randomization will be stratified by any prior TNFi use for hidradenitis suppurativa (Yes/No) and Hurley Stage (II or III).

[b] Subjects in Group 1 (placebo QW) will receive placebo QW until Week 15, then izokibep QW beginning at Week 16 until Week 51. Subjects in Group 2 (izokibep QW) will receive izokibep QW.

[c] An 'end of treatment visit' will be conducted at Week 52 (± 5 days). A 'safety follow-up visit' will be conducted at Week 59 (± 5 days). For subjects who early terminate, the end of treatment visit should be completed 1 week after the last dose of study drug and safety follow-up visit completed 8 weeks after the last dose of study drug (± 5 days), where possible.

1.3. Schedule of Activities

Table 1-1. Schedule of Activities

Procedures	Screening	Treatment Period [a]													EOT [b]	EOS Follow-up [b]
	≤ 28 D Prior to D1	W 0 (D 1)	W 1	W 2	W 3	W 4	W 8	W 12	W 16	W 17	W 20	W 24	W 32	W 40	W 52 or ET	W 59
Window			± 3 days												± 5 days	
Informed consent	X															
Eligibility criteria	X	X														
Hurley staging	X	X						X	X						X	
Demography	X															
Physical exam	X														X	
Weight	X	X														
Height	X															
Medical and medication history (including alcohol and nicotine use)	X	X														
Vital signs [c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Triplicate 12-lead ECG	X							X	X						X	X
Chest x-ray[d]	X															
C-SSRS[e]	X	X				X	X	X	X		X	X	X	X	X	X
AE reporting[f]		←═══														→
SAE reporting[f]	←═══															→
Prior and concomitant medication[g]	←═══															→
Efficacy Assessments																
Lesion count[h]	X	X		X		X	X	X	X			X	X		X	
NRS Patient Global Assessment of Skin Pain[i]	←═══								→|	X	X	X	X		X	
HS-PGA		X				X	X	X	X			X	X		X	
Photography (optional substudy)[j]		X				X	X	X	X			X			X	
HS-PGIC		X				X	X	X	X			X			X	
HiSQOL		X				X	X	X	X						X	
HADS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedures	Screening	Treatment Period [a]													EOT [b]	EOS Follow-up [b]
	≤ 28 D Prior to D1	W 0 (D 1)	W 1	W 2	W 3	W 4	W 8	W 12	W 16	W 17	W 20	W 24	W 32	W 40	W 52 or ET	W 59
Window			± 3 days												± 5 days	
DLQI		X				X	X	X	X			X			X	
EQ-5D		X				X	X	X	X						X	
SF-12v2		X					X	X	X			X			X	
Laboratory Assessments																
HBV, HCV testing	X															
TB test[k]	X															
HIV testing	X															
Hematology/Chemistry	X	X				X	X	X	X			X		X	X	X
Urinalysis	X	X				X		X	X			X				X
C-reactive protein	X	X		X		X	X	X	X			X	X	X	X	
Fasting lipid (total cholesterol, triglycerides & HDL)	X	X						X	X							X
Hemoglobin A1C		X						X	X						X	
Pregnancy test (WOCBP only)[l]	X	X				X	X	X	X	X	X	X	X	X	X	X
PK sampling		X		X		X		X	X			X	X		X	X
Fecal calprotectin[m]	X															
ADA sampling		X		X		X		X	X			X	X		X	X
Exploratory biomarker sampling (US only)		X				X		X	X				X		X	
Treatment Assignment and Study Drug Administration																
Treatment assignment/ randomization		X														
Study drug dispensation and dosing[a, n, o]		X[p]	X[p]	X	X	X	X	X	X[p]	X[p]	X	X	X	X		
Dosing diary[q]						←═══════════════════════→										

Footnotes are defined on the next page.

ADA = anti-drug antibody; AE = adverse event; AN = abscess and inflammatory nodule; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; d = day; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; EQ-5D = European Quality of Life 5-dimension; ET = early termination; HADS = Hospital Anxiety and Depression Scale; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HiSQOL = Hidradenitis Suppurativa Quality of Life; HIV = human immunodeficiency virus; HS-PGA = Hidradenitis Suppurativa-Physician's Global Assessment; HS-PGIC = Hidradenitis Suppurativa Patient Global Impression of Change; IGRA = interferon-gamma release assay; NRS = Numeric Rating Scale; PK = pharmacokinetic; SAE = serious adverse event; SF-12 = 12-Item Short Form Survey; TB = tuberculosis; US = United States; WOCBP = women of childbearing potential.

[a] Visit/dosing windows of ± 3 days on either side of the scheduled visits/dosing are permitted; however, the investigator should try to keep the subjects on the original visit/dosing schedule. In case of a delayed or missed dose, the investigator should return subjects on the original visit/dosing schedule in relation to Day 1 for subsequent doses. The window of ± 3 days is relative to Day 1 and applicable for all subsequent visits/dosing. The time between doses should be no less than 4 days and no more than 13 days.

[b] The EOT visit will be completed at Week 52 (± 5 days) and safety follow-up visit completed at Week 59 (± 5 days). For subjects who early terminate, these visits should be completed 1 week (± 5 days) and 8 weeks (± 5 days) after the last dose of study drug.

[c] Vital signs include measurements of temperature, respiratory rate, systolic and diastolic blood pressure, and pulse.

[d] Chest x-ray (posterior/anterior or anterior/posterior) will be performed at screening only for subjects who do not have a chest x-ray available within 3 months prior to screening. Women of childbearing potential must have a negative pregnancy test before x-ray is performed.

[e] The 'Baseline/Screening' version of the C-SSRS will be conducted during the screening visit and the 'Since Last Visit' version of the C-SSRS will be completed at all other timepoints.

[f] Serious AEs will be recorded from the signing of informed consent through the 8-week follow-up visit (ie, 8 weeks after the last dose of study drug); AEs will be recorded from Day 1 (ie, administration of study drug) until 4 weeks after the last dose of study drug.

[g] Confirm ongoing antiseptic wash requirement at every visit. From screening through Week 16, subjects will complete a daily diary of their analgesic use. For Week 17 through Week 52 subjects will be required to tell site staff if they took any analgesics within 24 hours of their site visit. Subjects will refrain from taking analgesics 12 hours before the site visit, if possible.

[h] Lesion count must address all relevant anatomical regions in each subject. The AN count is the sum of abscesses and inflammatory nodules. Any unscheduled visit for disease worsening based on the investigator judgment will include AN count and will be recorded in the appropriate CRF.

[i] From screening through Week 16, subjects will complete a daily diary of their skin pain at home. For Week 17 through Week 32 and Week 52 visits, subjects will complete a single skin pain assessment at the site. Note: Subject may not be randomized if pain diaries are not completed for ≥ 3 out of 7 days (at a minimum) prior to the Day 1 visit.

[j] For subjects who consent to the optional photography substudy at selected sites, photographs will be taken.

[k] IGRA TB test (QuantiFERON recommended) will be performed. Note: See Table 8-2 for guidance for handling various TB test results.

[l] Serum pregnancy test required for screening and urine pregnancy test required at all other visits for WOCBP. Local authorities may require more frequent pregnancy testing.

[m] Fecal calprotectin at screening only required if subject has a) prolonged or recurrent diarrhea b) prolonged or recurrent abdominal pain or c) blood in stool.

[n] Administration of study drug should be done last after all study procedures unless indicated otherwise.

[o] After Week 4, qualified subjects may perform home dosing of study drug at weeks without study visits (starting from Week 5) and do not need to return to the clinical site on those weeks. For example, prior to commencing study drug self-administration at home at Week 5, at the Day 1/Week 0, Week 1, and Week 2 site visits, site staff will administer study drug to the subject, and will train the subject on study drug handling, dose preparation, and self-administration of the study drug. At the Week 3 and 4 site visits, the subject will demonstrate their ability to self-administer study drug prior to the site allowing them to start home dosing at Week 5. Otherwise, the subject will need to return to the site for all injections. The last dose of study drug is Week 51.

[p] Subjects will be monitored at the site for at least 1 hour after study drug administration.

[q] A dosing diary will be completed for every home dosing administration.

2. Introduction

Izokibep is a potent and selective inhibitor of interleukin (IL)-17A that is being developed for the treatment of hidradenitis suppurativa (HS).

2.1. Study Rationale

Izokibep is a small protein molecule that acts as a selective, potent inhibitor of IL-17A, to which it binds with high affinity. Izokibep has been investigated in non-clinical and clinical studies in healthy subjects, and subjects with HS. The clinical development plan also includes axial spondyloarthritis, uveitis, psoriasis, and psoriatic arthritis (PsA). This study investigates izokibep in subjects with active HS, including tumor necrosis factor-alpha inhibitor (TNFi) naïve subjects, and those who had an inadequate response or intolerance to TNFi, or for whom TNFi is contraindicated. The study is intended to be 1 of 2 adequate and well-controlled studies to support a claim of efficacy of izokibep in subjects with HS.

2.2. Background

2.2.1. Disease Background

Hidradenitis suppurativa is a chronic inflammatory skin disease characterized by occlusion of hair follicles as a primary pathogenic factor associated with a chronic cycle of inflammation, healing, and scarring (Sabat et al, 2020). A recent meta-regression analysis found an overall HS prevalence of 0.40% (95% confidence interval [CI]: 0.26% to 0.63%) among the populations studied around the world (Jfri et al, 2021). In a population-based analysis, the overall point prevalence of HS in the United States (US) was 0.10%, or 98 per 100 000 persons. Prevalence was highest among women (137 per 100 000), those aged 30 to 39 years (172 per 100 000), and African American (296 per 100 000) and biracial (218 per 100 000) patient groups (Garg et al, 2017). Patients with HS develop painful inflamed nodules, abscesses, and pus-discharging tracts and fistulas, which typically occur in skin folds of axillary (armpits), inguinal (groin), gluteal, and perianal areas of the body. Hidradenitis suppurativa causes severe pain, purulent secretions that smell bad, and movement restrictions that have a profound negative influence on patients' lives (Sabat et al, 2020).

A genetic predisposition, smoking, obesity, and hormonal factors are established etiological factors for HS (Sabat et al, 2020). Cutaneous changes begin around hair follicles and involve activation of cells of the innate and adaptive immune systems, with pivotal roles for proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-17 (Sabat et al, 2020).

Clinical management of HS is challenging and consists of both medical and surgical approaches. Topical therapies, systemic antibiotics, hormonal therapies, and immunosuppressant medications have been used. However, there are patients where HS remains resistant to conventional treatment particularly those with moderate to severe disease (Alikhan et al, 2019). The TNFi, adalimumab is currently the only approved biologic immunomodulator by the US Food and Drug Administration for treating moderate to severe HS (HUMIRA® USPI 2021) Only around 50% of subjects achieved a clinical response at Week 12 in the 2 randomized, double-blind,

placebo-controlled studies of adalimumab in a total of 633 adult subjects with moderate to severe HS. During the second part of both studies (up to 36-week treatment duration), approximately 40% of subjects who initially responded to adalimumab weekly therapy continued to benefit from this drug (Kimball et al, 2016).

In summary, there continues to be a significant unmet medical need for additional therapies to treat patients with HS. Additional therapies are needed to manage pain, abscess formation, and disease progression. In addition, given the significant reduction in quality of life and functional impairment experienced by patients diagnosed with HS, there is an unmet need for medical therapies that can have a substantial impact on improving a patient's quality of life.

2.2.2. Interleukin-17

A broad range of immune mediators are highly expressed in established HS lesions compared with healthy control skin. Patients with HS have imbalances in the T-helper 17 cell (Th17) axis that are similar to those in patients with psoriasis (Wolk et al, 2020). They have high serum levels of the proinflammatory cytokine IL-17A, which leads to neutrophil recruitment and provides positive feedback to maintain the population of proinflammatory Th17 cells (Matusiak et al, 2017). These imbalances improved in patients treated with TNFi. It is hypothesized that by reducing circulating IL-17A, anti-IL-17A inhibitors like izokibep may also provide benefit for patients with HS. Clinical evidence for this benefit comes from 2 open-label studies with secukinumab 300 mg and brodalumab 270 mg, where 70% of 20 subjects and 100% of 10 subjects, respectively, responded at 24 weeks based on the hidradenitis suppurativa clinical response (HiSCR) (Casseres et al, 2020; Frew et al, 2020). In addition, bimekizumab 320 mg dosed every 2 weeks appeared to deliver greater efficacy than adalimumab dosed based on the prescribing information, at 12 weeks based on the HiSCR75 and HiSCR90 responses (Glatt et al, 2021). Phase 3 studies in subjects with HS for secukinumab and bimekizumab are underway.

2.2.3. Izokibep Background

Izokibep is a biologic that binds IL-17A with high affinity and with a potency corresponding to clinically tested monoclonal antibodies in terms of blocking the biological activity of IL-17A. Izokibep has the potential to be an efficacious treatment for a variety of IL-17A-related diseases. The smaller size of izokibep compared with monoclonal antibodies offers advantages in terms of required dosing volumes and potential for alternative pharmacological formulations.

Izokibep is based on a small protein binding to and blocking the biological effect of the cytokine IL-17A. The izokibep protein molecule also contains an albumin-binding domain, which confers specific binding to a single site on endogenous serum albumin and thereby a prolonged half-life ($t_{½}$) in the circulation and in tissues after parenteral administration.

IL-17 inhibitors have already demonstrated efficacy and a favorable safety profile in different inflammatory diseases, including psoriasis and PsA. These include secukinumab (Cosentyx®) and ixekizumab (Taltz®) in the US, Canada, and the European Union.

Doses up to 160 mg every other week (Q2W) have been tested and were well tolerated. A detailed description of the chemistry, pharmacology, efficacy, and safety of izokibep is provided in the Investigator's Brochure.

2.2.3.1. Non-clinical Studies

Assessments of target binding specificity have demonstrated high specificity and affinity of izokibep to IL-17A and to albumin. The *in vitro* and *in vivo* pharmacodynamics evaluations show that izokibep has a 3- to 5-fold higher potency than the anti-IL-17A monoclonal antibody secukinumab on a molar basis and appears to be approximately equipotent to ixekizumab.

Pharmacokinetic (PK) data for intravenous (IV)- and subcutaneous (SC)-administered izokibep have been obtained in rat and monkey. Pharmacokinetic assessments in rat and monkey indicate that the time course of izokibep concentrations after a bolus IV injection and SC injection is well described by a 2- or 3-compartment model. Pharmacokinetic assessments indicate that the elimination rate of izokibep is similar to that of albumin in the respective species.

Repeated (10-day to 3-month) SC or IV administration of izokibep to cynomolgus monkeys was well tolerated with no observed adverse effect levels (NOAELs) of 40 mg/kg/dose (IV, 28-day study) and 20 mg/dose (SC, 28-day) and 20 mg/kg/week (SC, 3-month study), being the highest dose levels tested in the respective studies.

In the 26-week repeated-dose toxicity study in cynomolgus monkeys, weekly SC injection of 10, 20, or 40 mg/kg/week izokibep to monkeys for 26 weeks was generally well tolerated. However, due to the presence of local abscesses and systemic sequelae in 1 female administered 40 mg/kg/week, which was considered adverse, the NOAEL for SC administration is considered to be 20 mg/kg/week.

In the enhanced pre- and post-natal developmental toxicity study in cynomolgus monkeys, SC izokibep administration of up to 40 mg/kg/week to pregnant monkeys for approximately 21 weeks was well tolerated. The NOAEL was 40 mg/kg/week.

The results from the immunotoxicity screening assays do not suggest that izokibep has an intrinsic capacity for immune system activation.

Metabolism and genotoxicity have not been investigated, since izokibep is a protein molecule and contains only naturally occurring amino acids.

For additional information, please refer to the Investigator's Brochure.

2.2.3.2. Clinical Overview

A first-in-human multipart clinical study (Study ABY-035-001, EudraCT number 2015-004531-13, NCT02690142) has been conducted with the parenteral formulation of izokibep. Izokibep was administered IV and SC to healthy subjects and subjects with plaque psoriasis, in doses ranging from 2 mg to 40 mg in a single- or multiple-dose regimen.

A Phase 2 dose-finding study in subjects with moderate to severe plaque psoriasis was recently completed with up to 3 years of exposure (Study ABY-035-002, EudraCT number 2017-001615-36, NCT03591887). One hundred eight subjects were randomized into 5 dose groups: 2 mg, 20 mg, 80 mg, and 160 mg izokibep or placebo. The treatment period consisted of an induction period (12 weeks), an optimization period (12 weeks), and an individualization

period including 4 weeks follow-up (28 weeks), and 2 further years of extension. The induction period was double blind and placebo controlled.

The primary endpoint of the study was the proportion of subjects who achieved a Psoriasis Area and Severity Index (PASI) response of 90% (PASI90) after 12 weeks of treatment. The PASI90 at 12 weeks was 71.4% and 59.1% in subjects treated with 80 mg and 160 mg Q2W of izokibep, respectively. In the lower dose groups, 2 mg and 20 mg izokibep, only 5.0% and 19.0% of subjects, respectively, reached the primary endpoint. None of the subjects receiving placebo reached PASI90 response at Week 12. At Week 24, PASI90 responses were comparable between the initial 80 mg and 160 mg treatment groups. The safety and efficacy data obtained from the 52-week core period of the study with izokibep suggest a favorable benefit-risk profile in plaque psoriasis.

A Phase 2 clinical study in subjects with active PsA has recently been completed (Study ABY-035-202). Study ABY-035-202 is a dose-finding study of 40 mg or 80 mg izokibep or placebo SC Q2W. The primary endpoint was the ACR 50% (ACR50) response at Week 16; further key secondary endpoints comprise other ACR responses, PASI scores, enthesitis endpoints, proportion of subjects achieving minimal disease activity, adverse events (AEs; safety), and izokibep blood levels (PK), and anti-drug antibody (ADA) assessments.

The primary endpoint of ACR50 at 16 weeks was met with 52% response rate in subjects receiving 80 mg Q2W of izokibep versus 13% for placebo (p-value = 0.0006). Subjects receiving 40 mg Q2W had an ACR50 response rate of 48%. The PASI response of 75%, in subjects with a minimum psoriasis body surface area ≥ 3% at baseline, at 16 weeks was 85% and 83% in subjects treated with 80 mg and 40 mg Q2W, respectively versus 14% for those receiving placebo. In subjects with enthesitis at baseline utilizing the Leeds Enthesitis Index, resolution of enthesitis was achieved by 88% of subjects receiving 80 mg Q2W, 63% of subjects receiving 40 mg Q2W of izokibep, and 10% receiving placebo.

Recent data from the primary analysis of the ongoing Phase 2b Study 21102 in subjects with moderate to severe HS showed early HiSCR100 responses in nearly 30% of subjects, consistency in directionality of the data for both izokibep doses (160 mg QW and 160 mg Q2W) compared with placebo, a consistent dose effect as seen with HiSCR responses favoring a 160 mg every week (QW) dose and aligned with dose-response analyses, and no evidence of safety or tolerability limitations. However, the primary endpoint of HiSCR75 at week 16 did not meet statistical significance. Assessment of the data determined that the lack of significance was primarily due to 2 factors: 1) unanticipated, historically high placebo (41% HiSCR50) response rates compared with 10% to 30% placebo response rates in previous HS studies (Ali et al, 2020), and 2) high drop-out rates among 160 mg QW HiSCR responders that were largely not related to safety but imputed as non-responders in the primary analysis.

2.2.3.3. Safety Overview

In the first-in-human study in healthy subjects and subjects with psoriasis (Study ABY-035-001), doses of up to 40 mg IV and SC of izokibep (n = 62) were well tolerated, with no deaths or treatment-related serious AEs (SAEs). Intravenous administration (single doses up to 40 mg in 46 subjects in total) resulted in the following treatment-emergent AEs (TEAEs) by preferred term: oropharyngeal pain (10.9%), nasopharyngitis (6.5%), diarrhea (4.3%), and headache

(4.3%). A further 9 TEAEs were reported, which affected 1 subject each (2.2% each). Subcutaneous administration (single and multiple doses up to 40 mg in 21 subjects in total) resulted in the following TEAEs by preferred term: injection site reaction (61.9%) and injection site pain (28.6%). A further 11 TEAEs were reported, which affected 1 subject each (5.2% each). The majority of the injection site reactions (ISR)s were of mild intensity and required no treatment or limited therapy.

In the Phase 2, 52-week core period in subjects with plaque psoriasis (ABY-035-002), multiple doses of up to 160 mg Q2W SC of izokibep (n = 108) were well tolerated with no deaths or treatment-related SAEs. A total of 65 subjects (60.2%) experienced at least 1 izokibep-related TEAE. The most common izokibep-related TEAEs (n/%) were ISR (42/38.9%), nasopharyngitis (13/12.0%), diarrhea (7/6.5%) and fatigue (6/5.6%) consistent with the first-in-human study.

In the Phase 2, randomized, double-blind, placebo-controlled clinical study in subjects with active PsA (ABY-035-202), doses of 40 mg and 80 mg Q2W were well tolerated. Safety evaluation showed no serious or severe AEs up to Week 16. Treatment-emergent AE rate overall was 52.3% for placebo, 65.9% for 40 mg Q2W and 55.3% for 80 mg Q2W. The most common AEs (≥ 5% in either arm with active treatment) were ISR or erythema, headache, hyperkalemia, and upper respiratory tract infection. Three subjects had AEs of special interest: 2 subjects experienced ISR and 1 subject experienced vulvovaginal candidiasis.

In the primary analysis from part A (Week 12) of the ongoing Phase 2b Study 21102 in subjects with moderate to severe HS, a total of 24 (80%) subjects experienced at least 1 TEAE during the study. Mild-to-moderate ISRs, injection site pruritus, and injection site erythema were the most common AEs. Three serious adverse events (SAEs) were reported in 2 subjects: Crohn's disease (1 subject) and colonic abscess/sepsis in another subject with known diverticulosis. No candida infections were reported during the first 12 weeks of part A.

In the primary analysis from part B (Week 16) of Study 21102, a total 135 of (77.1%) subjects experienced at least 1 TEAE during the study. The most common (> 5%) AEs were injection site erythema and injection site pruritus. A total of 7 SAEs occurred in 5 subjects. An event of Epstein-Barr (mononucleosis) virus infection was the only SAE considered possibly related to study drug by the investigator; this event was considered resolved and the subject resumed therapy and remained in the study. The other SAEs included arthritis, cutaneous vasculitis, elevated liver enzymes, scrotal abscess, staphylococcal wound infection, and sepsis, which affected 1 subject each. None of these events were considered related to study drug by the investigators. No deaths occurred during the study. Five events of candida, all mild, were reported. There were no reports of inflammatory bowel disease (IBD).

For more details on the safety and tolerability of izokibep, refer to the Investigator's Brochure.

2.2.3.4. Pharmacokinetics

Following SC administration of single izokibep doses in the first-in-human study (Study ABY-035-001), median time to maximum observed concentration (t_{max}) was 60 hours post-dose. After reaching maximum observed plasma concentration (C_{max}), plasma levels of izokibep declined in an apparent mono- or bi-phasic manner with the geometric mean $t_{½}$ being 278 hours, which was similar to that after IV administration (288 hours). Individual $t_{½}$ estimates

ranged from 199 to 464 hours and 220 to 340 hours for SC and IV treatments, respectively. In general, as assessed by the geometric percent coefficient of variation (CV%) low between-subject variability was noted for area under the concentration-time curve (AUC) extrapolated to infinity ($AUC_{0-\infty}$) and C_{max} for both dose routes, with values ranging from 20% to 22% and 14% to 15%, respectively.

Following 40 mg repeated SC doses, C_{max} occurred at a median t_{max} of 48.0 hours post-dose on Days 1 and 29 (individual range: 24.0 to 71.0 hours post-dose). On Day 85, median t_{max} was slightly later at 71.6 hours post-dose (individual range: 66.6 to 73.1 hours post-dose). After reaching C_{max} on Day 85, plasma concentrations of izokibep declined in an apparent mono- or bi-phasic manner with a geometric mean $t_{½}$ of 279 hours with individual subjects ranging from 229 to 423 hours. Pre-dose trough izokibep plasma concentrations showed that steady state was achieved by Day 71, following 5 doses of izokibep administered Q2W. There was evidence of accumulation following repeated dosing by Day 85 with geometric mean accumulation ratio, based on AUC over a dosing interval ($AUC_{0-\tau}$), of 1.95, and individual subjects ranging from 1.35 to 5.09. Between-subject variability, based on geometric CV%, was moderate on the monitored study days for $AUC_{0-\tau}$ with values ranging from 29.4% to 36.0%, and low-to-moderate for C_{max} with values ranging from 20.4% to 28.8%.

For more details on the PK of izokibep, refer to the Investigator's Brochure.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of izokibep may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Izokibep is a biologic that binds IL-17A with high affinity and with a potency corresponding to clinically tested monoclonal antibodies in terms of blocking the biological activity of IL-17A.

- IL-17A inhibitors, including secukinumab at 10 mg/kg and 30 mg/kg and ixekizumab as well as izokibep at doses up to 160 mg SC, do not appear to have dose-limiting AEs.
- Class effects and potential risks seen with other IL-17 inhibitors have not been identified with izokibep. Given small numbers of subjects treated to date, class effects and potential risks of IL-17 inhibitors will be explicitly monitored (ie, events of special interest) and have been taken into consideration in the development of inclusion and exclusion criteria. These events include candida infections, IBD, and suicidal ideation and behavior risk monitoring.
- Non-serious, mild-to-moderate ISRs are the most common AE reported in association with SC administration of izokibep. These are typically self-resolving, however additional measures to mitigate/manage ISRs include the following:
    - Allow study drug to warm to room temp prior to administration, about 15 to 20 minutes.
    - Administer study drug slowly.
    - Use ice/ice packs following study drug administration.
    - Rotate sites of administration; avoid injecting the same site twice during any visit.

  - Use of oral antihistamines.
  - Use of acetaminophen or ibuprofen for pain or discomfort.
  - Topical corticosteroids may be used for localized erythema, edema, or pruritis.
- No genotoxicity or carcinogenicity is foreseen as izokibep is a protein consisting of natural amino acids. However, since no data are available at this stage of clinical development on possible effects on the reproductive system, the following precautionary measure will be taken:
  - Females of childbearing potential as well as reproductive female partners of male subjects must use an adequate method of contraception while participating in the clinical study until at least 8 weeks after the last dose of study drug. Pregnancy testing will be performed at regular intervals prior to, during treatment, and after the end of treatment (ie, 8 weeks after the last investigational medicinal product [IMP] dosing).

2.3.2. Benefit Assessment

The potential benefit of izokibep is that it is designed to demonstrate whether treatment is associated with a reduction in the extent of inflammation in patients with moderate to severe HS, manifested as a specific reduction in the number of inflammatory nodules and abscesses. As these inflammatory lesions are associated with considerable pain and impairment in quality of life, a reduction in the number of such lesions could directly benefit patients.

Safety, efficacy, and PK data obtained in clinical studies with izokibep in healthy volunteers and in subjects with psoriasis, PsA, and HS suggest a favorable benefit-risk profile. Based on published data showing efficacy and safety for other IL-17 inhibitors, including in patients with HS, the benefit-risk relationship appears favorable and justifies clinical development of izokibep in HS as well. Due to its small molecular size as compared with monoclonal antibodies and its binding to albumin, izokibep may have the potential to better reach inflamed tissues and may provide higher exposure relative to monoclonal antibodies.

A 16-week, placebo-controlled period does not entail any additional risk of irreversible harm to subjects. Although there is no active comparator in Study 22107, the use of tetracyclines is in line with evidence-based treatment of HS (Gulliver et al, 2016; Deckers and Prens, 2016). The study permits concomitant use of oral antibiotic therapy (eg, minocycline or doxycycline) for the treatment of HS provided the dosing regimen (dose and frequency) has been stable for ≥ 4 consecutive weeks prior to the first dose of study drug and remains stable throughout the placebo-controlled period (Week 16 assessment). Specified analgesics are permitted for HS-associated pain. The study also requires that subjects use daily or at a minimum of 3 days a week topical antiseptic on areas of their body affected with HS lesions, throughout the duration of the study. For subjects with increases in abscess and inflammatory nodule (AN) counts (≥ 150% of Day 1 AN count), investigators may provide permitted antibiotic rescue therapy. Additionally, subjects with a draining fistula count > 20 at screening or Day 1 are excluded from enrolling in the study to exclude the most severe forms of the disease that may place subjects at a higher risk of disease-related complications. The implementation of these measures will prevent any irreversible harm to subjects particularly in the 16-week placebo-controlled period, therefore allowing the ability to adequately assess efficacy and safety of izokibep when compared with placebo.

Given the value in assessing the effect of study drug on a wide variety of subgroups in the target patient population, including subjects on chronic antibiotic treatment (as one of those subgroups), the study will permit enrollment of subjects with stable concomitant antibiotic use, as described above. Enrollment of subjects with stable concomitant antibiotic use will be capped at approximately 30%, which is considered a low enough proportion to not confound efficacy analysis outcomes.

The investigator is referred to the current Investigator's Brochure where additional and more detailed information (including non-clinical toxicology, metabolism, pharmacology, and safety experience) regarding potential risks and benefits of izokibep can be found.

2.3.3. Overall Benefit-Risk Conclusion

The following considerations are important for the benefit-risk assessment:

- Only subjects with moderate to severe HS will be enrolled. Subjects must have HS lesions present in at least 2 distinct anatomic areas, one of which is Hurley Stage II or Hurley Stage III and AN count of ≥ 5. Subjects with draining fistula count of > 20 at screening or Day 1 will be excluded.
- The inclusion and exclusion criteria will ensure that subjects who might be predisposed to a higher risk of drug-related TEAEs are either excluded or identified and treated with caution. Class effects seen with other IL-17 inhibitors have been considered when designing the eligibility criteria. Subjects with active infections or with a history of autoimmune, chronic inflammatory, or connective tissue disease will be excluded from participating in the study.
- Subjects will be monitored at the site for at least 1 hour after administration of izokibep at designated visits.
- After enrollment and through the end of the study, if the subject's AN count is ≥ 150% of Day 1 AN count, antibiotic rescue medication is permitted.
- Participation in the study is voluntary. Each subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Considering the measures taken to minimize risk to subjects participating in this study, and the lack of clear dose-limiting AEs associated with izokibep, the pre-existing data on the effects of IL-17 inhibitors in hidradenitis, the potential risks identified in association with izokibep are justified by the anticipated benefits that may be afforded to subjects with HS.

2.3.4. COVID-19 Benefit/Risk Assessment

A benefit-risk assessment related to severe acute respiratory syndrome coronavirus (SARS-CoV-2) has been considered for this study and concluded that the coronavirus disease of 2019 (COVID-19) pandemic does not alter the overall benefit-risk for conducting this study. Risk mitigation measures will be implemented based on the prevailing situation during study conduct, at the investigator's discretion and in accordance with local and institutional guidelines as applicable. The risk-benefit of the study in relation to the COVID-19 pandemic will continue

to be assessed during the study and additional or revised measures may be implemented based on any updates to the benefit-risk assessment.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate the efficacy of izokibep compared with placebo, as measured by percentage of subjects achieving HiSCR75[1] at Week 12	• HiSCR75[a] at Week 12
Secondary (Efficacy)	
To demonstrate that izokibep is efficacious compared with placebo as measured by:	
• Percentage of subjects achieving HiSCR90 at Week 12	• HiSCR90[b] at Week 12
• Percentage of subjects achieving HiSCR100 at Week 12	• HiSCR100[c] at Week 12
• Percentage of subjects achieving HiSCR50 at Week 12	• HiSCR50[d] at Week 12
• Percentage of subjects who experience ≥ 1 disease flare through 12 weeks of treatment[e]	• HS flares through Week 12
• Change in Dermatology Life Quality Index (DLQI)	• Change in DLQI from baseline to Week 12
• Percentage of subjects with baseline Hurley Stage II who achieve AN count of 0, 1, or 2 at Week 12	• AN count of 0, 1, or 2 at Week 12
• Percentage of subjects achieving at least 3-point reduction from baseline in NRS Patient Global Assessment of Skin Pain at its worst among subjects with baseline NRS ≥ 4	• Change from baseline in NRS Patient Global Assessment of Skin Pain at its worst at Week 12

Secondary (Other)	
To assess the safety and tolerability of izokibep as measured by the incidence of TEAEs, events of interest, SAEs, and clinically significant laboratory values and vital signs	• TEAEs and SAEs • Laboratory values and vital signs at collected timepoints
Exploratory	
To demonstrate that izokibep is efficacious compared with placebo at timepoints through Week 16 and to estimate izokibep efficacy at timepoints after Week 16, as measured by:	
• Percentage of subjects who achieve HiSCR75 at Weeks 2, 4, 8, 16, 32, and 52	• HiSCR75 at Weeks 2, 4, 8, 16, 24, 32, and 52
• Percentage of subjects who achieve HiSCR90 at Weeks 2, 4, 8, 16, 32, and 52	• HiSCR90 at Weeks 2, 4, 8, 16, 24, 32, and 52
• Percentage of subjects who achieve HiSCR100 at Weeks 2, 4, 8, 16, 32, and 52	• HiSCR100 at Weeks 2, 4, 8, 16, 24, 32, and 52
• Percentage of subjects who achieve HiSCR50 at Weeks 2, 4, 8, 16, 32, and 52	• HiSCR50 at Weeks 2, 4, 8, 16, 24, 32, and 52
• Percentage of subjects with baseline Hurley Stage II who achieve AN count of 0, 1, or 2 at Weeks 4, 8, 16, 24, 32, and 52	• AN count of 0, 1, or 2 at Weeks 4, 8, 16, 24, 32, and 52
• Percentage of subjects achieving at least 3-point reduction from baseline in NRS Patient Global Assessment of Skin Pain at its worst among subjects with baseline NRS ≥ 4	• Change from baseline in NRS Patient Global Assessment of Skin Pain at its worst at Weeks 4, 8, 16, 24, 32, and 52
• Mean change from baseline in NRS Patient Global Assessment of Skin Pain at its worst (all subjects)	• Mean change from baseline in NRS Patient Global Assessment of Skin Pain at its worst (all subjects) at Weeks 4, 8, 12, 16, 24, 32, 52
• Mean change from baseline in NRS Patient Global Assessment of Skin Pain on average (all subjects)	• Mean change from baseline in NRS Patient Global Assessment of Skin Pain on average (all subjects) at Weeks 4, 8, 12, 16, 24, 32, 52

• Modified Sartorius Score after 4, 8, 12, 16, 24, 32, and 52 weeks of treatment • HS flare rates through 4 and 52 weeks of treatment • IHS4, after 4, 8, 12, 16, 24, 32, and 52 weeks of treatment	• Modified Sartorius Score at baseline, Weeks 4, 8, 12, 16, 24, 32, and 52 • HS flares through Weeks 4 and 52 • IHS4 scores at Weeks 4, 8, 12, 16, 24, 32, and 52
• Hidradenitis Suppurativa-Physician's Global Assessment (HS-PGA) • Mean change from baseline in draining tunnel count	• Change from baseline to Weeks 4, 8, 12 and 16, 24, 32, and 52 in HS-PGA • Change from baseline in the number of draining tunnels at Weeks 4, 8, 12, 16, 24, 32, and 52
To explore the effect of izokibep on Patient-reported Outcomes (PROs) as measured by change from baseline over time in:	
• European Quality of Life-5 Dimensions (EQ-5D)	• Change from baseline to Weeks 4, 8, 12, 16, and 52 in EQ-5D
• Hidradenitis Suppurativa Quality of Life (HiSQOL)	• Change from baseline to Weeks 4, 8, 12, 16, and 52 in HiSQOL
• Hospital Anxiety and Depression Scale (HADS)	• Change from baseline to Weeks 4, 8, 12, 16, and 52 in HADS, HADS-anxiety and HADS-depression
• Patient Global Impression of Change (PGIC)	• PGIC at Weeks 4, 8, 12, 16, 24, and 52
• DLQI	• Change from baseline to Weeks 4, 8, 16, 24, and 52 in DLQI
• Short Form-12v2™ Health Survey (SF-12v2)	• Change from baseline to Weeks 8, 12, 16, 24, and 52 in SF-12v2
To estimate the mean trough plasma level izokibep in subjects with HS	• Trough plasma concentrations of izokibep at collected timepoints

To assess the immunogenicity of izokibep as measured by the presence of ADAs	• ADAs
To assess biomarkers of anti-IL-17A treatment and biomarkers associated with HS efficacy (United States Only)	• Change in inflammatory cytokines and biomarkers associated with HS pathophysiology

ADA = anti-drug antibody; AN = abscess and inflammatory nodule; HiSCR = hidradenitis suppurativa clinical response; HS = hidradenitis suppurativa; IHS4 = International Hidradenitis Suppurativa Severity Score; NRS = numeric rating scale; SAE = serious adverse event; SF-12v2 = Short Form-12v2; TEAE = treatment-emergent adverse event
[a] The HiSCR75 is defined as at least a 75% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[b] The HiSCR90 is defined as at least a 90% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[c] The HiSCR100 is defined as 100% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[d] The HiSCR50 is defined as at least a 50% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[e] Flare defined as ≥ 25% increase in AN count with a minimum increase of 2 AN relative to baseline.

Primary Estimand

Estimands are discussed in Section 9.3.2

The components of the estimand to address the primary objective are as follows:

- Treatment: izokibep versus placebo.
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria.
- Variable of interest: achievement of HiSCR75 after 12 weeks of treatment.
- Summary measure: response rate, achievement of HiSCR75 (Yes/No).
- Intercurrent event (ICE) handling: treatment policy strategy, in general, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication/rescue medication, protocol deviations, or other actions. Subjects who receive antibiotic therapy that could affect HS will be included in the primary analysis by assigning non-response at subsequent timepoints. Multiple imputation will be used to handle other types of missing data. Additional details described in Section 9.3.2.

Secondary Estimands

Estimands are discussed in Section 9.3.3

The 5 components of the estimand to address each secondary objective are as follows.

First secondary objective:

- Treatment: izokibep versus placebo
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria
- Variable of interest: percentage of subjects achieving HiSCR90 at Week 12

- Summary measure: response rate, achievement of HiSCR90 at Week 12 (Yes/No)
- ICE handling: treatment policy strategy, in general, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication/rescue medication, protocol deviations, or other actions. Subjects who receive antibiotic therapy that could affect HS will be included in the analysis by assigning non-response at subsequent timepoints. Multiple imputation and non-response imputation will be used to handle certain other types of missing data, analogously to the primary endpoint.

Second secondary objective:

- Treatment: izokibep versus placebo
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria
- Variable of interest: percentage of subjects achieving HiSCR100 at Week 12
- Summary measure: response rate, achievement of HiSCR100 at Week 12 (Yes/No)
- ICE handling: treatment policy strategy, in general, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication/rescue medication, protocol deviations, or other actions. Subjects who receive antibiotic therapy that could affect HS will be included in the analysis by assigning non-response at subsequent timepoints. Multiple imputation and non-response imputation will be used to handle certain other types of missing data, analogously to the primary endpoint.

Third secondary objective:

- Treatment: izokibep versus placebo
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria
- Variable of interest: percentage of subjects achieving HiSCR50 at Week 12
- Summary measure: response rate, achievement of HiSCR50 at Week 12 (Yes/No)
- ICE handling: treatment policy strategy, in general, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication/rescue medication, protocol deviations, or other actions. Subjects who receive antibiotic therapy that could affect HS will be included in the analysis by assigning non-response at subsequent timepoints. Multiple imputation and non-response imputation will be used to handle certain other types of missing data, analogously to the primary endpoint.

Fourth secondary objective

- Treatment: izokibep versus placebo
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria
- Variable of interest: change in HS flares after 12 weeks of treatment
- Summary measure: response rate, improvement in HS flare occurrence (Yes/No)

- ICE handling: treatment policy strategy, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication/rescue medication, protocol deviations, or other actions. All subjects with missing abscess, inflammatory nodule, and draining tunnel counts will be included using multiple imputation, analogously to the analysis of the primary endpoint. Subjects who receive antibiotic therapy that could affect HS will be included in the analysis by assigning non-response at subsequent timepoints. Multiple imputation and non-response imputation will be used to handle certain other types of missing data, analogously to the primary endpoint.

Fifth secondary objective

- Treatment: izokibep versus placebo
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria
- Variable of interest: change in Dermatology Life Quality Index (DLQI) after 12 weeks of treatment
- Summary measure: mean change from baseline in DLQI
- ICE handling: treatment policy strategy, in general, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication/rescue medication, protocol deviations, or other actions

Sixth secondary objective:

- Treatment: izokibep versus placebo
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria and with baseline Hurley Stage II
- Variable of interest: achievement of AN count of 0, 1, or 2 at Week 12
- Summary measure: response rate, achievement of AN count of 0, 1, or 2 at Week 12 (Yes/No)
- ICE handling: treatment policy strategy, in general, with all subjects included in the analysis regardless of treatment discontinuation, concomitant medication/rescue medication, protocol deviations, or other actions. Subjects who receive antibiotic therapy that could affect HS will be included in the analysis by assigning non-response at subsequent timepoints. Multiple imputation and non-response imputation will be used to handle certain other types of missing data, analogously to the primary endpoint.

Seventh secondary objective:

- Treatment: izokibep versus placebo
- Population of interest: subjects with HS who meet all inclusion/exclusion criteria and have a baseline numeric rating scale (NRS) ≥ 4
- Variable of interest: change in NRS score after 12 weeks of treatment
- Summary measure: response rate, reduction in NRS scores, specifically, at least a 3-point reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst, at Week 12 (Yes/No)
- ICE handling: hybrid estimand, with treatment policy strategy used for most ICEs and hypothetical strategy used to account for use of prohibited pain medications due to non-HS-related pain, when taken near a visit. All pain scores after such use of prohibited pain medication will be omitted from the dataset and replaced via multiple imputation in a model analogous to that used for multiple imputation of the primary endpoint. Multiple imputation and non-response imputation will be used to handle certain other types of missing data, analogously to the primary endpoint.

4. Study Design

4.1. Overall Design

This is a Phase 3, pivotal, confirmatory, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of izokibep in subjects with moderate to severe HS. Subjects must have HS lesions present in ≥ 2 distinct anatomic areas, one of which must be Hurley Stage II or Hurley Stage III, and a total AN count of ≥ 5. Subjects with draining fistula count of > 20 at screening or Day 1will be excluded.

Overall, 250 subjects (125 subjects per treatment group) with moderate to severe HS are planned to be enrolled at sites globally in North America, Europe, and Asia Pacific. Additional sites and regions may be added.

Subjects meeting eligibility criteria will be randomized into 1 of 2 treatment groups in a 1:1 ratio as follows:

- Group 1 (n = 125): placebo QW from Day 1/Week 0 through Week 15, then izokibep 160 mg QW from Weeks 16 to 51.
- Group 2 (n = 125): izokibep 160 mg QW from Day 1/Week 0 through Week 51.

The first dose of study drug (ie, izokibep or placebo) will be administered on Day 1 (Week 0).

Randomization will be stratified by prior TNFi use for HS (Yes/No) and Hurley Stage (II or III). The AN count is the sum of abscesses and inflammatory nodules. Subjects enrolled with stable concomitant antibiotic use (dosing regimen has been stable for ≥ 4 weeks prior to first dose of study drug) will be capped at approximately 30%.

Subjects will complete study assessments according to the study visits outlined in the schedule of activities (SoA) (Section 1.3). The primary endpoint will be assessed at Week 12. The last dose of study drug will be administered on Week 51.

An end of treatment visit will be conducted at Week 52 (± 5 days). A safety follow-up visit will be conducted at Week 59 (± 5 days). For subjects who early terminate, the end of treatment visit should be completed 1 week after last dose of study drug (± 5 days), and safety follow-up visit should be completed 8 weeks after last dose of study drug (± 5 days), where possible.

The final analysis of primary and secondary endpoints will be conducted after the last subject has had the opportunity to complete Week 12 assessments or early terminates from the study. Analysis of data at later timepoints may occur after all subjects have had the opportunity to complete that timepoint.

4.1.1. Independent Data Monitoring Committee

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 and to make recommendations on further development activities for izokibep.

The DMC will consist of at least 1 medical expert with expertise in the relevant therapeutic area and at least 1 statistician and will have a minimum of 3 members, 1 of whom will serve as the Chair. The DMC responsibilities, members (including their qualifications and possible conflicts of interest), authorities, meeting frequency to review unblinded interim data, and procedures will be documented in the DMC charter. The committee will meet as needed to review significant safety findings. After each review, the DMC will make recommendations regarding the continuation of the study based on safety.

4.1.2. Number of Sites

Approximately 95 sites across North America, Europe, and Asia Pacific will participate in this study. Additional sites and regions may be added. Sites that do not screen subjects within 2 months of site initiation may be closed.

4.1.3. Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects". The number of subjects planned to be enrolled is 250 (125 subjects per treatment group). Subjects who are withdrawn or removed from treatment or the study will not be replaced.

4.1.4. Study Duration for Subjects

The maximum planned length of participation in the study for an individual subject is up to 63 weeks, which includes the following:

- screening period of up to 28 days (4 weeks)
- treatment period of 51 weeks
- follow-up visit at 8 weeks after the last dose of study drug.

4.2. Scientific Rationale for Study Design

The design of this clinical study was chosen to evaluate the efficacy of izokibep in the treatment of subjects with moderate to severe HS.

The primary aim of the study is to evaluate the efficacy of izokibep administered SC 160 mg QW for the treatment of active HS. The primary endpoint of HiSCR75 response will be evaluated after all subjects have either completed Week 12 or terminated early from the study. Subjects will continue their randomized treatment until Week 16. After Week 16, subjects randomized to placebo will receive blinded active treatment (izokibep 160 mg QW) until Week 51. Long-term efficacy beyond Week 12 will be explored up to Week 52 and safety will be explored up to the end of study visit at Week 59.

Standard statistical procedures will be utilized in this study. Efficacy measurements in this study have been selected or designed to assess disease activity in subjects with active HS. All clinical and laboratory procedures in this study are standard and generally accepted.

Men and women 18 years of age and older with HS who meet all inclusion criteria and who do not meet any of the exclusion criteria are eligible for this study. 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.

4.3. Justification for Dose

In subjects randomized to izokibep, 160 mg SC QW will be administered from Day 1 (Week 0) through Week 51. Subjects randomized to placebo will switch to active treatment at Week 16 and will receive izokibep 160 mg QW through Week 51.

The selection of the dosing regimen is informed by the following facts. In the clinical setting, izokibep has not demonstrated dose-limiting safety/tolerability up to 160 mg Q2W with multiple doses. A dose of 160 mg QW has 10-fold margin for C_{max} and 9-fold margin for AUC_{tau} based on NOAEL from non-clinical cynomolgus monkey toxicity studies (Table 4-1).

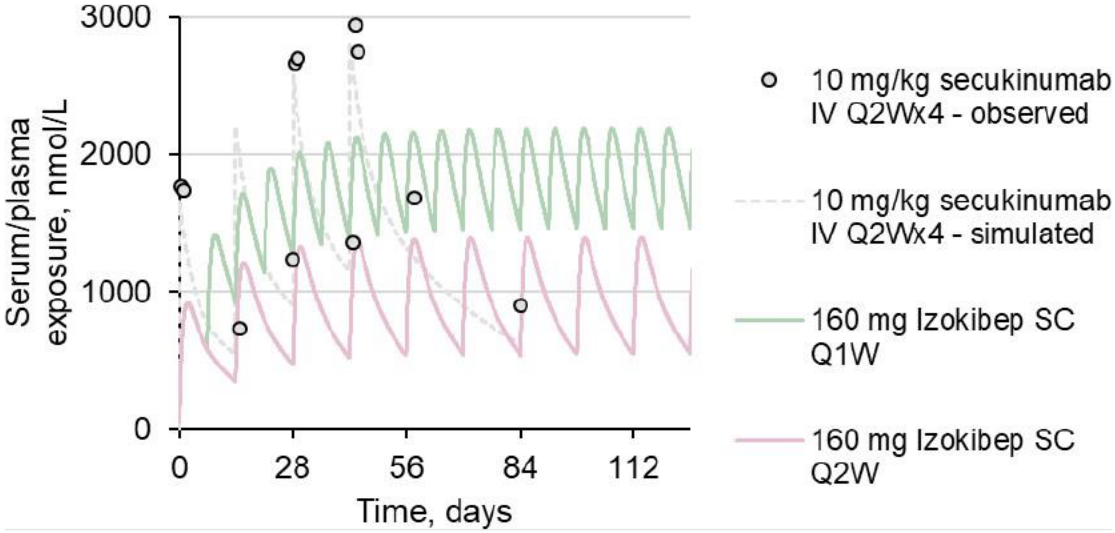
Finally, based on PK modeling of the izokibep and secukinumab plaque psoriasis data and the available data with secukinumab in uveitis, the sponsor aimed to approximate the observed exposure of 10 mg/kg secukinumab IV Q2W (administered on 4 occasions) with the 160 mg QW SC dose of izokibep as shown in Figure 2 and Table 4-2 (internal data to ACELYRIN INC.).

Table 4-1. C_{max} and $AUC_{0-\tau}$ at NOAEL in Cynomolgus Monkey Versus Predicted Exposure Levels in Humans and Respective Margins

Parameter	NOAEL in Cynomolgus	Predicted in Subjects at Steady State (QW)	Margin
C_{max}	409 µg/mL	40.8 µg/mL	10
AUC_{tau}	52500 h·µg/mL	5850 h·µg/mL	9.0

$AUC_{0-\tau}$ = area under the curve over a dosing interval; C_{max}= maximum observed plasma concentration; h = hour; NOAEL = no observed adverse effect level; QW = every week.

Figure 2. Observed and Simulated PK Profiles for 10 mg/kg IV Q2W x 4 Secukinumab Versus Simulated Profiles for 160 mg Izokibep SC Q1W and Q2W



Abbreviations: IV = intravenous; PK = pharmacokinetic; Q1W = once a week; Q2W = every 2 weeks; SC = subcutaneous.

Table 4-2. Predicted Exposure at Steady State for 160 mg Izokibep SC QW

Parameter	Unit	Value	Unit	Value
C_{max}	nmol/L	2190	µg/mL	40.8
C_{min}	nmol/L	1460	µg/mL	27.2
$C_{average}$	nmol/L	1870	µg/mL	34.8
$AUC_{0-\tau}$	h·nmol/L	$31.5 \cdot 10^4$	h·µg/mL	5850

$AUC_{0-\tau}$ = area under the concentration-time curve over the dose interval; $C_{average}$ = average observed plasma concentration; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration; h = hour; QW = once a week; SC = subcutaneous.

The doses of izokibep used in this study support the maximum likelihood of demonstrating the potential efficacy for izokibep in subjects with HS within an acceptable safety profile.

Measures have also been taken to ensure the well-being of subjects by applying appropriate inclusion and exclusion criteria to recruit a broad population that is most likely to benefit from treatment, while excluding subjects with an unacceptable risk to enter the study (Section 5).

Further, during the study, measures are in place to monitor the safety of subjects on a regular basis. An independent DMC will also review the data on an ongoing basis.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure including the final follow-up shown in the SoA for the last subject in the study globally.

A subject is considered to have completed the study if the subject has completed all periods of the study including the last scheduled procedure shown in the SoA.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

General

1. Subject has provided signed informed consent including consenting to comply with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
2. The inclusion criterion was removed and replaced with inclusion criterion 12.
12. Subject must be 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place) or older, at the time of signing the informed consent.

Type of Subject and Disease Characteristics

3. Diagnosis of HS for ≥ 6 months prior to first dose of study drug.
4. Hidradenitis suppurativa lesions present in ≥ 2 distinct anatomic areas (eg, left and right axilla; or left axilla and left inguino-crural fold), one of which is Hurley Stage II or Hurley Stage III at screening and Day 1 prior to enrollment/randomization.
5. A total AN count of ≥ 5 at screening and Day 1 prior to enrollment/randomization.
6. Subject must have had an inadequate response to oral antibiotics (defined as ≥ 3-month treatment with an oral antibiotic for treatment of HS) OR exhibited recurrence after discontinuation to, OR demonstrated intolerance to, OR have a contraindication to oral antibiotics for treatment of their HS as assessed by the investigator through subject interview and review of medical history.
7. Must agree to use daily or a minimum of 3 days a week (throughout the duration of the study) one of the following over-the-counter topical antiseptics on their body areas affected with HS lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, diluted bleach in bathwater, or as otherwise determined acceptable by ACELYRIN medical monitor.
8. Subject must be willing to complete a daily skin pain diary 7 consecutive days prior to Day 1; if skin pain diaries are not completed for at least 3 of the 7 consecutive days prior to the Day 1 visit, the subject may not be enrolled/randomized.

Other Inclusions

9. No known history of active tuberculosis (TB) unless adequately treated according to World Health Organization/Center for Disease Control and Prevention therapeutic guidance and determined to be fully recovered by a TB specialist (see Section 8.2.8).

10. Subject has a negative interferon-gamma release assay (IGRA) TB test (QuantiFERON recommended) at screening, is not at high risk of acquiring TB infection, and has no current or history of nontuberculous mycobacterium infection (see Section 8.2.8):

- For indeterminate IGRA TB test results, subjects are permitted to retest once. If retest results are negative, the subject is eligible for the study. If retest results are positive or remain indeterminate, the subject may not be randomized without further evaluation by a TB specialist.
- For positive IGRA TB test results, subjects may not be randomized without further evaluation by a TB specialist.

Sex and Contraceptive/Barrier Requirements

11. Male and female subjects:

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male subjects:

Male subjects are eligible to participate if they agree to the following during the study drug period and for at least 8 weeks after the last dose of study drug:

- Refrain from donating semen, plus either:
  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

  - *Must* agree to use contraception/barrier as detailed below:
    - Agree to use a male condom (and should also be advised of the benefit for a female partner to use a highly effective method of contraception as a condom may break or leak) when having sexual intercourse with a woman of childbearing potential (WOCBP) who is not currently pregnant.

b. Female subjects:

A female subject is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions applies:

- Is a woman of nonchildbearing potential as defined in the protocol (Section 10.4.1).

OR

- Is a WOCBP, and uses a contraceptive method that is highly effective, with a failure rate of < 1%, as described in the protocol (Section 10.4.2) during the study drug period and for at least 8 weeks after the last dose of study drug. The investigator should evaluate the potential for contraceptive

method failure (eg, non-compliance, recently initiated) in relationship to the first dose of study drug.

A WOCBP must have a negative highly sensitive serum pregnancy test at screening and a negative urine pregnancy test on Day 1 prior to the first dose of study drug.

5.2. Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Draining fistula count of > 20 at screening or Day 1 prior to enrollment/randomization.
2. Outpatient surgery ≤ 8 weeks prior or inpatient surgery ≤ 12 weeks prior to enrollment/randomization.
3. Other active skin disease or condition (eg, bacterial, fungal or viral infection) that could interfere with study assessments.
4. History of active IBD

   OR

   Any of the following symptoms (of unknown etiology) or any signs or symptoms within the last year that in the opinion of the investigator may be suggestive of IBD, with fecal calprotectin > 500 µg/g; OR if fecal calprotectin > 150 to < 500 µg/g without confirmed approval from a gastroenterology consultation that an IBD diagnosis is clinically unlikely (see Section 8.2.10) when the following clinical signs and symptoms are present:

   a. prolonged or recurrent diarrhea
   b. prolonged or recurrent abdominal pain
   c. blood in stool
5. Chronic pain not associated with HS (eg, fibromyalgia).
6. Uncontrolled, clinically significant system disease such as diabetes mellitus, cardiovascular disease including moderate to severe heart failure (New York Heart Association class III/IV), moderate to severe renal disease, moderate to severe liver disease or hypertension, as determined by investigator.
7. History of demyelinating disease (including myelitis) or neurological symptoms suggestive of demyelinating disease.
8. Malignancy within 5 years except treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.

9. Risk of self-harm or harm to others as evidenced by past suicidal behavior or endorsing items 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) assessed at screening. Subjects with major depressive disorder are permitted in the study if they are considered by the investigator to be stable and are taking no more than 1 medication. If on medication for major depressive disorder, subjects must have been on a stable antidepressant dose for at least 3 months prior to the first dose of study drug and agree to continue for the duration of the study or as indicated by their treating psychiatrist.
10. History or evidence of any clinically significant disorder (including psychiatric), condition, or disease that, in the opinion of the investigator, may pose a risk to subject safety or interfere with the study evaluation, procedures, or completion.
11. Active infection or history of infection as follows:
    a. Any active infection for which oral anti-infectives (antibiotics, antivirals, antifungals) were used ≤ 14 days prior to first dose of study drug (except for the use of a stable dose allowable antibiotics [doxycycline or minocycline only] for HS).
    b. A serious infection requiring hospitalization or IV anti-infectives (antibiotics, antivirals, antifungals) ≤ 30 days prior to first dose of study drug.
    c. Recurrent or chronic infections or other active infections that in the opinion of the investigator might cause this study to be detrimental to the subject.
12. *Candida* infection requiring systemic treatment within 3 months prior to first dose of study drug.
13. Tuberculosis or fungal infection seen on available chest x-ray taken within 3 months prior to screening (Exception: documented evidence of completed treatment and clinical resolution).
14. Known history of human immunodeficiency virus (HIV) or positive HIV test at screening.

Washout and Non-permitted Drugs

15. Previous exposure to izokibep or any other IL-17 inhibitor and IL-17 receptor inhibitors (eg, secukinumab, ixekizumab, bimekizumab, brodalumab).
16. Prior exposure to biologics that had a potential or known association with progressive multifocal leukoencephalopathy (ie, natalizumab [Tysabri], rituximab [Rituxan], or efalizumab [Raptiva]).
17. Exposure to TNFi, IL-1, IL-12, IL-23, or IL-12/23 receptor inhibitors within 5 half-lives prior to first dose of study drug.
18. Exposure to any of the following.

- Exposure to the following ≤ 12 weeks prior to first dose of study drug
  - Other experimental or commercially available biologic or biosimilar therapies (within 12 weeks or 5 half-lives, whichever is longer).
  - IV gamma-globulin or Prosorba column therapy.

- Exposure to the following ≤ 4 weeks prior to first dose of study drug
  - Janus-kinase (JAK) inhibitors (eg, tofacitinib, upadacitinib)
  - Oral or injectable corticosteroids (including intralesional injections)
  - Cyclosporine, azathioprine, tacrolimus
  - Other systemic treatments for autoimmune/inflammatory conditions not listed above or below (eg, mycophenolate mofetil, retinoids, fumarates, apremilast, or phototherapy [eg, psoralen plus ultraviolet-A radiation, ultraviolet-B radiation]), except for allowable stable dose antibiotics (doxycycline or minocycline)
  - Laser or intense pulse light therapy in anatomic areas of HS lesions

19. Exposure of the following ≤ 2 weeks prior to first dose of study drug

- Prescription topical therapies
- Opioid analgesics
- Non-oral concomitant analgesics (eg, IV, SC).

20. For subjects entering study with a permitted oral antibiotic treatment (doxycycline or minocycline only) for HS: not on a stable dose for ≥ 4 weeks prior to first dose of study drug.
21. For subjects entering study with oral, non-opioid analgesics: not on a stable dose for ≥ 5 days prior to first dose of study drug. Exception is acetaminophen is allowed ≤ 2 g per day.
22. Required or is expected to require, opioid analgesics for any reason (excluding tramadol) during the study.
23. History of hypersensitivity or allergy to izokibep or its excipients.
24. Received live vaccination ≤ 12 weeks prior to dosing or scheduled to receive a live vaccine ≤ 12 weeks following the last dose of study drug.
25. Participating in another clinical study or participated in a clinical study involving administration of an IMP within the following time period prior to dosing: 12 weeks, 5 half-lives, or twice the duration of the biological effect of the IMP (whichever is longer).

Diagnostic Assessments

26. Concurrent acute or chronic viral hepatitis B or C. Note: subjects who have evidence of or tested positive for hepatitis B or hepatitis C at screening are excluded.

- A positive test for the hepatitis B virus is defined as any of the following:
  - Positive for hepatitis B surface antigen
  - Positive for anti-hepatitis B core antibody
  - Hepatitis B virus DNA detected on polymerase chain reaction
- A positive test for the hepatitis C virus (HCV) is defined as positive for hepatitis C antibody (anti-HCV antibody)

27. Laboratory abnormalities at screening:
    - Hemoglobin < 9 g/dL
    - Platelet count < 100 000/mm^3
    - White blood cell count < 3000 cells/mm^3
    - Aspartate aminotransferase and/or alanine aminotransferase ≥ 2.5 times the upper limit of normal
    - Moderate or severe renal impairment (ie, creatinine clearance < 60 mL/min) (Modification of Diet in Renal Disease formula)
    - Note: Laboratory assessments due to value(s) out of range due to sampling error or that could be within range with repeat sampling may be repeated up to 2 times
28. Any other laboratory abnormality that in the opinion of the investigator will pose a risk to subject safety or interfere with the study evaluation, procedures, or completion

Other Exclusion Criteria

29. Previously enrolled, randomized to, or withdrawn from this study.
30. Active substance abuse (drug or alcohol) within 24 weeks prior to first dose of study drug, as determined by the investigator.
31. Any condition that compromises the ability of the subject to give written informed consent, or the subject's unwillingness or inability to comply with study procedures.

5.3. Lifestyle Considerations

The investigator should encourage subjects to limit alcohol consumption to ≤ 2 per day, ≤ 7 alcoholic drinks per week. An alcoholic drink is defined as a 6 oz (175 mL) glass of wine, a 1 oz (30 mL) glass of hard liquor (eg, whiskey), or an 8 oz (250 mL) glass of beer.

5.4. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled/randomized to the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times (ie, total of 3 screens including initial screen). Refer to Section 6.3.2 for details on rescreening.

5.5. Criteria for Temporarily Delaying Dosing

Subject should be dosed within the window as detailed in the SoA (Section 1.3).

All missed or delayed doses should be documented. If the investigator determines a subject should not be dosed within the defined window for a safety reason (eg, an AE, SAE), then a missed dose should be recorded.

5.6. COVID-19-related Precautions

Risk mitigation measures, including COVID-19-related precautions and procedures (including SARS-CoV-2 testing/screening) will be implemented based on the prevailing situation during the study conduct, at the investigator's discretion, and in accordance with local and institutional guidelines as applicable.

Subjects should be routinely monitored for any AEs at every visit, including signs or symptoms of infection. Should subjects demonstrate any symptoms or AEs (including known COVID-19 symptoms or tested positive for COVID-19), the symptoms or AEs will be reported to the site as per study procedures and assessed by the investigator. As with any AEs, AE data will be collected on the appropriate electronic case report form (eCRF).

If a subject has received, or is planning to receive, COVID-19 vaccination, the investigator should refer to vaccine considerations in eligibility criteria (Section 5.2) and concomitant medications (Section 6.8) requirements in the protocol.

6. Study Drug(s) and Concomitant Therapy

Study drugs are all pre-specified, investigational, and non-IMPs, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study subjects during the study conduct.

6.1. Study Drug(s) Administered

Table 6-1. Study Drug(s) Administered

	Investigational Drug	Placebo
Drug name:	Izokibep	Placebo
Pharmacological group:	Biologic: IL-17A inhibitor	None
Dosage formulation:	Solution for injection	Solution for injection
Unit dose strength(s)/Dosage level(s):	Each 2R (2 mL) glass vial contains 1.2 mL of izokibep (nominal concentration 80 mg/mL ± 10%)	Not applicable
Route of administration:	SC injection	SC injection
Non-active ingredients (excipients)	10 mM sodium phosphate 150 mM NaCl 0.5 mM EDTA	10 mM sodium phosphate 150 mM NaCl 0.5 mM EDTA
Packaging and labeling	Each vial will be labeled as required per country requirement.	Each vial will be labeled as required per country requirement.
Special storage recommendations	Vials are to be stored at 2°C to 8°C. The filled syringe must be stored in the refrigerator at 2°C to 8°C (protected from light) if not used for immediate dose administration. Once removed from the refrigerator, the solution should be allowed to warm to room temperature (about 15 to 20 minutes) prior to administration. For further details, refer to Pharmacy Manual.	Store at room temperature (do not store above 25°C). Given placebo and izokibep will be provided in blinded, matching vials, both should be stored at 2°C to 8°C. Once removed from the refrigerator, the solution should be allowed to warm to room temperature (about 15 to 20 minutes) prior to administration. For further details, refer to Pharmacy Manual.

EDTA = ethylenediaminetetraacetic acid; IL = interleukin; NaCl = sodium chloride; SC = subcutaneous

6.1.1. Dosage, Administration, and Schedule

Study drug (izokibep 160 mg QW or placebo) will be dosed by SC injection as described below. Study drug vials for placebo and izokibep will be visually indistinguishable.

Study drug doses are fixed and will not be adjusted for individual subjects during the study. Throughout treatment period, 2 SC injections are to be given for each study drug administration. The anatomical sites for administration of study drug are the upper arm, upper thigh, or abdomen.

At the site, only authorized investigational site staff members are to administer study drug (see Section 6.2). Subjects should be monitored for 1 hour after the first 2 study drug administrations at Visits Day 1/Week 0, Week 1, Week 16, and Week 17.

- Group 1: placebo QW from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Week 16 to Week 51
- Group 2: izokibep 160 mg QW from Day 1/Week 0 to Week 51

After Week 4, qualified subjects may perform home dosing of study drug. Site staff will administer the first 2 doses of study drug and train the subject on handling and self-administration of study drug during those study visits. The subject must self-administer the next 2 doses of study drug at the site and demonstrate competency prior to being allowed to perform home dosing. A subject's caregiver or designee can also be trained on home dosing based on the subject's preference. Only those subjects/caregivers or designees who demonstrate competency to perform home dosing will be allowed to do so; otherwise, the subject will need to return to the site for all study drug administrations.

The dosing schedule is described by a schema in Section 1.2.

6.2. Preparation, Handling, Storage, and Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received, and any discrepancies are reported and resolved before use of the study drug.
- Only subjects randomized in the study may receive study drug. All study drug must be stored prior to dispensing in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study drugs are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Subject Enrollment

Before subjects begin participation in any study-specific activities/procedures, the sponsor or designee requires a copy of the site's written Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval of the protocol, ICF, and all other subject information and/or recruitment material, if applicable (see Section 10.1.3). All subjects must personally sign and date the ICF before the commencement of study-specific activities/procedures.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria and registered the subject as enrolled/randomized within the Interactive Voice/Web Response System (IXRS). The investigator is to document this decision and date in the subject's medical record. The screening period starts when the subject signs and dates the 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. (Note: Repeating procedures during the original initial screening period

is a part of screening and is not considered "rescreening.") These procedures include laboratory assessments due to value(s) out of range due to a potential sampling error or that could be within range with repeat sampling. Laboratory value(s) out of range due to sampling error or that might be within range after medically appropriate supplementation may be repeated up to 2 times within the screening window before the subject is considered a screen failure.

All subjects who enter the screening period for the study receive a unique subject identification number assigned by the IXRS. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. The subject identification number must remain constant throughout the entire clinical study; it must not be changed after initial assignment, including if a subject is rescreened.

The subject identification number consists of 12 digits that correspond to the site number (9 digits) plus the sequential number (3 digits) as follows:

- Site number (first 9 digits)
  - First 3 digits correspond to the last 3 digits of the study protocol number (ie, 107)
  - Middle 3 digits correspond to the 3-digit ISO 3166-1 number code for the country (eg, US country code = 840; For country codes with only 2 digits, a lead "0" will be added)
  - Last 3 digits are sequential numbers given to sites within a country (eg, For a US site = 107840**001)**
- Sequential numbering of subjects within a site (last 3 digits)
  - The last 3 digits are sequential numbers assigned by IXRS within a site (eg, For US Site 107840001, their first subject = 107840001**001)**

A subject who is determined to be ineligible must be registered as a screen fail in the IXRS.

6.3.2. Rescreening

Investigators may rescreen a subject if the investigator is reasonably certain that reasons for screen failure will be resolved prior to or during a repeat screening attempt. Reasons to rescreen may include but are not limited to the following:

- Laboratory value(s) out of range due to sampling error or that might be within range after medically appropriate supplementation. (Note: Before screen failing and then rescreening the subject, efforts should be made to repeat the laboratory assessment(s) during the original initial screening period.).
- The subject has a medical condition that can be stabilized or resolved prior to the repeat screening/rescreening attempt; or
- Additional time is required following the subject's last dose of an excluded medication.

Investigators are encouraged to consult with the medical monitor prior to rescreening subjects for other reasons.

A subject must provide informed consent prior to the initiation of any rescreening procedures only if 30 or more days have elapsed since the date of the subject's initial informed consent. The subject is entered into rescreening in the IXRS, and all screening procedures must be repeated

except as noted in the inclusion/exclusion criteria. A subject may be screened up to 3 times (ie, no more than 2 rescreens). Near to the end of study enrollment, sites may be notified when no additional subjects will be screened or rescreened.

If a subject rescreens, a chest x-ray does not need to be repeated if a previous chest x-ray was performed ≤ 3 months prior to Day 1.

If a subject rescreens, hepatitis, TB, HIV, urinalysis, and electrocardiogram (ECG) tests do not need to be repeated if a previous test was performed < 60 days prior to Day 1.

6.3.3. Treatment Assignment/Randomization

Subjects will be randomized to the study drug or placebo (in a 1:1 ratio) on Day 1 by the IXRS. The subject, site personnel, and sponsor/Contract Research Organization (CRO) study personnel and designees will be blinded to the randomization treatment group assignment (ie, izokibep or placebo). The randomization dates are to be documented in the subject's medical record.

Randomization will be stratified by prior TNFi use for HS (Yes/No) and Hurley Stage (II or III). Izokibep and matching placebo will be visually indistinguishable to prevent unblinding during preparation or administration of study material.

6.3.4. Site Personnel Access to Individual Treatment Assignments

A subject's treatment assignment should be unblinded only when knowledge of the treatment is essential for the further management of the subject in this study. Unblinding at the site for any other reason will be considered a protocol deviation. The investigator should contact the medical monitor before unblinding any subject's treatment assignment, whenever possible. If an urgent therapeutic intervention is necessary that warrants unblinding prior to contacting the medical monitor, the investigator can directly access the IXRS, or call the 24-hour emergency medical coverage line to unblind without medical monitor notification or agreement but must contact the medical monitor within 1 working day after the unblinding event.

If an SAE requires an expedited regulatory report to be sent to 1 or more regulatory agencies, sponsor/designee's safety staff may unblind the intervention assignment for the subject. A copy of the report, identifying the subject's intervention assignment, may be sent to that regulatory agency in accordance with local regulations.

Please refer to the Study Pharmacy Manual for details.

6.4. Study Drug Compliance

When subjects are dosed at the site, they will receive study drug directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents.

When study drug is administered at home by the subject/caregiver, compliance with study drug will be assessed at each visit. Compliance will be assessed by review of the subject dosing diary during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded and reported to the sponsor (or designee).

A record of the quantity of study drug dispensed and administered to each subject must be maintained and reconciled with study drug and compliance records. Study drug dose dates, including study drug delays will also be recorded. Partial dose administration will be explained.

6.5. Dose Modification

No dose modifications are allowed in the study.

6.6. Continued Access to Study Drug After the End of the Study

There is no plan to continue access to study drug after the end of study. The choice of further therapy for HS at the end of the clinical study depends on the subject's individual needs and is left at the physician's discretion.

6.7. Overdose

Excessive dosing (beyond that prescribed in this protocol and including overdose) should be recorded in the case report form (CRF). Any SAE or non-serious AE associated with excessive dosing must be followed as any other SAE or non-serious AE as specified in (Section 10.3.3).

These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt).

6.8. Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including route, dose, and frequency.

Concomitant medications should be used in alignment with the approved label in the respective country, and per doses as outlined below.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.8.1. Prior Therapies

Any treatments used for HS since the initial diagnosis (as determined through medical history records or through subject interview) prior to study entry will be recorded in the source documents and on the CRF, along with the reason for discontinuation.

A detailed history of prior antibiotic and biologic (including but not limited to TNFi, IL-1, IL-12, IL-23, or IL-12/23 receptor inhibitors) use, response, and reason for discontinuation will be collected.

6.8.2. Concomitant Therapies

Upon initiation or discontinuation of investigational product, investigators should consider potential effects on metabolism of cytochrome P450 substrates with narrow therapeutic indices including, but not limited to, methotrexate, tacrolimus, cyclosporine, certain tricyclic antidepressants (including amitriptyline and nortriptyline), baricitinib, warfarin, and tamoxifen. The concomitant medications/treatments in the following sections are permitted during the study.

6.8.2.1. Antiseptic Therapy

Subjects are required to use an antiseptic wash on their HS lesions daily or at a minimum of 3 days a week. Antiseptic wash use should be consistent during the study. Allowable antiseptic washes are limited to one of the following: chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater. If a different antiseptic wash is required during the study, the medical monitor should be consulted.

6.8.2.2. Wound Care

Concomitant use of wound care dressings on HS wounds is allowed; however, options are limited to alginates, hydrocolloids, and hydrogels. If a different option for wound care is required during the study, the medical monitor should be consulted.

6.8.2.3. Analgesic Therapy

For a subject entering the study on oral non-opioid analgesic:

- If taken for a non-HS medical condition (eg, osteoarthritis), the subject may continue the analgesic, provided the dose is stable for 5 days prior to the first dose of study drug and is anticipated to remain stable throughout study participation.
- If taken for HS-related pain but is not any of the oral non-opioid analgesics permitted for HS-related pain listed below, the non-permitted analgesic can be continued only if the HS-related pain is under control and the dose is stable for 5 days prior to the first dose of study drug and is anticipated to remain stable throughout study participation. If the HS-related pain becomes uncontrolled after Day 1, the subject must switch to permitted analgesics for HS-related pain listed below.

If an enrolled subject experiences pain (HS-related or non-HS-related) after Day 1, they may initiate analgesic therapy at any time as follows:

<u>For HS-related pain, permitted analgesics are limited to:</u>

- Ibuprofen (at a dose of up to 800 mg by mouth every 6 hours) not to exceed 2.0 grams/per 24 hours; AND/OR acetaminophen/paracetamol as per local labeling.
- If HS-related pain is uncontrolled with ibuprofen or acetaminophen/paracetamol at the above dosing regimens after the Day 1 visit, subjects can be prescribed tramadol (at a dose of up to 100 mg po every 4 hours), not to exceed 400 mg per 24 hours.
- From screening through Week 16, subjects will complete a daily diary of their analgesic use. From Week 16 through Week 59, subjects will be required to tell site staff if they took any analgesics within 24 hours of their site visit. All analgesics and dose adjustments will be captured in the source and on the appropriate CRF.

- Subjects will be encouraged not to take analgesics 12 hours prior to a study visit.

For non-HS-related Pain:

- Opioid analgesics are prohibited.
- All other analgesics (including tramadol) are allowed at the recommended or prescribed dose.

6.8.2.4. Antibiotic Therapy

In approximately 30% of subjects, concomitant antibiotic use is permitted if dosing regimen has been stable for ≥ 4 weeks prior to first dose of study drug, and dosing regimen is maintained through the placebo-controlled period (Week 16 assessment). Antibiotics taken on an 'as-needed' basis are not considered a stable dose.

Permitted oral concomitant antibiotics include:

- Oral: doxycycline (at a dose of up to 100 mg twice daily [BID]); minocycline (at a dose of up to 100 mg, BID).
- If another oral concomitant antibiotic for HS is medically necessary at the time of enrollment/randomization, the medical monitor must be contacted for approval. If systemic antibiotics are used concomitantly, the dose should remain stable and constant.

For non-HS-related AEs requiring antibiotic use:

Concomitant antibiotic use for the treatment of an AE other than HS may be permitted per standard of care (eg, for treatment of pneumonia, tonsillitis) and should be captured and documented appropriately.

6.8.2.5. Lesion Intervention

If an acutely painful lesion occurs that requires an immediate intervention, the investigator will have the option to perform protocol-allowed interventions. Only 2 types of interventions are allowed: injection with intralesional triamcinolone acetonide suspension (at a concentration of up to 5 mg/mL, up to 1 cc) and incision and drainage.

If incision and drainage is performed, the required over-the-counter antiseptic wash should continue to be used. New systemic and topical therapies following incision and drainage (including antibiotics), are prohibited. Concomitant use of wound care dressings is allowed; however, options are limited to alginates, hydrocolloids, and hydrogels.

Subjects should continue using any ongoing oral and topical therapies (including antibiotics, with the constraints as described in Section 6.8.2.4) during the study.

Concomitant medications associated with the lesion intervention(s) must be captured in the source and on the appropriate CRF.

A total of 2 protocol-allowed interventions are permissible up until Week 16 visit. An intervention can occur on maximally 2 different lesions at the same or different visits or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same

visit. If a subject requires more than 2 interventions within the first 16 weeks, then they must be discontinued from study drug. After Week 16, maximally 2 interventions every 4 weeks are permitted. If a subject requires more than 2 interventions within a 4-week period or has 2 of the same interventions on the same lesion within that period, then they must be discontinued from the study drug.

All study visit evaluations must occur before any interventions are performed. Any lesion that undergoes an intervention will be documented in the source documents. The site will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention and must account for it in the source documents and on the appropriate CRF.

6.8.3. Prohibited Medications

The following medications are prohibited from enrollment through 2 weeks after the last dose of study drug:

- All other biologic therapies with a potential therapeutic impact on HS including but not limited to TNFi, IL-1, IL-12, IL-17, IL-23, or IL-12/23 inhibitors
- Any other immunomodulatory therapy (eg, cyclosporine, azathioprine, tacrolimus, IV gamma-globulin, or Prosorba column therapy)
- JAK inhibitors (eg, tofacitinib, upadacitinib)
- Other systemic treatments for HS including but not limited to antibiotics (except as specified in Section 6.8.2.4 or Section 6.8.4), methotrexate, cyclosporine, retinoids, and fumaric acid esters
- Prescription topical therapies for HS. Prescription topical therapies are allowed for other indications (other than HS) only if approved by the medical monitor (exception: prescription topical corticosteroids can be used to treat localized erythema, edema, or pruritis at the injection site without medical monitor approval)
- Oral analgesics for HS not listed in Section 6.8.2.3
- Oral opioid analgesics
- Non-oral concomitant analgesics (eg, IV, SC)
- Live vaccines (during the study and for 12 weeks after the last dose of study drug)
- Oral or injectable corticosteroids (except as allowed per Section 2.3.1)
- Phototherapy
- Any investigational agents
- Over-the-counter topical antiseptic washes, creams, soaps, ointments, gels and liquids containing antibacterial agents to treat HS not listed in Section 6.8.2.1
- Surgical or laser intervention for an HS lesion except as outlined in Section 6.8.2.5.

6.8.4. Rescue Medicine

If a subject experiences an increase in their AN count such that the total count is ≥ 150% of their Day 1 AN count, antibiotic rescue medication may be initiated.

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 appropriate electronic CRF. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7. Discontinuation of Study Drug and Subject Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.1.8.

7.1. Discontinuation of Study Drug

In rare instances, it may be necessary for a subject to permanently discontinue study drug. The reason for permanent discontinuation of drug will be documented. If study drug is permanently discontinued, the subject should, if at all possible, remain in the study to be evaluated for safety and efficacy.

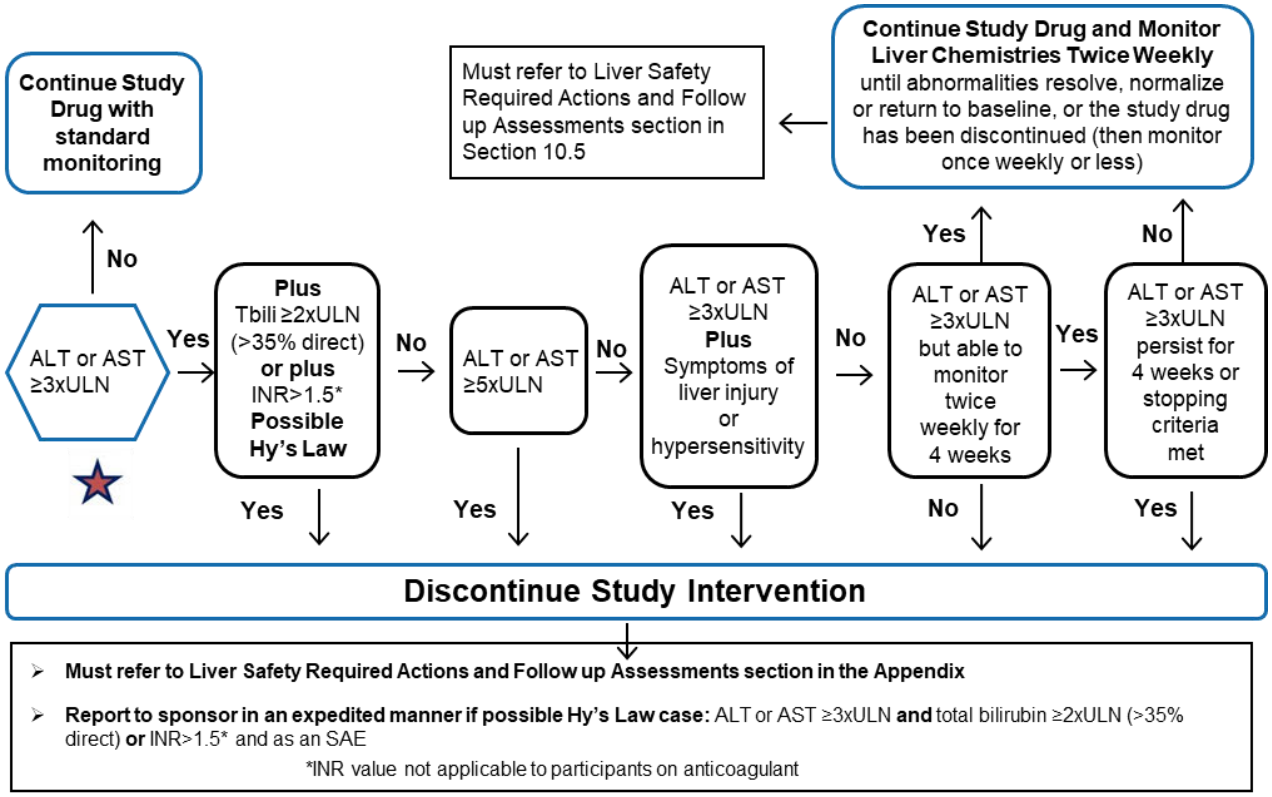
Subjects should continue to complete study assessments as outlined in the SoA (Section 1.3) where possible, with the exception of study drug administration. Reasons for removal from study drug include any of the following:

- death
- eligibility criteria violation(s) after the subject started study drug that may put the subject at risk by continued administration of study drug, as determined by the medical monitor and investigator
- non-compliance with study procedures, study drug, or concomitant medications (including TB prophylaxis) that may put the subject at risk by continued administration of study drug, as determined by the investigator
- AE that may put the subject at risk by continued administration of study drug, as determined by the investigator (see Section 10.3.5):
- lost to follow-up
- lack of efficacy:
    - subject requires more than 2 lesion interventions within the first 16 weeks of the study
    - after Week 16, subject requires more than 2 lesion interventions within a 4-week period or has 2 of the same interventions on the same lesion within that period
- study terminated by sponsor
- subject pregnancy
- disease progression
    - subjects with disease progression or not responding to treatment, at the investigator's discretion
- withdrawal of consent

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study drug for abnormal liver tests is required by the investigator when a subject meets one of the conditions outlined in the algorithm or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the investigator believes that it is in best interest of the subject.

Figure 3. Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm[a]



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; Tbili = total bilirubin; ULN = upper limit of normal.
[a]Liver chemistry stopping criteria are outlined in detail in Section 10.5.

7.1.2. Rechallenge

7.1.2.1. Study Drug Restart or Rechallenge After Liver Stopping Criteria Met

Study drug restart/rechallenge after liver chemistry stopping criteria are met is allowed in this study. If the subject meets liver chemistry stopping criteria, do not restart/rechallenge the subject with study drug unless:

- Liver tests have returned to the subject's baseline values.
- Sponsor medical monitor approval is granted.
- Ethics and/or IRB approval is obtained, if required.

NOTE: If study drug was interrupted for suspected intervention-induced liver injury, the subject should be informed of the risk of death, liver transplantation, hospitalization, and jaundice before resumption of dosing.

Refer to Section 10.5 for details on the restart/rechallenge process.

If sponsor medical monitor approval to restart/rechallenge the subject with study drug is not granted, then the subject must permanently discontinue study drug and may continue in the study for protocol-specified study assessments.

7.2. Subject Discontinuation/Withdrawal from the Study

Reasons for removal of a subject from the study are:

- termination of study by sponsor
- death
- withdrawal of consent from study
- lost to follow-up.

Withdrawal of consent from study:

- A subject may withdraw from the study at any time without jeopardizing subsequent medical care.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA (Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The subject will be permanently discontinued from the study drug and the study at that time.
- If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records and notify the sponsor or its designee.

7.3. Lost to Follow-up

A subject will be considered lost to follow-up if the subject repeatedly fails to return for scheduled visits and is unable to be contacted by the site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject (where possible, [3] telephone calls, and if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Where permitted by local regulations and approved by IRBs/IECs, third-party vendors may be employed by the site (funded by the sponsor) to assist the site in re-establishing contact.

8. Study Assessments and Procedures

- Informed consent must be obtained before any study-related procedures are performed. In regions where the legal age of consent is older than 18 years, informed consent must be obtained from and signed by the subject.
- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Day 1 corresponds to the date of the first dose of study drug.
- Visit/dosing windows of ± 3 days on either side of the scheduled visits/dosing are permitted; however, the investigator should try to keep the subjects on the original visit/dosing schedule. The window of ± 3 days is relative to Day 1 and applicable for all subsequent visits/dosing. The time between doses should be no less than 4 days and no more than 13 days.
- All assessments are to be completed before study drug administration, unless otherwise specified. It is recommended that patient-reported outcome assessments be completed first.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, x-rays) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

Planned timepoints for all efficacy and/or immunogenicity assessments are provided in the SoA. The site should make every attempt to have the same investigator conduct efficacy assessments throughout the study for each subject.

8.1.1. Hidradenitis Suppurativa Clinical Response

The HiSCR was developed to address issues with available HS scoring systems and is a validated measure that is responsive to improvement in disease activity, simplifies the scoring process, and increases the sensitivity to detect HS-specific lesions (Kimball et al, 2014; Kimball et al, 2016). The HiSCR50 is defined as at least a 50% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count. HiSCR75,

HiSCR90, and HiSCR100 are defined as at least 75%, 90% or 100% reduction respectively from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.

8.1.2. Lesion and AN Count

The number of inflammatory and non-inflammatory nodules, abscesses, draining and nondraining fistulas, and hypertrophic scars, as well as the physical location (eg, right/left axilla, right/left inframammary, intermammary, right/left buttock, right/left inguino-crural fold, perianal, perineal, other) will be recorded at the designated study visits listed in SoA (Section 1.3). The AN count is the sum of abscesses and inflammatory nodules. In addition, lesions counts will be performed at any time if the subject experiences a disease flare. The longest distance between 2 relevant lesions (if only 1 lesion, measure diameter of lesion) and whether the lesions are clearly separated by normal-appearing skin (yes or no) will be measured. The calculation of the HiSCR, International Hidradenitis Suppurativa Severity Score System (IHS4), and modified Sartorius score will be performed by the sponsor or designee based on the lesion counts entered by the study investigator(s) on the appropriate CRFs. In addition, the sponsor or designee will utilize the lesions counts entered by the investigator on the CRF to establish the rate of flares.

Treatment decisions made during the conduct of the study will not be based on the HiSCR.

8.1.3. Hurley Stage

The Hurley Stage is a severity classification for HS that was developed in 1989 and is widely used for the determination of the severity of HS (Hurley, 1989). The Hurley Stage is defined by the following criteria:

- Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
- Stage II: Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions.
- Stage III: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

The study investigator will determine the Hurley Stage in each affected anatomical region at the designated study visits listed in the SoA (Section 1.3). If more than 1 stage is present in a region, the worst state in each region should be entered.

8.1.4. Numeric Rating Scale Patient Global Assessment of Skin Pain

The NRS Patient Global Assessment of Skin Pain will be completed on a daily diary by subjects from screening through Week 16, and at the designated study visits after Week 16, listed in SoA (Section 1.3). If pain diaries are not completed for at least 3 of the 7 consecutive days prior to the Day 1 visit, the subject may not be randomized.

The Patient Global Assessment of Skin Pain is a unidimensional NRS that allows for rapid (often 1 item) measures of pain that can be administered multiple times with minimal administrative burden. The NRS consists of scores from 0 to 10 with 0 indicating “no skin pain” and 10

indicating “pain as bad as you can imagine”. The pain will be described as “skin pain at its worst in the last 24 hours” and “skin pain on average in the last 24 hours”.

The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject’s response.

8.1.5. Dermatology Life Quality Index

Subjects will complete the DLQI questionnaire at the designated study visits listed in SoA (Section 1.3). The DLQI will be used to assess the symptoms and the impact of skin problems on quality of life. The DLQI can be used to evaluate 6 areas: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment (Finlay and Khan 1994). Subjects will be asked to respond to the 10 items of the DLQI based on a recall period of “the last week”. Decreased scores indicate improved health-related quality of life. The subject should complete the questionnaire before site personnel perform any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject’s response.

8.1.6. Modified Sartorius Score

The Sartorius scale was created as a more detailed and dynamic HS severity scale and was modified in order to further develop and simplify this assessment for the clinical setting (Sartorius et al, 2009; Sartorius et al, 2010). The modified Sartorius score was the first disease-specific instrument for dynamically measuring clinical severity. The main parameter in the modified Sartorius score is the counting of individual nodules and fistulas. 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).

8.1.7. International Hidradenitis Suppurativa Severity Score System

The IHS4 is a validated tool to dynamically assess HS severity to be used both in real-life and clinical study setting. The determination of IHS4 requires counting the nodules, abscesses, and draining fistulas/sinus tracts. The IHS4 score (points) = (number of nodules × 1) + (number of abscesses × 2) + (number of draining tunnels [fistulae/sinuses] × 4). A score of ≤ 3 signifies mild HS, a score of 4 to 10 signifies moderate HS, and a score of ≥ 11 signifies severe (Zouboulis et al, 2017).

8.1.8. Hidradenitis Suppurativa-Physician’s Global Assessment

The hidradenitis suppurativa-Physician’s Global Assessment (HS-PGA) is a validated 6-point scale that is used to measure improvement in inflammatory nodules, abscesses, and draining fistulas (Kimball et al, 2012; Zouboulis et al, 2015). The HS-PGA scale is defined by the following:

- 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 nodule 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.

8.1.9. European Quality of Life-5 Dimensions

The European Quality of Life-5 Dimensions (EQ-5D) comprises 5 questions on mobility, self-care, pain, usual activities, and psychological status with 3 possible answers for each item (1 = no problem, 2 = moderate problem, 3 = severe problem). A summary index with a maximum score of 1 can be derived from these 5 dimensions by conversion with a table of scores. The maximum score of 1 indicates the best health state, by contrast with the scores of individual questions, where higher scores indicate more severe or frequent problems. In addition, there is a visual analog scale to indicate the general health status with 100 indicating the best health status.

8.1.10. Short Form 12

The acute Short Form-12v2™ Health Survey (SF-12v2) is a 7-day recall, 12-item subset of the Short Form-36v2™ questionnaire that measures the same 8 domains of health including physical functioning, role-function, bodily pain, general health, vitality, social functioning, role-emotional, and mental health. The SF-12 is a brief, reliable measure of overall health status with scores general for physical component and mental components. Each item on the SF-12 is score on 3- or 5-item Likert scales and the domains scales are standardized to 0 to 100 scale where 0 represents lower quality of life and 100 represents higher quality of life. The subject should complete the questionnaire before site personnel performs any clinic assessments and before any interaction with the site personnel has occurred to avoid biasing the subject's response.

8.1.11. Hidradenitis Suppurativa Quality of Life

Subjects will complete Hidradenitis Suppurativa Quality of Life (HiSQOL) scale at the designated study visits listed in the SoA (Section 1.3). The 17-item HiSQOL questionnaire includes 4 symptom items, 8 activity-adaptation items, and 5 psychosocial items. The item scores are summed to create a total ranging from 0 to 68, with higher scores indicating a more severe impact on health-related quality of life (Kirby et al, 2020).

8.1.12. Hidradenitis Suppurativa Patient Global Impression of Change

Subjects will complete the HS Patient Global Impression of Change (PGIC) questionnaire at the designated study visits listed in SoA (Section 1.3). The PGIC consists of 1 self-administered item that assesses change in the severity of skin pain due to HS. Subjects are asked to indicate their impression of change compared with their last visit, except at Week 12 and Week 16, when the subject will also be asked about their pain since treatment began on this study.

8.1.13. Hospital Anxiety and Depression Scale

In addition, depression and anxiety will be monitored with the Hospital Anxiety and Depression Scale (HADS). The HADS was chosen for its well-established psychometric properties and its use in clinical research on biological therapy in subjects with other inflammatory skin diseases

(Langley et al, 2010). The HADS scores for anxiety and for depression range from 0 to 21 with higher scores indicating a worse state. A score < 8 is considered to be normal, whereas a score of ≥ 11 is considered clinically significant (Snaith, 2003).

The HADS questionnaire will be presented in local language and is to be completed by the subject at the designated study visits listed in the SoA (Section 1.3).

8.1.14. Photography (Optional Substudy)

Subjects at a subset of selected sites will be invited to participate in an optional substudy to have photographs taken of their disease response during the study. Subjects who consent to this optional substudy will have photographs taken at the designated study visits listed in the SoA (Section 1.3). Sites participating in the photography substudy will be trained and receive standardized photographic equipment from the central photography vendor. Sites will submit the digital images to the central photography vendor. Photographs will be anonymized.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Medical and Medication History

A complete medical and medication history, as well as a history of alcohol and nicotine use, will be obtained from each subject during the screening visit. An updated medical history will be obtained at the Day 1 visit prior to study drug administration and updated as necessary throughout the study.

A HS history obtained at screening will capture date of onset of HS.

Any systemic treatment for HS since diagnosis will be recorded. Any other treatment used for any other reasons (including contraception) prior to randomization will be recorded as per eCRF Completion Guidelines.

Any changes in concomitant medication will be recorded throughout the study, from Day 1 until end of study at Week 59.

8.2.2. Physical Examinations

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 first dose of study drug.

8.2.3. Vital Signs

Vital signs will be measured in a sitting position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

8.2.4. Physical Measurements

Height and weight measurements are to be performed at the timepoints indicated in the SoA and data will be recorded in centimeters and kilograms respectively. Height and weight are to be measured without shoes.

8.2.5. Electrocardiograms

Triplicate 12-lead ECGs will be obtained after subject has been supine for at least 5 minutes as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT intervals.

8.2.6. Chest X-ray

Only subjects with a positive or indeterminate IGRA TB test will undergo a chest x-ray (posterior/anterior or anterior/posterior). A subject must not be included in the study if his/her chest x-ray reveals evidence of active TB (refer to Section 5.1). Women of childbearing potential must have a negative pregnancy test before an x-ray is performed.

8.2.7. Clinical Safety Laboratory Tests

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the subject's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 8 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
    - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
    - All protocol-required laboratory tests, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    - If laboratory values from non-protocol-specified laboratory tests performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded within source documents.

8.2.8. Tuberculosis Test

Determination of TB status will be required before the subject's inclusion in the study. An IGRA TB test (QuantiFERON recommended), chest x-ray (unless already performed within 3 months prior to screening), and examination for signs and symptoms of TB will be performed on each

subject to assess TB status at screening. Table 8-1 provides TB terms and definitions for the purpose of the study, and Table 8-2 provides guidance for handling various TB test results.

Table 8-1. Tuberculosis Terms and Definitions

Term	Definition
Known TB	• Active TB or presence of symptoms (pulmonary or extra-pulmonary) consistent with TB • History of active TB or findings consistent with TB, unless there is documented evidence of completed treatment and clinical resolution, by a TB specialist • Radiological or other imaging modalities findings consistent with previously active TB that is not reported in the subject's medical history
High risk of acquiring TB	• Close contact with a person with active TB within the 3 months prior to screening • Working in or attending a healthcare setting or facility housing persons with TB where there is a high risk of transmission
Latent TB	• Positive IGRA TB test (or 2 indeterminate IGRA TB test results) with absence of symptoms (pulmonary or extra-pulmonary) and radiological or other imaging modalities findings consistent with active TB • If available, respiratory or other specimens must also be smear and culture negative for TB (Center for Disease Control diagnosis of latent TB; http://www.cdc.gov/TB/topic /testing/default.htm)
Nontuberculous mycobacterial infection	• Clinical manifestation of infection caused by mycobacteria species other than M tuberculosis

CDC = Centers for Disease Control and Prevention; IGRA = interferon-gamma release assay; TB = tuberculosis; WHO = World Health Organization

Table 8-2. Tuberculosis Testing Results and Required Actions

Initial IGRA TB Test[a] Results for Eligibility		
Negative	**Indeterminate**	**Positive**
Required action		
No further action is needed, subject is eligible for the study	Repeat IGRA TB test (must be completed during the protocol-defined screening period) • If negative, no further action is needed, subject is eligible for the study • If indeterminate or positive, subject must be referred to a TB specialist for further evaluation ○ If subject is determined to be negative for latent or active TB by the TB specialist, subject is eligible for the study ○ If diagnosed with active TB by the TB specialist, subject is **NOT** eligible for the study ○ If diagnosed with latent TB by the TB specialist, eligibility must be discussed with the medical monitor and the subject must complete at least 4 weeks of prophylaxis in accordance with WHO/CDC guidelines prior to first dose of study drug and continue to the full treatment course to completion	• Subject must be referred to a TB specialist for further evaluation ○ If subject is determined to be negative for latent or active TB by the TB specialist, subject is eligible for the study ○ If diagnosed with active TB by the TB specialist, subject is **NOT** eligible for the study ○ If diagnosed with latent TB by the TB specialist, to be eligible for the study, subject must complete at least 4 weeks of prophylaxis in accordance with WHO/CDC guidelines prior to first dose of study drug and continue to the full treatment course to completion

CDC = Centers for Disease Control and Prevention; IGRA = interferon-gamma release assay; TB = tuberculosis; WHO = World Health Organization
[a]QuantiFERON recommended.

8.2.9. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing in WOCBP will be conducted throughout the study. A serum pregnancy test will be performed at screening and urine pregnancy testing will be performed at subsequent visits as detailed in the SoA (Section 1.3).

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation or regulatory agency, to establish the absence of pregnancy at any time during the subject's participation in the study.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

8.2.10. IBD Screening

Given that subjects with HS appear to have a higher lifetime risk of IBD compared with the general population and given that approved IL-17 inhibitors have reported worsening or new onset IBD in clinical studies, all subjects will be screened for IBD by history and a subset will undergo additional laboratory screening.

During screening, all subjects will be assessed for the following symptoms within the last year:

- prolonged or recurrent diarrhea without established etiology
- prolonged or recurrent abdominal pain without established etiology
- blood in stool without established etiology
- any other symptoms in the opinion of the investigator that may be suggestive of IBD. If any are marked affirmative, a fecal calprotectin test must be performed.
- If the resulting fecal calprotectin level is > 150 to 500 µg/g, the subject must undergo a gastrointestinal consultation and obtain documented approval from the gastrointestinal consultation to enroll in the clinical study before continuing with the screening process. If the consultation cannot be completed within the screening window, the subject will be screen failed but may rescreen.
- Fecal calprotectin levels > 500 µg/g will be exclusionary.

8.2.11. Suicidal Ideation and Behavior Risk Monitoring

Subjects with HS may occasionally develop suicidal ideation or behavior. Furthermore, suicidal ideation and behavior has been identified as a potential risk with other IL-17 class products.

Suicidal ideation and behavior will be assessed during the study by trained study personnel using the C-SSRS. The visits at which the C-SSRS assessments will be performed are specified in the SoA (Section 1.3). The C-SSRS is a standardized and validated instrument developed for the assessment of the severity and frequency of suicidal ideation and behavior (Posner et al, 2011). Subjects respond to standardized clinical questions that are presented in a uniform fashion. The C-SSRS defines 5 subtypes of suicidal ideation and behavior in addition to self-injurious behavior with no suicidal intent. The C-SSRS takes approximately 3 to 10 minutes to complete.

Subjects should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of study drug. Subjects who experience signs of suicidal ideation and behavior should undergo a risk assessment which may or may not include examination by a mental health care

professional. All factors contributing to suicidal ideation and behavior should be evaluated and consideration should be given to discontinuation of the study drug.

8.2.12. Home Study Drug Administration Diary

The subject (or caregiver/designee) will complete a diary for every study dose taken outside of the site (ie, at home). The study drug should be administered on the dates as directed by the site staff. Information regarding the study drug administration (eg, date and time of study drug administration, if the full dose was administered) will be recorded on the study drug administration diary. Instructions on proper study drug administration will be provided to the subject (caregiver/designee). Subjects will be instructed to call the site if they are having problems administering the study drug or have missed or delayed administering a dose. Subjects will be instructed to bring the study drug administration diary to each study visit.

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

The definitions of AEs and SAEs can be found in Section 10.3.1 and Section 10.3.2, respectively.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, 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 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 (see Section 7).

Currently all SAEs require immediate reporting by the investigator to ACELYRIN. There are no SAEs that do not require immediate reporting. If this changes during the study, the protocol will be amended, as appropriate.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.3 and Section 10.3.4, respectively.

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

All SAEs will be collected from the signing of the ICF until the 8-week follow-up visit as specified in the SoA (Section 1.3).

All AEs will be collected from the first dose of study drug until 4 weeks after the last dose of study drug as specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded as medical history/current medical conditions, not as AEs.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from investigator's knowledge of the event, as

indicated in Section 10.3.4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after the conclusion of the study participation. However, if the investigator learns of any SAE, including death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably related to the study drug or study participation, the investigator must promptly notify the sponsor or its designee (see Section 10.3.4).

8.3.2. Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

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

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 10.3.2 and Section 8.3.6, respectively) will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3.3.

8.3.4. Regulatory Reporting Requirements for Serious Adverse Events

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study drug under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators. This includes reporting of events that meet suspected unexpected serious adverse reaction (SUSAR) criteria via Eudravigilance, as applicable.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female subjects and, if indicated, female partners of male subjects will be collected after the start of study drug and until 8 weeks after the last dose of study drug.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor or designee within 24 hours of learning of the

female subject or female partner of male subject (after obtaining the necessary signed informed consent from the female partner) pregnancy.

- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The subject/pregnant female partner will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject/pregnant female partner and the neonate, and the information will be forwarded to the sponsor or designee.
- Any post-study pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor or designee as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study subjects/pregnant female partner, they may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study will discontinue study drug.

8.3.6. Adverse 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
- IBD
- 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)
- TB
- Infections (opportunistic, serious, or fungal only)
- Cytopenias (anemia, neutropenia, lymphopenia, monocytopenia, thrombocytopenia)
- Systemic hypersensitivity reactions.

8.3.7. Overdose

These events are only considered AEs or SAEs if there are associated clinical signs and symptoms or if the act of taking the excess medicine itself is an AE or SAE (eg, suicide attempt). Refer to Section 6.7.

If an overdose occurs associated with an SAE in the course of the study, then the investigator follows the immediate safety reporting requirement for SAE with describing the overdose in an SAE description.

8.4. Pharmacokinetics

- Blood samples will be collected for measurement of plasma concentrations of izokibep as specified in the SoA (Section 1.3).
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual by the sponsor or designee. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of izokibep. Each plasma sample may be divided into 2 aliquots (1 each for PK and a backup). Samples collected for analyses of izokibep (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Genetic analyses will not be performed on these plasma samples.
- Study drug concentration information will not be reported to investigative sites.
- Pharmacokinetic samples collected may be used for assay validation and related assay development purposes.
- Pharmacokinetic samples will be shipped frozen from clinical sites to the central laboratory and later shipped from central laboratory to the PK laboratory for analysis. The PK plasma samples will be stored in a secure storage space with adequate measures to protect confidentiality.
- The PK samples will be retained while research on izokibep or study drugs of this class or HS continues but no longer than 20 years or other period as per local requirements.

8.5. Genetics

Genetics are not evaluated in this study.

8.6. Biomarkers (United States Only)

- Serum and blood (PAXgene) samples will be collected for exploratory biomarker analysis as specified in the SoA (Section 1.3). These samples will be tested by the sponsor or sponsor's designee.
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual by the sponsor or designee.
- Samples will be used to assess biomarkers of anti-IL-17A treatment and biomarkers associated with HS efficacy. mRNA transcriptomic analyses will be performed on the whole blood PAXgene samples.
- Exploratory biomarker samples will be shipped frozen from clinical sites to the central laboratory and later shipped from central laboratory to the laboratory for analysis. The

samples will be stored in a secure storage space with adequate measures to protect confidentiality.

- The exploratory samples will be retained while research on izokibep or study drugs of this class or HS continues but no longer than 20 years or other period as per local requirements.

8.7. Immunogenicity Assessments

- Antibodies to izokibep will be evaluated in serum samples collected from all subjects according to the SoA (Section 1.3). Additionally, serum samples should also be collected at the final visit from subjects who discontinued study drug or were withdrawn from the study. These samples will be tested by the sponsor or sponsor's designee.
- Instructions for the collection and handling of biological samples will be provided in the Laboratory Manual by the sponsor or designee.
- Samples testing positive for binding antibodies may be further characterized and may be tested for neutralizing antibodies.
- The detection and characterization of antibodies to izokibep will be performed using a validated assay method by or under the supervision of the sponsor.
- Antibody samples collected may be used for assay validation and related assay development purposes.
- ADA serum samples will be shipped frozen from clinical sites to the central laboratory and later shipped from the central laboratory to the ADA laboratory for analysis. The ADA serum samples will be stored in a secure storage space with adequate measures to protect confidentiality.
- Samples will be retained while research on izokibep or study drugs of this class or HS continues but no longer than 20 years or other period as per local requirements.

8.8. Health Economics

Refer to Section 8.1.9 EQ-5D and Section 8.1.10 Short Form-12v2.

9. Statistical Considerations

This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.1. Statistical Hypotheses

The primary objective of this study is to demonstrate that izokibep is superior to placebo in the proportion of subjects achieving HiSCR75 at Week 12 of the study. 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 achieving HiSCR75 at Week 12 among subjects randomly assigned to receive izokibep and placebo, respectively.

Analogous statistical hypotheses will be used for the secondary objective of assessing the percentage of subjects who achieve HiSCR90 at Week 12, who achieve HiSCR100 at Week 12, who achieve HiSCR50 at Week 12, who experience a flare through Week 12, who achieve an AN count of 0, 1, or 2 at Week 12, or who achieve a 3-point reduction in pain NRS at Week 12. For the last secondary objective, to demonstrate that izokibep is efficacious compared with placebo, as measured by change in DLQI, the statistical null and alternative hypotheses are:

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

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

where μ_{ABY} and μ_{PBO} are the mean changes in DLQI from baseline to Week 12 among subjects randomly assigned to receive izokibep and placebo, respectively.

9.1.1. Multiplicity Adjustment and Type I Error Rate

Hypotheses tested will be adjusted to control the familywise error rate in the strong sense at $\alpha = 0.050$, 2-sided.

As described in Section 9.4, 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 for the primary efficacy endpoint and the secondary endpoints, all at Week 12, will be carried out in sequential order. The primary endpoint, comparing izokibep to placebo, will be tested first, with significance concluded if $p < 0.0499$. Testing of secondary endpoints will only be carried out if all prior tests, including the test of the primary endpoint, first show significance with $p < 0.0499$. If all prior tests are significant, testing will proceed in the following order:

- The first secondary endpoint, proportion of subjects achieving HiSCR90 at Week 12.
- The second secondary endpoint, proportion of subjects achieving HiSCR100 at Week 12.

- The third secondary endpoint, proportion of subjects achieving HiSCR50 at Week 12.
- The fourth secondary endpoint, proportion of subjects who experience flares through Week 12.
- The fifth secondary endpoint, change in DLQI from baseline to Week 12.
- The sixth secondary endpoint, achieving AN count of 0, 1, or 2 at Week 12 among subjects with baseline Hurley Stage II.
- The seventh secondary endpoint, proportion of subjects who achieve a reduction in pain NRS of at least 3 points from baseline to Week 12, among subjects with a pain NRS score of at least 4 at baseline.

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.

9.2. Analysis Sets

The following analysis sets will be used for reporting.

Full Analysis Set (FAS)

For assessing the primary and secondary efficacy objectives, all subjects randomized will be included in the analyses as FAS. Intercurrent events such as missed assessments, missed or discontinued treatment, and protocol deviations, will be addressed as described in the definition of the estimands in Section 9.3. Subjects will be included according to randomized treatment.

For assessment of the sixth secondary endpoint, the proportion of subjects who achieve AN of 0, 1, or 2 at Week 12, only the subset of subjects in the FAS who have Hurley Stage II at baseline will be included in the assessment. For the seventh secondary endpoint, achievement of a reduction in pain NRS of at least 3 points, only the subset of subjects in the FAS who have pain NRS of at least 4 at baseline will be included in this assessment. Both will be called the FAS for reporting purposes.

The FAS analyses for timepoints after Week 16 will include all subjects who receive any amount of izokibep at or after Week 16. Subjects will be summarized according to the original randomization (izokibep or placebo) for such summaries.

Safety Analysis Set

For assessing the safety objectives, all subjects randomized who receive at least 1 administration of test material will be included in the summaries and analyses. If a subject receives incorrect study treatment, that subject will be grouped according to treatment received. If a subject receives both treatments, the subject will be grouped with the treatment received most often.

The safety analysis set summaries for timepoints after the Week 16 visit will include all subjects who receive any amount of izokibep at or after Week 16 visit. Subjects will be summarized according to the original randomization (izokibep or placebo) for such summaries.

PK Analysis Set

For assessing PK parameters, all subjects who receive at least 1 administration of test material and have at least 1 sample collected and analyzed for drug concentration will be included in summaries and analyses.

ADA Analysis Set

For assessing ADA, all subjects who receive at least 1 administration of test material and have both baseline ADA and at least 1 post-dose ADA measurement will be included in summaries and analyses.

9.3. Statistical Analyses

9.3.1. General Considerations

All data collected will be summarized by planned timepoint without imputation. Continuous data will be summarized with count, mean, median, standard deviation, minimum, and maximum. Change from baseline will additionally include standard error. Categorical data will be summarized with count and percent. Time to event data will be summarized with product-limit estimators of median and quartiles.

All hypothesis tests will be reported with 2-sided p-values. All CIs will be 2-sided with nominal 95% coverage. Hypotheses tested will be adjusted to control the familywise error rate in the strong sense at $\alpha = 0.050$, 2-sided. All hypothesis tests will use a type I error rate of 5%.

Data will be summarized by planned timepoint, using data collected at the visit. Study day will be calculated as post-baseline date minus randomization date, plus 1 (except that study day for pre-randomization dates will not include the plus 1). Day range windows will not be applied for summaries (but may be applied for protocol deviations). Baseline values will be the last value collected before randomization and change from baseline will be calculated as post-baseline value minus baseline value.

Stratified tests will use the 4 strata from the randomization process. If a subject is incorrectly classified during the randomization process, the analysis will use the correct classification, not the classification used during randomization.

After Week 16, efficacy and safety data will be summarized. Data for subjects who were randomly assigned to receive placebo during the first 16 weeks will be summarized separately from data for subjects who were randomly assigned to receive izokibep during the first 16 weeks.

Subgroup analyses (including, age, race, sex, baseline disease characteristics, geography, concomitant antibiotic use, and other factors) will be reported.

Any deviation from the planned analyses made after breaking the blind will be documented in the clinical study report.

9.3.2. Primary Endpoint and Estimand

The primary endpoint 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, as defined in Section 8.1.1. The primary timepoint for analysis is Week 12.

The treatment policy strategy approach for the estimand will be used in general for intercurrent events, so subjects will be included using observed data at Week 12 regardless of treatment compliance, use of rescue medications except as noted below, or any other protocol deviations.

The null hypothesis of equal response rates will compare the izokibep group to the placebo group. A stratified test of response rates will be used. Within each of the 4 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 4 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 other timepoints when data to calculate the HiSCR75 scores are collected will also be presented using the same methodology. The p-values from earlier timepoints will be presented for descriptive purposes and will not be part of the alpha-preserving multiple testing strategy.

Subjects who receive antibiotic therapy that could affect HS will be included in the primary analysis by assigning non-response at subsequent timepoints. 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. Similarly, subjects who discontinue treatment due to an AE or lack of efficacy, and subsequently have missing efficacy responses, will be included by imputing non-response. Other subjects with missing data will have efficacy data imputed using multiple imputation. The imputation model will use data from placebo subjects and include baseline characteristics and demographics, factors used for stratification of randomization, and observed efficacy at earlier timepoints, and will be fully defined before unblinding. The model will impute components of the primary endpoint (abscess count, inflammatory nodule count, and draining tunnel count) separately. The imputation model will be run multiple times (eg, 100 times) and the results analyzed for each run using the primary analysis methodology. Results from all runs will be combined using Rubin's rule, resulting in a single point estimate, a single CI, and a single p-value. The number of subjects imputed with non-response imputation and the number imputed with multiple imputation will be tabulated with reasons for imputation at Week 12.

Supportive analyses using other assumptions about ICEs will also be reported. These will be defined before the database is locked and treatment assignments are unblinded.

9.3.3. Secondary Endpoints and Estimands

The secondary endpoints are HiSCR90; HiSCR100; HiSCR50; percentage of subjects who experience flare through Week 12; percentage of subjects with baseline Hurley Stage II who achieved an AN count of 0, 1, or 2; percentage of subjects with a decrease in pain score of at

least 3 points at Week 12; and change in DLQI at Week 12. The treatment policy strategy will be used to construct estimands for each secondary endpoint analogously to the primary estimand, except as noted below.

The secondary endpoint of experiencing flare will be analyzed using multiple imputation for subjects who have missing assessments. All subjects with missing abscess, inflammatory nodule, and draining tunnel counts will be included using multiple imputation, analogously to the analysis of the primary endpoint.

The secondary endpoint of pain score will use a hybrid estimand, with treatment policy strategy used for most ICEs and hypothetical strategy used to account for use of prohibited pain medications due to non-HS-related pain, when taken near a visit. All pain scores after such use of prohibited pain medication will be omitted from the dataset and replaced via multiple imputation in a model analogous to that used for multiple imputation of the primary endpoint. The imputed pain scores will be used to determine which subjects meet the criteria of a decrease of at least 3 points. Sensitivity analyses will include a nonlinear mixed effects model with repeated measures (MMRM), using observed change in pain score at all scheduled post-baseline assessments.

The secondary endpoints of percentage of subjects who experience flare and percentage of subjects with baseline Hurley Stage II who achieved AN count of 0, 1, or 2 will be analyzed analogously to the primary endpoint. 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.

The secondary endpoint of change in DLQI will use MMRM to account for subjects with missing data. The factors used for stratification will be included as covariates in the model, as will baseline DLQI score.

9.3.4. Exploratory Endpoints

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. 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.

Pharmacokinetic concentration data will be summarized at all planned collections with mean, geometric mean, minimum, and maximum. Pharmacokinetic data collected from this study may also be combined with PK data collected from other studies for comprehensive modeling of drug concentrations.

9.3.5. Safety Analyses

Safety data will include summaries of exposure, AEs, SAEs, and laboratory data. No inferential statistics (p-values) will be reported for safety data.

Exposure will include the number of doses administered (including complete and incomplete doses) and reasons for missed or incomplete doses. Exposure will be reported through the planned collection at Week 12, Week 16, and for the entire study. For subjects assigned to receive placebo who later receive izokibep, exposure will further be summarized by placebo and izokibep.

Adverse events and SAEs reported before the first administration of study drug will be listed. All summaries will include only treatment-emergent events. The number of subjects who report 1 or more AEs, the number who report 1 or more severe AEs, the number who report 1 or more SAEs, and the number who report 1 or more AEs that leads to discontinuation of study drug will be summarized by treatment during the primary phase of the study and overall. Subjects who receive placebo during the primary phase will additionally be summarized by phase (placebo-controlled and after crossing over to active).

Laboratory data and vital signs will be summarized at each planned collection timepoint. Subjects with positive ADA results will be summarized by timepoint.

9.4. Interim Analysis and Early Stopping Rules

Data may be summarized for a DMC at regular intervals during the study to ensure safety of study subjects. The type I error rate for hypothesis tests at the end of the study will be decreased by 0.0001 to account for each interim summary of unblinded data. An assessment for futility may be performed at the DMC, when at least 100 randomized subjects (50 subjects in each arm) have completed the Week 12 visit or permanently discontinued the study early.

The futility assessment, if undertaken, will be based on a combination of the calculated conditional power and the observed difference between treatment groups of selected study efficacy endpoints, calculated using the interim data cut.

The details of the futility analysis plan including futility criteria; logistics of generating data, reviewing unblinded data; and making nonbinding recommendation to sponsor will be documented before any unblinding of the data. The sponsor will not see the unblinded data unless the DMC determines it is necessary for the sponsor to understand a recommendation to stop the study for futility.

After all subjects have had an opportunity to complete the Week 12 visit (complete the visit, or complete a subsequent visit, or permanently discontinue the study before Week 12), the primary endpoint analyses may be conducted. 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 and the database lock has occurred.

At various points after the primary analysis, analyses of data collected after Week 12 will be reported for regulatory submission purposes or other reasons. These analyses will be documented. No adjustment to the type I error rate will be applied due to these summaries, because the inferential statistics will already have been determined.

9.5. Sample Size Determination

In prior studies (Glatt et al, 2021; Kirby et al, 2022), HiSCR75 response rates among placebo recipients after 12 to 16 weeks of treatment have been approximately 10% to 20%. At Week 12 in this study, HiSCR75 response rates are expected to be 15% for placebo recipients and 35% for izokibep recipients. With 125 subjects receiving each treatment, this study will have approximately 95% power to demonstrate a difference in HiSCR75 response rates between arms. This calculation uses an unstratified test, with $\alpha = 0.05$, two-sided.

10. Supporting Documentation and Operational Considerations

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines.
    - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines.
    - Applicable laws and regulations, including 21 Code of Federal Regulations (CFR) and European Regulation 536/2014 for clinical studies.
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following, as applicable:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies, and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or the investigator's representative will explain, in a language and at a level of complexity understandable by the subject, the nature of the study, including the risks and benefits, to the potential subject and answer all questions regarding the study and its alternatives.
- Potential subjects must be informed that their participation is voluntary, and they may withdraw their consent to participate in the study at any time. They will be required to sign and date a statement of informed consent that meets the requirements of 21 CFR 50, Clinical trials Regulation (EU) 536/20141, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is amended during the study, subjects must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject.
- A subject who is rescreened is not required to sign another ICF if the rescreening occurs within 30 days from the previous ICF signature date.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier to pseudonymize the subject records by the IXRS. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred to the sponsor.
- Subjects' data will be captured in an electronic cloud-based data capture system. Access to the production servers requires multi-factor authentication through a virtual private network and all communication is encrypted. Access to the public facing application is encrypted via transport layer security encryption protocols. Transport layer security is provisioned to help ensure secure transmission over the Internet for the platform. In addition, a virtual firewall is utilized to restrict access.
- The subject must be informed that the subject's personal study-related data will be used by the sponsor in accordance with the data protection and privacy principles set forth by institutional policies, regulatory agencies, local and country-specific laws, regulations, and guidelines including the European Union General Data Protection Regulation [2016/679] ("GDPR") or other country-specific privacy regulation. The level of disclosure must also be explained to the subject who will be required to give consent for their data to be used as described in the informed consent.
- The subject must be informed that their personal study-related data may be transferred by or on behalf of the sponsor to countries outside the country where the study subject's personal data is being collected. In any event, these transfers will be in accordance with all applicable data protection laws including Article 46 of the GDPR, and that the sponsor has implemented measures to ensure that the subject's personal study-related data will remain protected at all

times to the same level as required in the country where the study subject's personal data is being collected. Subjects will also be advised of their rights under applicable data protection laws to access and control their personal data and documented via informed consent.

- The subject must be informed that the subject's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from competent regulatory authorities, including in the United States.
- The sponsor and investigator will implement appropriate measures to monitor and identify any breach of security leading to accidental or unlawful destruction, loss, alteration, unauthorized disclosure or access to that data (a "data breach"). In the event of a personal data breach, the sponsor and investigator will take appropriate measures to address the breach, including measures to mitigate its adverse effects. The investigator will notify the sponsor or its designee without undue delay after having become aware of the breach. Such notification will contain the details of a contact point where more information can be obtained, a description of the nature of the breach (including, where possible, categories and approximate number of data subjects and personal data records concerned), its likely consequences, and the measures taken or proposed to address the breach including, where appropriate, measures to mitigate its possible adverse effects. Upon becoming aware of any data breach, the sponsor and investigator will ensure that all competent data protection authorities are notified of the breach, where required by local regulations. Where feasible and permissible by applicable law, such notification will occur within 72 hours of the responsible controller becoming aware of the data breach. Such notification will contain the details of a contact point where more information can be obtained, a description of the nature of the breach in accordance with applicable laws, its likely consequences, and the measures taken or proposed to address the breach including, where appropriate, measures to mitigate its possible adverse effects.
- Considering the nature, scope, context and purpose of the processing, and the risks for the rights and freedoms of natural persons, the investigator will implement technical and organizational measures to ensure adequate security and confidentiality of the data. Such measures will include without limitation pseudonymization and data encryption in transit and at rest. Additional measures may include measures to prevent unauthorized physical access to premises and facilities holding personal data; logical identity and access management procedures to prevent authorized users from accessing data beyond their authorized access rights and the unauthorized input, reading, copying, removal, modification, or disclosure of personal data; and network perimeter and endpoint protection using firewalls and other intrusion detection systems. All such measures will be in accordance with regularly updated documented policies taking account of the state-of-the-art, and regular training of all personnel responsible for the processing of personal data.

10.1.5. Dissemination of Clinical Study Data

The results of the study will be reported in a clinical study report generated by the sponsor and will contain eCRF data from all sites that participated in the study. Recruitment performance or specific expertise related to the nature and the key assessment parameters of the study will be used to determine a coordinating investigator. Study subject identifiers will not be used in publication of results. Any work created in connection with the performance of the study and

contained in the data that can benefit from copyright protection (except any publication by the investigator see Section 10.1.9) shall be the property of the sponsor as author and owner of copyright in such work.

Registration of Clinical Studies and Disclosure of Results

The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law including posting company-sponsored study information on the US National Institutes of Health's website www.clinicaltrials.gov.

10.1.6. Monitoring and Data Quality Assurance

- Qualified, assigned monitors from the sponsor (or designee) will conduct regular on-site and remote monitoring visits to monitor various aspects of the study. These visits and communications, along with regular inspection of the eCRFs, will be conducted to assess subject enrollment, compliance with protocol procedures, completeness and accuracy of data entered on the eCRFs, verification of data against source documents, and occurrence of AEs, etc. The investigator must provide the monitor with full access to all source and study documents.
- All subject data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by signing the eCRF.
- Guidance on completion of eCRFs will be provided.
- The investigator or site staff will promptly report to the sponsor (or designee) all deviations that occur at their clinical site, and report protocol deviations to their IRB/EC according to local requirements.
- Sponsor (or designee) may audit investigator sites regarding, but not limited to, the informed consent process, presence of required documents, adherence to protocol, accountability and storage of drug supplies, comparison between eCRF with source documents, etc. All medical records and study-related documents must be available for audit, and the investigator and study staff agree to participate and cooperate in audits conducted in a reasonable manner.
- Government regulatory authorities and ethics committees may also inspect the investigator site during or after the study. The investigator or designee should contact the sponsor (or designee) immediately if this occurs. The investigator must cooperate fully with regulatory authorities or other audits conducted in a reasonable manner.
- The sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (eg, CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be

retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.

- No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- Quality Tolerance Limits will be defined before the start of the study and monitored by the CRO and sponsor during the study. They will also be reported in the clinical study report.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments. Information from medical records and other source documents will be promptly transcribed to the appropriate section of the eCRF. The eCRF is not considered and should not be used as source documentation.
- Data reported on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.8. Study and Site Start and Closure

Study Start

The study start date is the date on which the first subject is enrolled into the study.

Study/Site Termination

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

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

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

For study termination:

- Discontinuation of further study drug development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the investigator
- Total number of subjects included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator should promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements.

10.2. Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- All study-required laboratory tests will be performed by a central laboratory, with the exception of:
  - urine pregnancy test
- Investigators must document their review of each laboratory safety report.

Table 10-1. Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC indices: Mean corpuscular volume Mean corpuscular hemoglobin %Reticulocytes	White blood cell count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical chemistry[a,b]	HemoglobinA1C	Alanine aminotransferase/serum glutamic-pyruvic transaminase	Alkaline phosphatase[c]	Aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
	Blood urea nitrogen	Calcium	C-reactive protein[d]	Creatinine
	Glucose (nonfasting)	High-density-lipoprotein (HDL) (fasting)	Triglyercides (fasting)	Potassium
	Sodium	Total cholesterol (fasting)	Total and direct bilirubin	Total protein
Coagulation	International normalized ratio (INR)			
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 pregnancy test (as needed for women of childbearing potential) at screening[e]			
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Hepatitis B virus testing: hepatitis B surface antigen, hepatitis B surface antibodies, hepatitis B core antibodies, hepatitis B virus DNA • Hepatitis C virus testing: hepatitis C antibody • Human immunodeficiency virus testing • Interferon-gamma release assay (IGRA) tuberculosis testing (QuantiFERON recommended) • Fecal calprotectin			
Other tests	• Pharmacokinetics • Anti-drug antibody • Exploratory biomarkers (United States Only)			

[a] Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.1 Liver Chemistry Stopping Criteria and Section 10.5 Liver Safety: Suggested Actions and Follow-up Assessments.
[b] Estimated glomerular filtration rate will be calculated at screening using the modification of diet in renal disease study equation.
[c] If alkaline phosphatase is elevated, consider fractionating.
[d] Post-baseline C-reactive protein results will be blinded to sites/investigators.
[e] After screening, local urine pregnancy testing will be performed unless serum testing is required by local regulation, regulatory agency, or Institutional Review Board/Independent Ethics Committee.

10.3. AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease, or more severe than expected for the subject's condition)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE

Events <u>NOT</u> Meeting the AE Definition

- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the first dose of study drug that do not worsen; such events should be recorded as medical history eCRF
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions not resulting in hospitalization, or development of intervention dependency or intervention abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the required eCRF and SAE Report Form (if applicable).
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee of in lieu of completion of the required eCRF and SAE Report Form (if applicable).
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, **should be fully redacted** on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The investigator is responsible for assessing the severity for each AE and SAE according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0:

- **Mild (Grade 1)**: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- **Moderate (Grade 2)**: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- **Severe (Grade 3)**: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL. Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- **Life-threatening (Grade 4)**: Life-threatening consequences; urgent intervention indicated.
- **Death (Grade 5)**: Events that result in death.

Many common AEs are able to be graded according to CTCAE. Adverse events that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in CTCAE version 5.0 as stated above. Additional considerations when assessing severity are outlined below:

- The seriousness of an AE should not be confused with its severity. Severity is a measure of intensity (eg, Grades 1 through 5 or mild, moderate, severe), whereas seriousness is based on subject/event outcome as defined by the criteria in Section 10.3.2.
- It is important to distinguish between category (AE versus SAE) and intensity (Grades 1 to 5) of AEs. Seriousness, not severity, serves as a guide for defining regulatory reporting obligations.
- An AE of severe intensity is not necessarily considered serious. For example, nausea that persists for several hours may be considered grade 3 nausea, but not an SAE. On the other hand, minor cardiac chest pain that results in hospitalization may be considered grade 1 but would be an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE. The investigator will use clinical judgment in the assessment of causality according to the following categories:
  - **Not related**: Another documented cause of the AE is most plausible; and/or the administration of study drug and occurrence of AE are not reasonably related in time; and/or causal relationship is considered biologically implausible.
  - **Related**: There is clear evidence to suggest that the AE is more likely explained by the study drug and other possible contributing factors can be ruled out; a causal relationship is clinically/biologically plausible, and there exists a plausible time sequence between onset of the AE and administration of the study drug.

Additional factors in the assessment of causality include the following:

- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration, will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or product information, for marketed products, in his/her assessment.

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor or designee.
- The investigator may change his/her opinion of causality considering follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to the sponsor/designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor/Designee via the SAE Report Form

- The primary mechanism for reporting an SAE to the sponsor/designee will be the SAE Report Form.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours from investigator's knowledge of the event.
- Email transmission of the SAE Report Form is the preferred method to transmit this information to the sponsor/designee.
- In the rare circumstance email is not available, the SAE Report Form may be sent by facsimile as a backup reporting method.
- Investigator signature is required to be collected on the SAE Report Form prior to submission. With rare exception, the form may be sent without signature to meet the reporting deadline; however, investigator signature is required to be obtained as soon as possible after submission.
- Contacts for SAE reporting can be found on the SAE Report Form.

10.3.5. AEs and Laboratory Abnormalities That Could Lead to Discontinuation of Study Drug

The following lists should not be viewed as exhaustive but serve to provide examples of AEs and laboratory abnormalities that could lead to a decision to discontinue the subject from study drug.

AEs:

- SAE or AE CTCAE version 5.0 grade 3, considered related to study drug
- serious infections (eg, sepsis) that cannot be adequately controlled within 4 weeks by anti-infective treatment or may put the subject at risk by continued administration of study drug, as determined by the investigator
- malignancy, except for localized non-melanoma skin cancer or carcinoma in situ of the cervix
- CTCAE version 5.0 grade 3 or higher cardiovascular AE(s) that would put the subject at risk by continued administration of study drug, as determined by the investigator or medical monitor
- CTCAE version 5.0 grade 4 AE (life-threatening consequences; urgent intervention indicated, considered related to study drug)
- subject develops an illness where, in the opinion of the investigator, the risk of continuing with study drug outweighs the potential benefit
- subject with newly diagnosed IBD during the study
- active suicidal ideation as indicated by a positive response (Yes) to questions 4 or 5 of the C-SSRS, or any suicidal behavior since the last visit
- liver chemistry stopping criteria (see Section 7.1.1)

Laboratory abnormalities:

- neutrophil count < 1.0 × 109/L
- platelets < 50 000/mm3
- hemoglobin < 8.5 g/dL with decrease of at least 2 g/dL from baseline
- creatinine >2 × baseline
- any other laboratory abnormality that may put the subject at risk by continued administration of study drug, as determined by the investigator

10.4. Contraceptive and Barrier Guidance

10.4.1. Definitions

Woman of Childbearing Potential
Women in the following categories are considered WOCBP (fertile):

1. Following menarche

- From the time of menarche until becoming postmenopausal unless permanently sterile (see below)
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than 1 FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator's discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

- If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

10.4.2. Contraception Requirements

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: Documentation of azoospermia for a male subject can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation – oral – intravaginal – transdermal – injectable
Progestogen-only hormone contraception associated with inhibition of ovulation – oral – injectable
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject.)*
Effective Methods[c] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)

[a] Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

[b] Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

[c] Considered effective but not highly effective - failure rate of ≥ 1% per year.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condoms and female condoms should not be used together (due to risk of failure from friction).

10.5. Liver Safety: Required Actions and Follow-up Assessments

Phase 2 liver chemistry stopping criteria are designed to assure subject safety and to evaluate liver event etiology. The guidelines provided below are based on the European Association for the Study of the Liver Clinical Practice Guidelines: Drug-induced Liver Injury (2019) and Food and Drug Administration 2009 Guidance for Industry Drug-induced Liver Injury: Premarketing Clinical Evaluation.

Phase 2 Liver Chemistry Stopping Criteria and Follow-up Assessments

Liver Chemistry Stopping Criteria	
ALT or AST-absolute	ALT or AST ≥ 5 × ULN
ALT or AST Increase	ALT or AST ≥ 3 × ULN persists for ≥ 4 weeks
Bilirubin[a,b]	ALT or AST ≥ 3 × ULN **and** total bilirubin ≥2 × ULN (> 35% direct bilirubin)
International Normalized Ratio (INR)[b]	ALT or AST ≥ 3 × ULN **and** INR > 1.5
Cannot Monitor	ALT or AST ≥ 3 × ULN and cannot be monitored twice weekly for 4 weeks
Symptomatic[c]	ALT or AST ≥ 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Suggested Actions, Monitoring, and Follow-up Assessments	
Actions	**Follow-up Assessments**
• **Immediately** discontinue study drug. • Report the event to the sponsor/designee **within 24 hours**. • Complete an SAE eCRF if the event met the criteria for an SAE.[b] • Perform follow-up assessments as described in the Follow-up Assessment column. • Monitor the subject until liver chemistry test abnormalities resolve, stabilize, or return to baseline.	• Viral hepatitis serology.[c] • Obtain blood samples for PK analysis after the most recent dose.[d] • Obtain serum creatine phosphokinase, lactate dehydrogenase, gamma glutamyl transferase, glutamate dehydrogenase, and serum albumin. • Fractionate bilirubin if total bilirubin ≥ 2 × ULN. • Obtain complete blood count with differential to assess eosinophilia.

MONITORING: **<u>If ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver event follow-up assessments within **24 hours**. • Monitor subject twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A hepatology consultation is recommended. **<u>If ALT or AST ≥ 3 × ULN AND total bilirubin < 2 × ULN and INR ≤1.5:</u>** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, total bilirubin, and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours**. • Monitor subjects twice weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline, or the study drug has been discontinued; then decrease monitoring to once weekly or less. • **Do not restart/rechallenge** subject with study drug unless allowed per-protocol and sponsor approval is granted.	• Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the eCRF. • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF. • Record alcohol use on the liver event alcohol intake form. If ALT or AST ≥ 3 × ULN AND total bilirubin ≥ 2 × ULN or INR > 1.5 obtain the following in addition to the assessments listed above: • Antinuclear antibody, anti-smooth muscle antibody, type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G or gamma globulins. • Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week. • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease. • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In subjects when serology raises the possibility of autoimmune hepatitis. o In subjects when suspected drug-induced liver injury progresses or fails to resolve on withdrawal of study drug.

	○ In subjects with acute or chronic atypical presentation. • If liver biopsy conducted provides biopsy information.

Abbreviation: ALT = alanine transaminase; AST = aspartate transaminase; eCRF = electronic case report form; PK = pharmacokinetic; SAE = serious adverse event; ULN = upper limit of normal.

[a] Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.

[b] All events of ALT or AST ≥3 × ULN **and** total bilirubin ≥2 × ULN (> 35% direct bilirubin) or ALT or AST ≥3 × ULN **and** INR > 1.5 may indicate severe liver injury **(possible "Hy's Law") and must be reported to sponsor in an expedited manner and as an SAE.** The INR stated threshold value will not apply to subjects receiving anticoagulants.

[c] New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).

[d] Record the date/time of the PK blood sample draw and the date/time of the last dose of study drug prior to the blood sample draw on the eCRF. If the date/time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the Study Laboratory Manual.

10.6. Abbreviations and Definitions

Abbreviation	Definition
ADA	anti-drug antibody
ADL	activities of daily living
AE	adverse event
AN	abscess and inflammatory nodule
AUC	area under the concentration-time curve
$AUC_{0-\infty}$	area under the plasma concentration-time curve extrapolated to infinity
$AUC_{0-\tau}$	area under the plasma concentration-time curve over a dosing interval
BID	twice daily
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus disease of 2019
CRF	case report form
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CV%	percent coefficient of variation
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	European Quality of Life-5 Dimensions
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HiSCR50	hidradenitis suppurativa clinical response 50 is defined as at least a 50% reduction from baseline in the total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining fistula count
HiSCR75	HiSCR75 defined as at least a 75% reduction from baseline in the total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining fistula count
HiSCR90	HiSCR90 defined as at least a 90% reduction from baseline in the total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining fistula count
HiSCR100	HiSCR100 defined as a 100% reduction from baseline in the total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining fistula count
HiSQOL	Hidradenitis Suppurativa Quality of Life
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
HS	hidradenitis suppurativa
HS-PGA	Hidradenitis Suppurativa-Physician's Global Assessment
IBD	inflammatory bowel disease
ICE	intercurrent event
ICH	International Council for Harmonisation

Abbreviation	Definition
ICF	informed consent form
IGRA	interferon-gamma release assay
IEC	Independent Ethics Committee
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
IL-17A	Interleukin-17A
IMP	investigational medicinal product
IRB	Institutional Review Board
ISR	injection site reaction
IV	intravenous(ly)
IXRS	Interactive Voice/Web Response System
JAK	Janus-kinase
MMRM	nonlinear mixed effects model with repeated measures
NOAEL	no observed adverse effect level
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index
PASI90	Psoriasis Area and Severity Index response of 90%
PGIC	Patient Global Impression of Change
PK	pharmacokinetic(s)
PsA	psoriatic arthritis
QW	every week
Q2W	every other week
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus
SC	subcutaneous(ly)
SF-12v2	Short Form-12v2™ Health Survey
SoA	Schedule of Activities
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
TB	tuberculosis
TEAE	treatment-emergent adverse events
Th17	T-helper 17 cell
t_{max}	time to maximum observed concentration
TNF-α	tumor necrosis factor-α
US	United States
USPI	United States prescribing information
WOCBP	women of childbearing potential

11. References

Izokibep [Investigator's Brochure] ACELYRIN INC., Version 8.0, 2022

Ali AA, Seng EK, Alavi A, Lowes MA. Exploring changes in placebo treatment arms in hidradenitis suppurativa randomized clinical trials: A systematic review. *J Am Acad Dermatol*. 2020;82(1):45-53.

Alikhan A, Sayed C, Afsaneh A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian hidradenitis suppurativa foundations: Part I: Diagnosis, evaluation, and the use of complementary and procedural management. *J Am Acad Dermatol.* 2019;81(1):76-90. https://doi.org/10.1016/j.jaad.2019.02.067.

Casseres RG, Prussick L, Zancanaro P, et al. Secukinumab in the treatment of moderate to severe hidradenitis suppurativa: Results of an open-label trial. *J Am Acad Dermatol*. 2020;82(6):1524-1526. https://doi.org/10.1016/j.jaad.2020.02.005.

Deckers IE, Prens EP. An update on medical treatment options for hidradenitis suppurativa. *Drugs*. 2016;76(2):215-229.

Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. *Clin Exp Dermatol.* 1994;19(3):210–216. https://doi.org/10.1111/j.1365-2230.1994.tb01167.x.

Frew JW, Navrazhina K, Grand D, et al. The effect of subcutaneous brodalumab on clinical disease activity in hidradenitis suppurativa: An open-label cohort study. *J Am Acad Dermatol.* 2020;83(5):1341–1348. https://doi.org/10.1016/j.jaad.2020.05.007.

Garg A, Kirby JS, Lavian J, Lin G, Strunk A. Sex- and age-adjusted population analysis of prevalence estimates for hidradenitis suppurativa in the United States. *JAMA Dermatol.* 2017;153(8):760-764. https://doi.org/10.1001/jamadermatol.2017.0201.

Glatt S, Jemec GBE, Forman S, et al. Efficacy and safety of bimekizumab in moderate to severe hidradenitis suppurativa: A phase 2, double-blind, placebo-controlled randomized clinical trial. *JAMA Dermatol.* 2021;157(11):1279-1288. https://doi.org/10.1001/jamadermatol.2021.2905.

Gulliver W, Zouboulis CC, Prens E, Jemec GB, Tzellos T. Evidence-based approach to the treatment of hidradenitis suppurativa/acne inversa, based on the European guidelines for hidradenitis suppurativa. *Rev Endocr Metab Disord*. 2016;17(3):343-351.

HUMIRA® USPI. 2021. "HUMIRA® USPI. 2021, Highlights of Prescribing Information." www.fda.gov/medwatch.

Hurley H. Axillary hyperhidrosis, apocrine bromhidrosis, hidradenitis suppurativa, and familial l benign pemphigus: Surgical approach. In Roenigk RK, Roenigk HH, eds. *Dermatological Surgery. New York: Marcel Dekker*;1989:729-739.

Jfri A, Nassim D, O'Brien E, Gulliver W, Nikolakis G, Zouboulis CC. Prevalence of hidradenitis suppurativa: A systematic review and meta-regression analysis. *JAMA Dermatol.* 2021;157(8):924–931. https://doi.org/10.1001/jamadermatol.2021.1677.

Kimball AB, Kerdel F, Adams D, et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: A parallel randomized trial. *Ann Intern Med.* 2012;157(12):846-855. https://doi.org/10.7326/0003-4819-157-12-201212180-00004.

Kimball AB, Jemec GB, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the hidradenitis suppurativa clinical response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol.* 2014;171(6):1434-1442. https://doi.org/10.1111/bjd.13270.

Kimball B, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375(5):422-434. https://doi.org/10.1056/NEJMoa1504370.

Kirby JS, Okun MM, Alavi A, et al. Efficacy and safety of the janus kinase 1 inhibitor povorcitinib (INCB054707) in patients with hidradenitis suppurativa: Results from a randomized, placebo-controlled, phase 2 dose-ranging study. Poster presented at: 31st European Academy of Dermatology and Venereology (EADV) Congress, September 7-10, 2022. Milan, Italy.

Kirby JS, Thorlacius L, Villumsen B, et al. The Hidradenitis Suppurativa Quality of Life (HiSQOL) Score: Development and validation of a measure for clinical trials. *Br J Dermatol.* 2020;183(2):340-348. https://doi.org/10.1111/bjd.18692.

Langley R, Feldman S, Han C, et al. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad of Dermatol*. 2010;63(3):457-465.

Matusiak Ł, Szczęch J, Bieniek A, Nowicka-Suszko D, Szepietowski JC. Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: Implications for treatment with anti-IL-17 agents. *J Am Acad Dermatol.* 2017;76(4):670-675. https://doi.org/10.1016/j.jaad.2016.10.042.

Posner K, Brown GK, Stanley B, et al. The Columbia-Suicide Severity Rating Scale: Initial validity and internal consistency findings from three multisite studies with adolescents and adults. *Am J Psychiatry.* 2011;168(12):1266-1277. https://doi.org/10.1176/appi.ajp.2011.10111704.

Sabat R, Jemec GBE, Matusiak Ł, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers.* 2020;6(1):18. https://doi.org/10.1038/s41572-020-0149-1.

Sartorius K, Emtestam L, Jemec GBE, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. *Br J Dermatol.* 2009;161(4):831-839. https://doi.org/10.1111/j.1365-2133.2009.09198.x.

Sartorius K, Killasli H, Heilborn J, Jemec GBE, Lapins J, Emtestam L. Interobserver variability of clinical scores in hidradenitis suppurativa is low. *Br J Dermatol.* 2010;162(6):1261-1268. https://doi.org/10.1111/j.1365-2133.2010.09715.x.

Snaith RP. The Hospital Anxiety and Depression Scale. *Health Qual Life Outcomes.* 2003;1:29. https://doi.org/10.1186/1477-7525-1-29.

Wolk K, Join-Lambert O, Sabat R. Aetiology and pathogenesis of hidradenitis suppurativa. *Br J Dermatol.* 2020;183(6):999-1010. https://doi.org/10.1111/bjd.19556.

Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol.* 2017;177(5):1401–1409. https://doi.org/10.1111/bjd.15748.

Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GBE. Hidradenitis suppurativa/acne inversa: Criteria for diagnosis, severity assessment, classification and disease evaluation. *Dermatology.* 2015;231(2):184-190. https://doi.org/10.1159/000431175.

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