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

Protocol Reference Number: 21102

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Title Page

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

Protocol Number: 21102

Protocol Version: 4.0

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Compound: Izokibep

Brief Title: Hidradenitis Suppurativa Phase 2b Pivotal Study of Izokibep

Study Phase: Phase 2b

Sponsor Name: ACELYRIN, INC.

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The medical monitor's name and contact information will be provided separately.

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Previous versions	**Date**
1.0	04 November 2021
2.0	28 July 2022
3.0	26 April 2023

Amendment 3 (11 December 2023)
This amendment is considered nonsubstantial 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 because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment:
The main purpose of this amendment is to improve the method of handling missing data for the secondary endpoint of percentage of subjects who experience flare; align the power calculation with the primary endpoint of hidradenitis suppurativa clinical response with 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 (ie, HiSCR75); and better define the adverse events of special interest. A tabular summary of the changes is provided on the next page.

Protocol Amendment Summary of Changes Table

Section # and Name	Description of Change	Brief Rationale
Title Page	Removed sponsor signatory.	Sponsor approval is provided and maintained within the regulatory information management system.
2.3.1 Risks	Removed 2 examples of potential risks of IL-17 inhibitors and added cross reference to Section 8.3.6 Events of Special Interest for the full list.	The previous list of potential risks was incomplete. To reduce redundancy, a cross reference to the appropriate section was added.
8.3.6 Events of Special Interest	• Clarified that major adverse cardiovascular and cerebrovascular events includes cerebrovascular accident and transient ischemic attack, non-fatal myocardial infarction or unstable angina, 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.
9.3.3 Secondary Endpoints and Estimands	Updated the method of handling missing data for the secondary endpoint of percentage of subjects who experience flare from non-response imputation (NRI) to multiple imputation.	The multiple imputation analysis method better represents missing data than NRI. The number of subjects with missing data may be larger than the number of subjects who experience a flare, so using NRI may result in an analysis dominated by missing data.
9.5 Sample Size Determination	Updated the power calculation for Part B to align with the primary endpoint of HiSCR75.	Corrected power calculation in Part B in line with HiSCR75, which was inadvertently missed in the previous amendment when the primary endpoint was updated from HiSCR to HiSCR75.
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.

Table of Contents

1. Protocol Summary

1.1. Synopsis

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

Brief Title: Hidradenitis Suppurativa Phase 2b Pivotal Study of Izokibep

Rationale:

Izokibep is a small protein molecule that acts as a selective, potent inhibitor of interleukin 17A (IL-17A), to which it binds with high affinity. This study investigates izokibep in subjects with moderate to severe hidradenitis suppurativa (HS) and is intended to be one of 2 adequate and well-controlled studies to support a claim of efficacy of izokibep in subjects with HS.

Overall Design:

This is a phase 2b pivotal, multi-center, dose-finding study to evaluate the efficacy, safety, and immunogenicity of izokibep in subjects with moderate to severe HS. Subjects must have HS lesions present in ≥ 2 distinct anatomic areas, one of which is Hurley Stage II or Hurley Stage III and a total abscess and inflammatory nodule count of ≥ 5. Subjects with draining fistula count of > 20 at screening will be excluded.

This study consists of 2 parts. Part A is an exploratory open-label, single-arm investigation in which a minimum of 20 and up to 30 subjects will be enrolled. Once Part A is fully enrolled, subsequent subjects will be enrolled into Part B. Part B is a randomized, double-blind, placebo-controlled, parallel-group, dose-finding investigation in which approximately 170 subjects will be enrolled.

This study will be conducted at study sites in North America and Europe. Additional sites and regions may be added.

Objectives and Endpoints

Objectives	Endpoints
Primary	
Part A	
• To explore the efficacy of izokibep as measured by HiSCR75[1] at Week 12	• HiSCR75[1] at Week 12
Part B	
• To demonstrate that one or both treatment regimens of izokibep is efficacious compared to placebo, as measured by HiSCR75[1] at Week 16	• HiSCR75[1] at Week 16
Secondary	
Part A	
• To explore the safety and tolerability	• TEAEs and SAEs • Laboratory values and vital signs at collected timepoints
• To explore the immunogenicity of izokibep as measured by the presence of ADAs	• ADAs
Part B	
To demonstrate that one or both regimens of izokibep is efficacious, as measured by: • Percentage of subjects achieving HiSCR90[1] at Week 16 • Percentage of subjects achieving HiSCR100[1] at Week 16 • Percentage of subjects achieving HiSCR50[1] at Week 16	• HiSCR90[1] at Week 16 • HiSCR100[1] at Week 16 • HiSCR50[1] at Week 16
• Percentage of subjects who experience ≥ 1 disease flare through 16 weeks of treatment[2]	• HS flares through Week 16
• Percentage of subjects with baseline Hurley Stage II who achieve AN count of 0, 1, or 2 at Week 16	• AN count of 0, 1, or 2 at Week 16

Objectives	Endpoints
• Percentage of subjects achieving at least 3-point reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among subjects with baseline NRS ≥4	• NRS in Patient Global Assessment of Skin Pain at its worst at Week 16
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, events of interest, and SAEs • Laboratory values and vital signs at collected timepoints
To assess the immunogenicity of izokibep as measured by the presence of ADAs	• ADAs

ADAs = anti-drug antibodies; 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; TEAE = treatment-emergent adverse event
[1] HiSCR50/75/90/100 is defined as at least a 50%, 75%, 90%, or 100% reduction from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.
[2] Flare is defined as ≥ 25% increase in AN count with a minimum increase of 2 AN relative to baseline.

Brief Summary:

Overall, approximately 200 subjects with moderate to severe HS will be enrolled.

Part A is an open-label, single-arm, investigation consisting of up to a 28-day screening period, a 31-week treatment period and a follow-up period that includes 2 visits to be completed by all subjects at Week 39 and Week 45. For subjects who early terminate, the follow-up visits should be completed 8 weeks (± 5 days) and 14 weeks (± 5 days) after the last dose of study drug. A minimum of 20 subjects and up to 30 subjects meeting eligibility criteria will be enrolled into Part A (Group 0). Subjects will be assigned to treatment with open-label izokibep subcutaneous (SC) 160 mg every week (QW) from Day 1/Week 0 to Week 31. Once enrollment in Part A has finished, enrollment will begin into Part B.

Part B is a randomized, double-blind, placebo-controlled, parallel-group, dose-finding investigation to evaluate the efficacy, safety, and immunogenicity of izokibep in subjects with moderate to severe HS. Subjects will complete up to a 28-day screening period, followed by a 16-week double-blind treatment period. At completion of the Week 16 visit procedures, subjects randomized to placebo will be switched to active treatment in a blinded manner for the Week 16 dose through Week 30 (Q2W dose group) or Week 31 (QW dose group). Subjects randomized to izokibep will remain on the same dose through Week 30 (Q2W dose group) or Week 31 (QW dose group). After their respective treatment periods, all subjects will enter a follow-up period that includes 2 visits to be completed at Week 39 and Week 45. For subjects who early terminate, the follow-up visits should be completed 8 weeks (± 5 days) and 14 weeks (± 5 days) after the last dose of study drug.

In Part B, approximately 170 subjects will be randomized into 1 of 4 groups in a 1:1:2:2 ratio as follows:

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

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

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

The primary endpoint will be assessed at Week 16 in Part B only. The last dose of study drug will be administered on Week 31 for QW dosing groups and at Week 30 for Q2W dosing groups.

Number of Subjects:

Approximately 200 subjects will be enrolled in the study.

Study Drug Groups and Duration:

- Group 0 (n = minimum 20 subjects and up to 30 subjects): izokibep SC 160 mg QW from Day 1/Week 0 to Week 31.
- Group 1 (n = 28-29): placebo SC QW from Day 1 (Week 0) to Week 15, then izokibep SC 160 mg QW from Week 16 to Week 31.
- Group 2 (n = 28-29): placebo SC every other week (Q2W) from Day 1 (Week 0) to Week 14, then izokibep SC 160 mg Q2W from Week 16 to Week 30.
- Group 3 (n = 56-57): izokibep SC 160 mg QW from Day 1 (Week 0) to Week 31.
- Group 4 (n = 56-57): izokibep SC 160 mg Q2W from Day 1 (Week 0) to Week 30.

Study drug doses are fixed and will not be adjusted for individual subjects during the study. Subjects assigned to placebo SC QW and placebo SC Q2W will be grouped together into a single placebo group for comparison to each dosing regimen of izokibep for Part B.

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.

The DMC will consist of at least one medical expert with the relevant therapeutic area expertise and at least one statistician. The DMC will also have a minimum of 3 members, one of whom will serve as the Chair. The DMC responsibilities, authorities, and procedures will be documented in the DMC charter. The committee will meet approximately every 6 months to review interim data. After each review, the DMC will make recommendations regarding the continuation of the study based on safety.

Part A

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

Part B

In Part B, no formal interim analysis is planned for the purpose of stopping or altering this study. The DMC will review unblinded data when the first approximately 105 subjects randomized into Part B have had the opportunity to complete the Week 8 visit to make a recommendation on further development activities for izokibep. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The type I error rate for hypothesis tests at the end of the study will be decreased by 0.0001 to account for this interim summary of unblinded data. The study team and the investigators will remain blinded to these interim results until after the study is completed. After all subjects have had the opportunity to complete the Week 16 assessment in Part B, the analysis of the primary endpoint may be completed. Site staff and all members of the study team who interact with site staff will remain blinded to individual subject treatment assignment until all subjects have completed all visits in the study.

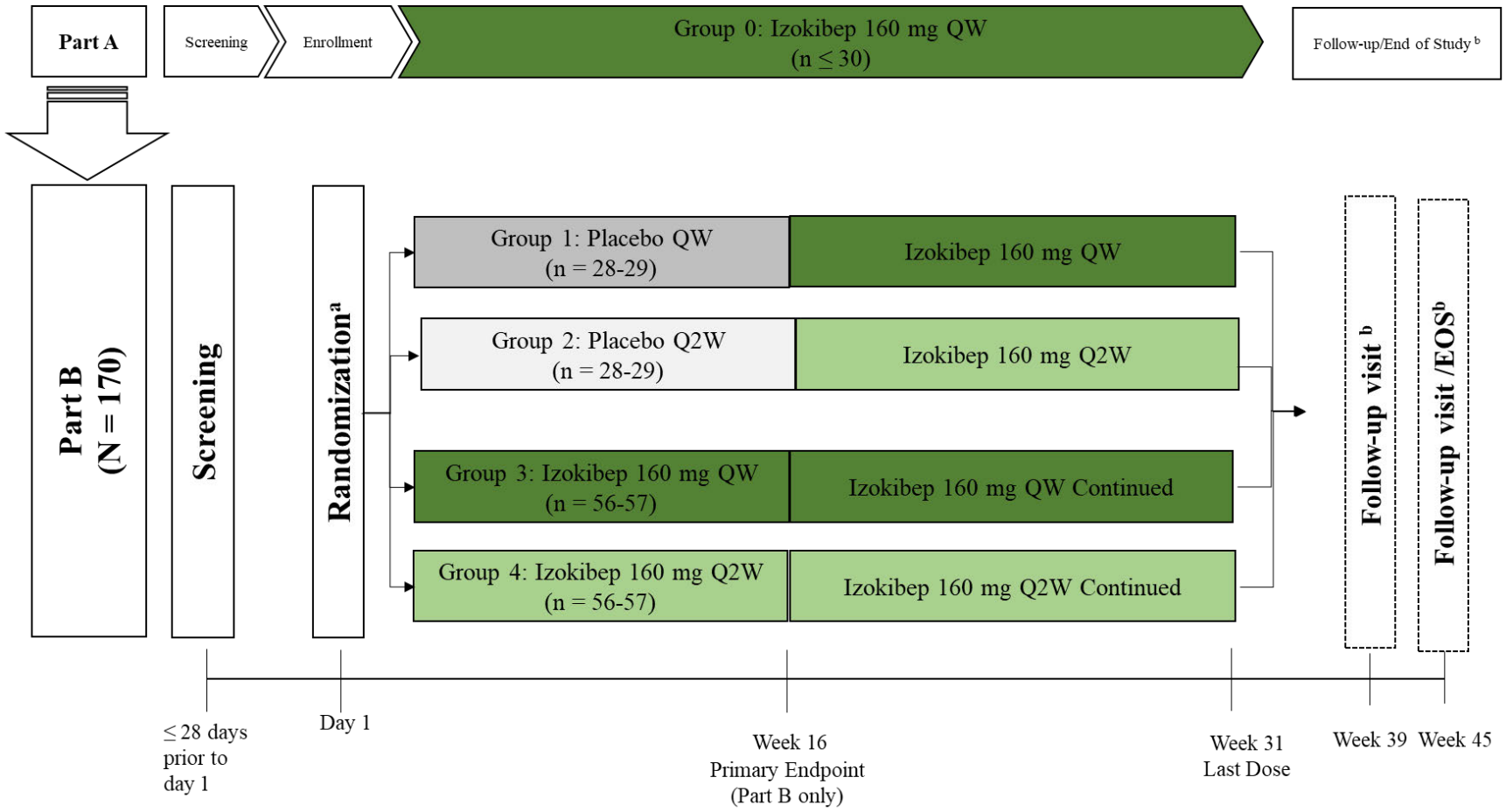
Statistical Considerations

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

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

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

1.2. Schema



EOS = end of study; FU = follow-up; QW = once weekly; Q2W = every other week

[a] Randomization will be stratified by any prior biologic/Janus Kinase (JAK) inhibitor use for hidradenitis suppurativa (Yes/No) and Hurley Stage (II or III).
[b] Two follow-up visits will be completed by all subjects at Week 39 (± 5 days) and Week 45 (± 5 days). For subjects who early terminate, the follow-up visits should be completed at 8 weeks (± 5 days) and 14 weeks (± 5 days) after the last dose of study drug.

1.3. Schedule of Activities for Part A and Part B

																			Follow-up[b]	
Procedures	**Screen**	**Treatment Period (weeks)[a]**																	**8 weeks after last dose**	**14 weeks after last dose/EOS**
	≤ 28 d prior to d1	**0 (d1)**	**1**	**2**	**3[a]**	**4**	**8**	**12**	**13[a]**	**14**	**15[a]**	**16**	**17[a]**	**18**	**20**	**24**	**28**	**32 or ET[p]**	**39**	**45**
Informed consent	X																			
Eligibility criteria	X	X																		
Hurley staging	X	X										X								
Demography	X																			
Physical exam	X																	X		
Weight	X	X																		
Height	X																			
Medical and medication history	X	X																		
Alcohol and nicotine use	X																			
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[d]	X											X						X	X	
Chest X-ray[e]	X																			
C-SSRS	X	X				X	X	X				X			X	X	X	X	X	
AE reporting[f] (through 4 weeks after last dose)		→																	→	
SAE reporting[f] (through 8 weeks after last dose)	X	→																	→	

																			Follow-up[b]	
Procedures	**Screen**	**Treatment Period (weeks)[a]**																	**8 weeks after last dose**	**14 weeks after last dose/EOS**
	≤ 28 d prior to d1	**0 (d1)**	**1**	**2**	**3[a]**	**4**	**8**	**12**	**13[a]**	**14**	**15[a]**	**16**	**17[a]**	**18**	**20**	**24**	**28**	**32 or ET[p]**	**39**	**45**
Prior & Concomitant medication[g]	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	
Efficacy Assessments																				
Lesion count[h]	X	X				X	X	X				X				X	X	X		
NRS Patient Glob. Ass. Skin Pain[i]	X	→	→	→	→	→	→	→	→	→	→	→	X	X		X	X	X		
PGA		X				X	X	X				X				X	X	X		
Erythema score		X				X	X	X				X				X	X	X		
Photography (opt. substudy)[j]		X					X					X						X		
HS-PGIC		X				X	X	X				X				X	X	X		
HADS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
DLQI		X					X					X				X		X		
EQ-5D		X					X					X				X		X		
SF-12		X					X					X				X		X		
Laboratory Tests																				
Serology (HBsAg, HCV)	X																			
TB test[k]	X																			
HIV testing	X																			
Hematology/Chemistry	X	X				X	X	X				X				X		X	X	

																			Follow-up[b]	
Procedures	**Screen**	**Treatment Period (weeks)[a]**																	**8 weeks after last dose**	**14 weeks after last dose/EOS**
	≤ 28 d prior to d1	**0 (d1)**	**1**	**2**	**3[a]**	**4**	**8**	**12**	**13[a]**	**14**	**15[a]**	**16**	**17[a]**	**18**	**20**	**24**	**28**	**32 or ET[p]**	**39**	**45**
Urinalysis	X	X					X	X				X						X	X	
C-reactive protein	X	X				X	X	X				X				X		X		
Fasting lipid (total cholesterol, triglycerides & HDL)	X											X								X
Hemoglobin A1C		X										X						X		
Pregnancy test (WOCBP only)[l]	X	X				X	X	X				X			X	X	X	X	X	
PK sampling[m]		X		X		X	X	X				X				X		X	X	X
ADA sampling[m]		X		X		X	X	X				X				X		X	X	X
Exploratory biomarker sampling[m]		X				X	X					X						X		
Treatment Assignment																				
Treatment assignment/Randomization		X																		
Study drug administration and Dosing Diary																				
QW dosing (at site)[a, n]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X			
Q2W dosing (at site)[a, n]		X		X		X	X	X		X		X		X	X	X	X			
Dosing diary[o]						→												→		

ADA = anti-drug antibody; AE = adverse event; AN = abscess and inflammatory nodule; d = day; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; ECG = electrocardiogram; EOS = end of study; EQ-5D = European Quality of Life 5-dimension;

ET = early termination; HADS = Hospital Anxiety and Depression Scale; HBsAg = hepatitis B surface antigen, HCV = hepatitis C virus; HS-PGIC = HS Patient Global Impression of Change; NRS = Numeric Rating Scale; PGA = Physician's Global Assessment; PK = pharmacokinetic; PPD = purified protein derivative; Q2W = every other week; QW = once weekly; SAE = serious adverse event; SF-12 = 12-Item Short Form Survey; TB = tuberculosis; 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. For QW dosing, the time between doses should be no less than 4 days and no more than 10 days. For Q2W dosing, the time between doses should be no less than 11 days and no more than 17 days. Study visits for QW dosing are not required at Weeks 5 to 7, 9 to 11, 18, 19, 21 to 23,25 to 27, or 29 to 31 if subject/caregiver completes study drug administration at home. Subjects randomized to Q2W arms are not required to complete visits on Weeks 1, 3, 13, 15, and 17. Study visits for Q2W dosing not required at Weeks 6, 10, 22, 26, or 30 if subject/caregiver completes study drug administration at home. See footnotes n and o below.

[b] The follow-up period consists of 2 visits to be completed by all subjects at Week 39 and Week 45. For subjects who early terminate, the follow-up visits should be completed 8 weeks (± 5 days) and 14 weeks (± 5 days) after the last dose of study drug.

[c] Vital signs include measurements of temperature, respiratory rate, systolic and diastolic blood pressure, and pulse. Measurements should be taken in a sitting position after 5 minutes of rest.

[d] Electrocardiograms in triplicate will be recorded after subject has been supine for at least 5 minutes.

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

[f] Serious adverse events 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); adverse events 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. From Week 16 through Week 32, subjects will be required to tell site staff if they took any analgesics within 24 hours of their site visit. See Section 10.10. Subjects will refrain from taking analgesics 12 hours before the site visit, if possible.

[h] Lesion count will be performed at every study visit marked in the Schedule of Activities and must address all relevant anatomical regions in each subject. The AN count includes counts of draining tunnels (fistulas and sinuses). See Section 8.1.1 for more details. 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. See Section 8.1.5. No in-site assessment of skin pain will be completed at the Week 16 visit. From Week 16 through Week 32, subjects will complete skin pain assessments at the site. Note: subjects 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] QuantiFERON® test or PPD test for TB will be performed. Note: T-SPOT® testing may be allowed after consultation with medical monitor.

[l] Serum pregnancy test required for screening and urine pregnancy test required at all other times for women of childbearing potential.

[m] Pharmacokinetic and ADA blood sampling will be taken prior to administration of study drug (pre-dose) on dosing days.

[n] Administration of study drug should be done last after all study procedures unless indicated otherwise. Subjects will be monitored at the study site for at least one hour after study drug administrations at the following visits: for subjects enrolled to QW arms, on Day 1 and Weeks 1, 16, and 17; for subjects enrolled to Q2W arms, on Day 1 and Weeks 2, 16, and 18. After Week 4, qualified subjects may perform home dosing of study drug at weeks without study visits (see footnote a) and do not need to return to the clinical site on those weeks. Subjects may begin self-administration of study drug from Week 5 (QW dosing) or Week 6 (Q2W dosing). Subjects will be trained on study drug handling and self-administration of study drug at the study visits prior to beginning self-administration. A subject's caregiver or designee can also be trained on home dosing based on the subject's preference. Study-site staff will administer study drug at the first 2 visits. Thereafter, if home dosing is a consideration, the subject or subject's caregiver or designee must administer and demonstrate competency

for at least 2 visits prior to being allowed to dose at home. Otherwise, the subject will need to return to the site for all injections. The last dose of study drug for subjects dosed QW is Week 31 and for subjects dosed Q2W is Week 30.

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

[p] Subjects who end the study early will complete an early termination visit and complete the procedures described at the Week 32 visit within 2 weeks of the last dose of study drug.

2. Introduction

Izokibep is a potent and selective inhibitor of interleukin 17A (IL-17A) that is being developed for 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 including healthy volunteers and subjects with psoriasis and psoriatic arthritis (PsA) and is currently being studied in uveitis, PsA and axial spondyloarthritis. The current phase 2b, double-blind, randomized, placebo-controlled, dose-finding study will evaluate the efficacy, safety, and immunogenicity of izokibep administered subcutaneously (SC) in adult subjects with moderate to severe HS. This is intended to be one 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%-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. 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), interleukin (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 TNF-α inhibitor, 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, 2016a).

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. IL-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 TNF-α inhibitors. 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 trials with secukinumab 300 mg and brodalumab 270 mg, where 70% of 20 patients and 100% of 10 patients 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 trials in patients with HS for secukinumab and bimekizumab are underway.

2.2.3. Izokibep Background

Izokibep is a biologic drug 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 to monoclonal antibodies offers advantages in terms of required dosing volumes and potential for alternative pharmacological formulations.

Izokibep is based on a small protein (Affibody® molecule) 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 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.

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 intravenously (IV) and 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 study) 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 abscessation and systemic sequelae in one 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 No. 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 to 40 mg in a single or multiple dose regimen.

A phase 2 clinical trial in 108 randomized and treated subjects with moderate to severe plaque psoriasis is ongoing (Study ABY-035-002, EudraCT No. 2017-001615-36, NCT03591887). Study ABY-035-002 is a dose-finding trial comparing 2-, 20-, 80- and 160-mg dose SC izokibep groups to placebo for 48 weeks of treatment (52-week core study). The 52-week core study has been completed and results are summarized in the investigator's brochure. The primary endpoint of the study was the proportion of subjects that achieved a Psoriasis Area and Severity Index 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 every other week (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- and 160-mg treatment groups. Safety and efficacy data obtained from this 52-week core study izokibep suggest a favorable benefit-risk profile in plaque psoriasis (investigator's brochure).

In HS, data from adalimumab and bimekizumab clinical studies demonstrate that exposures are lower for HS as compared to other indications, such as plaque psoriasis (Kimball et al, 2016a; Glatt et al, 2021). In addition, there is evidence that clinical responses do increase as the dose of adalimumab is increased to double the approved dose (Zouboulis et al, 2020). This suggests higher exposures are important to optimize clinical benefit in patients with HS. As reviewed below, there is no dose-limiting adverse events (AEs) for izokibep which supports 160 mg once weekly (QW) and 160 mg Q2W dosing (see Section 4.2).

2.2.3.3. Safety Overview

In the first in human clinical 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) was well tolerated, with no deaths or treatment related serious adverse events (SAE).

Intravenous administration (single doses up to 40 mg in 46 subjects in total) resulted in the following TEAEs by preferred term: oropharyngeal pain (10.9%), nasopharyngitis (6.5%), diarrhea (4.3%), and headache (4.3%). A further 9 TEAEs were reported, affecting one subject each (2.2% each). Subcutaneous administration (single and multiples 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, affecting one subject each (5.2% each). The majority of the injection site reactions were of mild intensity.

In the phase 2, 52-week core period in subjects with plaque psoriasis (ABY-035-002), multiple doses of up to 160 mg SC of izokibep (n = 108) were well tolerated with no deaths or treatment-related SAE. A total of 65 subjects (60.2%) experience at least 1 izokibep-related TEAE. The most common izokibep-related TEAEs (n/%) were injection site reaction (42/38.9%), nasopharyngitis (13/12%), diarrhea (7/6.5%), and fatigue (6/5.6%) consistent with the first in human study.

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, median time to maximum observed concentration (t_{max}) was 60 hours postdose. 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 half-life ($t_{½}$) 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 plasma concentration-time curve from time zero to infinity ($AUC_{0-\infty}$) and C_{max} for both dose routes, with values ranging from 19.7% to 21.6% and 13.6% to 15.4%, respectively.

Following 40 mg SC repeated doses, maximum plasma concentrations 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 area under the plasma concentration-time curve 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 all trial 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 drug 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 and ixekizumab as well as izokibep 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 and inflammatory bowel disease (IBD). See Section 8.3.6 for the list of potential risks of IL-17 inhibitors.
- 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 trial until 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.

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 trials with izokibep in healthy volunteers and in subjects with psoriasis and PsA suggest a favorable benefit-risk profile in HS. Based on published data showing efficacy and safety for other IL-17 inhibitors, including in patients with HS, the benefit-risk relationship also in patients with HS appears favorable and justifies clinical development of izokibep in HS as well. Due to its small molecular size as compared to 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. Specified analgesics are permitted for HS-associated pain, and for subjects with increases in abscess and inflammatory node counts (≥ 150% of Day 1 abscess and inflammatory nodule [AN] count), investigators may provide permitted oral antibiotic rescue therapy. Additionally, subjects with a draining fistula count > 20 at the baseline visit 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 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. However, subjects with draining fistula count of > 20 at screening 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 taken into account 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 study site for at least one hour after the first 2 study drug administrations of izokibep.
- 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.

- In Part B of the study, placebo treatment will be limited to 16 weeks. After Week 16, subjects randomized to placebo will begin blinded active treatment (izokibep 160 mg) in order to potentially derive benefit from the disease-relevant effect of IL-17 inhibition.
- Participation in the trial is voluntary. Each subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

Taking into account 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	
Part A	
• To explore the efficacy of izokibep as measured by HiSCR75[1] at Week 12	• HiSCR75[1] at Week 12
Part B	
• To demonstrate that one or both treatment regimens of izokibep is efficacious compared to placebo, as measured by HiSCR75[1] at Week 16	• HiSCR75[1] at Week 16
Secondary	
Part A	
• To explore the safety and tolerability	• TEAEs and SAEs • Laboratory values and vital signs at collected timepoints
• To explore the immunogenicity of izokibep as measured by the presence of ADAs	• ADAs
Part B	
To demonstrate that one or both regimens of izokibep is efficacious, as measured by: • Percentage of subjects achieving HiSCR90[1] at Week 16 • Percentage of subjects achieving HiSCR100[1] at Week 16 • Percentage of subjects achieving HiSCR50[1] at Week 16	• HiSCR90[1] at Week 16 • HiSCR100[1] at Week 16 • HiSCR50[1] at Week 16
• Percentage of subjects who experience ≥ 1 disease flare through 16 weeks of treatment [2]	• HS flares through Week 16
• Percentage of subjects with baseline Hurley Stage II who achieved AN count of 0, 1, or 2 at Week 16.	• AN count of 0, 1, or 2 at Week 16

Objectives	Endpoints
• Percentage of subjects achieving at least 3-point reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among subjects with baseline NRS ≥ 4	• NRS in Patient Global Assessment of Skin Pain at its worst at Week 16
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, events of interest, and SAEs • Laboratory values and vital signs at collected timepoints
To assess the immunogenicity of izokibep as measured by the presence of ADAs	• ADAs
Exploratory	
Part B	
To explore if one or both regimens of izokibep is efficacious, as measured by: • Percentage of subjects who achieve HiSCR75[1] at Weeks 2, 4, 8, 12, and 32.	• HiSCR75[1] at Weeks 2, 4, 8, 12, and 32
• Percentage of subjects who achieve HiSCR90[1] at Weeks 2, 4, 8, 12, and 32	• HiSCR90[1] at Weeks 2, 4, 8, 12, and 32
• Percentage of subjects who achieve HiSCR100[1] at Weeks 2, 4, 8, 12, and 32	• HiSCR100[1] at Weeks 2, 4, 8, 12, and 32
• Percentage of subjects who achieve HiSCR50[1] at Weeks 2, 4, 8, 12, and 32	• HiSCR50[1] at Weeks 2, 4, 8, 12, and 32
• Percentage of subjects with baseline Hurley Stage II who achieved AN count of 0, 1, or 2 at Weeks 4, 8, 12, 24, and 32	• AN count of 0, 1, or 2 at Weeks 4, 8, 12, 24, and 32
• NRS Patient Global Assessment of Skin Pain from baseline after 4, 8, 12, 16, 24, and 32 weeks of treatment	• Change in pain score from baseline at Weeks 4, 8, 12, 16, 24, and 32
• Modified Sartorius Score after 4, 8, 12, 16, 24, and 32 weeks of treatment	• Modified Sartorius Score at baseline, Weeks 4, 8, 12, 16, 24, and 32
• HS flare rates through 4 and 32 weeks of treatment	• HS flares through Weeks 4 and 32

Objectives	Endpoints
• IHS4, after 4, 8, 12, 16, 24, and 32 weeks of treatment	• IHS4 scores at Weeks 4, 8, 12, 16, 24, and 32
• Hidradenitis Suppurativa-Physician's Global Assessment (HS-PGA)	• Change from baseline to Week 16 in HS-PGA
To explore the effect of izokibep on PROs as measured by change from baseline over time in: • EQ-5D	• Change from baseline to Week 16 in EQ-5D
• DLQI	• Change from baseline to Week 16 in DLQI
• HADS	• Change from baseline to Week 16 in HADS, HADS-anxiety and HADS-depression
To evaluate the pharmacokinetics of izokibep in subjects with HS	• Trough plasma concentrations of izokibep at collected timepoints

ADAs = anti-drug antibodies; AN = abscess and inflammatory nodule; DLQI = Dermatology Life Quality Index; EQ-5D = European Quality of Life-5 Dimensions; HADS = Hospital Anxiety and Depression Scale; HiSCR = hidradenitis suppurativa clinical response; HS = hidradenitis suppurativa; IHS4 = International Hidradenitis Suppurativa Severity Score; NRS = numeric rating scale; PRO = patient-reported outcomes; SAE = Serious Adverse Event; TEAE = treatment-emergent adverse event.
[1] HiSCR50/75/90/100 is defined as at least a 50%, 75%, 90%, or 100% reduction from baseline in the total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining fistula count.
[2] Flare is defined as ≥ 25% increase in AN count with a minimum increase of 2 AN relative to baseline.

Primary estimand

Please refer to Section 9.3.2.

Secondary estimand(s)

Please refer to Section 9.3.3.

4. Study Design

4.1. Overall Design

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

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

4.1.1. Part A: Single-arm, Open-label

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

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 16.

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 (Section 6.8.3).

Once Part A is fully enrolled, subsequent subjects will be enrolled into Part B.

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

Part B is a randomized, double-blind, placebo-controlled, parallel-group, dose-finding investigation to evaluate the efficacy, safety, and immunogenicity of izokibep in subjects with moderate to severe HS. Subjects will complete up to a 28-day screening period, followed by a 16-week double-blind treatment period. At completion of the Week 16 visit procedures, subjects randomized to placebo will be switched to active treatment in a blinded manner for the Week 16 dose through Week 30 (Q2W dose group) or Week 31 (QW dose group). Subjects randomized to izokibep will remain on the same dose through Week 30 (Q2W dose group) or Week 31 (QW dose group). After their respective treatment periods, all subjects will enter a follow-up period that includes 2 visits to be completed at Week 39 and Week 45. For subjects who early terminate, the follow-up visits should be completed 8 weeks (± 5 days) and 14 weeks (± 5 days) after the last dose of study drug.

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

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

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

Subjects will complete study assessments according to the study visits outlined in the SoA.

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

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

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

After randomization and through the end of the study if the AN count is ≥ 150% of Day 1 AN count, antibiotic rescue medication is permitted (Section 6.8.3).

4.1.3. 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.

The DMC will consist of at least one medical expert with the relevant therapeutic area expertise and at least one statistician. The DMC will also have a minimum of 3 members, one of whom will serve as the Chair. The DMC responsibilities, authorities, and procedure will be documented in the DMC charter. Over the course of the study the DMC will meet every 6 months to review interim data. After each review, the DMC will make recommendations regarding the continuation of the study based on safety. In addition, the DMC will meet as indicated below to review data from Part A and Part B.

Part A

The DMC will review data in Part A, after all subjects have had the opportunity to complete the Week 8 visit (or discontinued the study early). Based on this review, the DMC may recommend continuing, stopping, or altering Part B (Section 9.4).

Part B

In Part B, no formal interim analysis is planned for purposes of stopping or altering this study (Section 9.4). The DMC will review unblinded data when the first approximately 105 subjects randomized into Part B have had the opportunity to complete the Week 8 visit to make a recommendation on further development activities for izokibep. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The type I error rate for hypothesis tests at the end of the study will be decreased by 0.0001 to account for this interim summary of unblinded data. The study team and the investigators will remain blinded to these interim results until after the study is completed.

4.1.4. Number of Sites

Approximately 50 sites across North America and Europe 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.

4.1.5. Number of Subjects

Participants in this clinical investigation shall be referred to as "subjects." A minimum of 20 subjects and up to 30 subjects will be enrolled into Part A and approximately 170 subjects will be enrolled/randomized into Part B. Subjects who are withdrawn or removed from treatment, or the study will not be replaced.

4.1.6. Study Duration for Subjects

The maximum planned length of participation in the study for an individual subject is up to 49 weeks, which includes the following:

- Screening period of up to 28 days (4 weeks)
- 31-week treatment period
- Follow-up visit at Week 45

4.1.7. Scientific Rationale for Study Design

The design of this clinical trial was chosen to evaluate izokibep in subjects with moderate to severe HS. Part A is a proof-of-concept, single-arm, open-label part to generate preliminary data on the efficacy and safety of izokibep. The purpose of Part B (Weeks 0 to 16) is to provide 16-week placebo-controlled data demonstrating the safety and efficacy of izokibep administered SC at a dose of 160 mg QW and 160 mg Q2W for the treatment of HS. After Week 16, subjects randomized to izokibep will continue on the same blinded dosing regimen and subjects randomized to placebo will receive blinded active treatment (izokibep 160 mg QW or 160 mg Q2W) until Week 31. Long term safety and efficacy beyond Week 16 will be explored from Week 16 to Week 32 and will provide information on flares for subjects who achieved HiSCR on izokibep during the first 16 weeks of treatment.

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 moderate to severe HS. All clinical and laboratory procedures in this study are standard and generally accepted.

Males and females ≥ 18 years and ≤ 75 years with moderate to severe HS (AN count of ≥ 5) 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.

4.2. Justification for Dose

The dose of izokibep in Part A is 160 mg SC QW administered from Day 1 through Week 31.

The doses of izokibep in Part B are: 160 mg SC QW and 160 mg SC Q2W administered from Day 1 through Week 30 (Q2W dosing) and Week 31(QW dosing) in subjects randomized to

izokibep. Subjects randomized to placebo will switch to active treatment at Week 16 and will receive either izokibep 160 mg QW or 160 mg Q2W until Week 31 or Week 30, respectively.

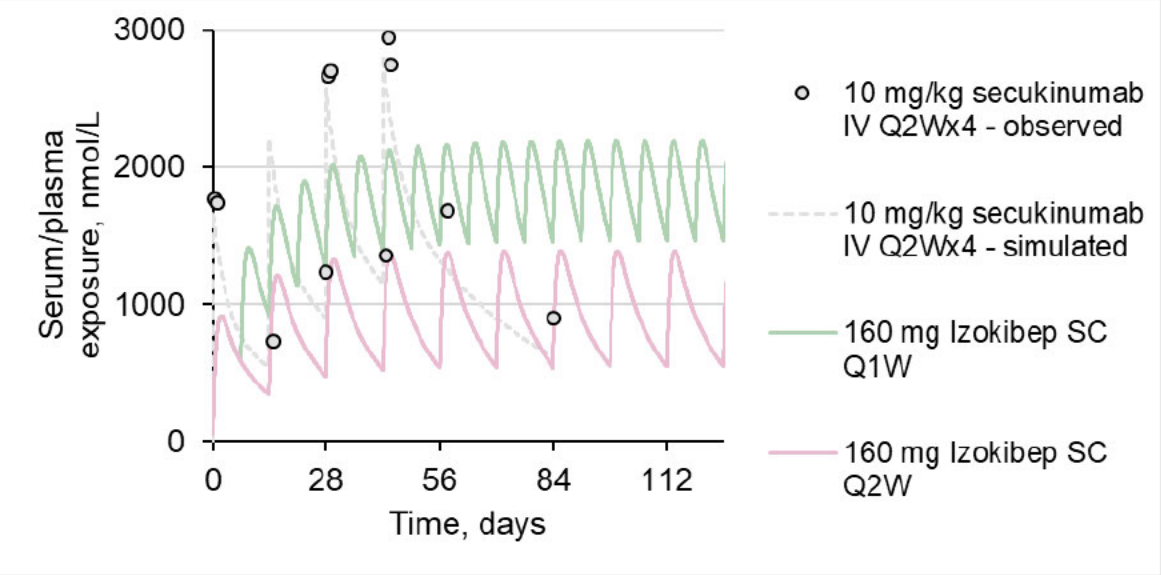
The selection of the doses in Part A and Part B is informed by the following facts. Izokibep has not demonstrated dose-limiting toxicity up to 160 mg Q2W with multiple doses. A dose of 160 mg QW has 10-fold margin for C_{max} and 9-fold margin for AUC_{tau} based on the NOAEL from non-clinical cynomolgus studies (Table 1). Hidradenitis suppurativa patients have achieved lower drug exposures compared to patients with other diseases, such as psoriasis, as demonstrated for both adalimumab and bimekizumab (Kimball et al, 2016; Glatt et al, 2021). In addition, higher doses of adalimumab have been shown to provide greater clinical benefits, including on pain, quality of life, and the International Hidradenitis Suppurativa Severity Score (IHS4) (Zouboulis et al, 2020). Further it is evident that doses of secukinumab 10 mg/kg (approximately 800 mg) IV and 30 mg/kg (2400 mg) IV dosed Q2W for 4 and 2 doses respectively in patients with uveitis disclosed no dose related toxicity (Letko et al, 2015). Furthermore, based on PK modeling of the izokibep psoriasis data against the available data with secukinumab in uveitis, we can approximate the 10 mg/kg exposures seen with secukinumab with a weekly injection of izokibep 160 mg as shown in Figure 1 and Table 2 (internal data to ACELYRIN).

Table 1. C_{max} and AUC_{tau} at NOAEL in Cynomolgus Monkey *vs.* 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_{tau} = area under the curve over a dosing interval; C_{max}= maximum observed plasma concentration; h = hour; NOAEL = no observed adverse effect level.

Figure 1. Observed and Simulated PK Profiles for 10 mg/kg IV Q2Wx4 Secukinumab vs. Simulated Profiles for 160 mg Izokibep SC Q1W and Q2W



IV = intravenous(ly); PK = pharmacokinetic; Q1W = once a week; Q2W = every 2 weeks; SC = subcutaneous.

Table 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	h·nmol/L	$31.5 \cdot 10^4$	h·µg/mL	5850

AUC = area under the concentration-time curve; $C_{average}$ = average observed plasma concentration; C_{max}= maximum observed plasma concentration; C_{min} = minimum observed plasma concentration; QW = once weekly; SC = subcutaneous.

The dose of izokibep used in this study supports the maximum likelihood of demonstrating the potential efficacy for izokibep in subjects with moderate to severe HS with 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, including assessment of suicidal ideation and behavior. An independent DMC will also review the data on an ongoing basis, as detailed in Section 4.1.3.

4.3. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure including the final follow-up visit (ie, Week 45) 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 (ie, final follow-up visit (ie, Week 45).

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are 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. Subject must be ≥ 18 (or the legal age of consent in the jurisdiction in which the study is taking place) and ≤ 75 years of age, at the time of signing the informed consent.
Type of Subject and Disease Characteristics
3. Diagnosis of HS for ≥ 1 year 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 (throughout the duration of the study) one of the following over-the-counter topical antiseptics on their body areas affected with HS suppurativa lesions: chlorhexidine gluconate, triclosan, benzoyl peroxide, or diluted bleach in bathwater. 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. 10. Subject has a negative tuberculosis test at screening, as defined by[1]: o Negative QuantiFERON test OR o Negative purified protein derivative (PPD) test (< 5 mm of induration at 48 to 72 hours after test is placed).

- Subjects with a positive PPD test and a history of Bacillus Calmette-Guerin vaccination will be allowed with a negative QuantiFERON test.
- Subjects with a positive or indeterminate QuantiFERON test are allowed if all of the following is satisfied:
  - No symptoms of tuberculosis as determined by investigator.
  - Documented history of adequate prophylaxis initiation prior to receiving first dose of study drug.
  - No known exposure to a case of active tuberculosis after most recent prophylaxis.
  - No evidence of active tuberculosis on chest radiograph within 3 months prior first dose of study drug.

[1] T-SPOT® tuberculosis test may be used to establish eligibility if agreed upon with the medical monitor.

Sex and Contraceptive/Barrier Requirements

11. Male and Female

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 fresh unwashed 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 who is not currently pregnant.

b. Female subjects:

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of nonchildbearing potential as defined in Section 10.4 (Contraceptive and Barrier Guidance)

OR

- Is a woman of childbearing potential (WOCBP) and using a contraceptive method that is highly effective, with a failure rate of < 1%, as described in (Section 10.4) 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, noncompliance, 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 negative urine pregnancy test on Day 1 prior to the first dose of study drug, see Section 8.2.5.

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. Active IBD within 3 years prior to enrollment.
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. The subject is at 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. Subjects must have been on a stable dose within the 3 months prior to the first dose of study drug.
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. Exclusion criterion removed with Amendment 1 because it was a duplicate with Exclusion criterion 9.
12. Do not capture Exclusion 12, please select from 13, 14, or 15. Active infection or history of infection as follows:
13. 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).
14. A serious infection requiring hospitalization or IV anti-infectives (antibiotics, antivirals, antifungals) ≤ 30 days prior to first dose of study drug.
15. 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.
16. *Candida* infection requiring systemic treatment ≤ 3 months prior to first dose of study drug.
17. Tuberculosis or fungal infection seen on available chest x-ray taken ≤ 3 months of screening or at screening (Exception: documented evidence of completed treatment and clinically resolved).
18. Known history of human immunodeficiency virus (HIV).

Prior/Concomitant Therapy

19. Previous exposure to izokibep or any other IL-17 receptor inhibitors (eg, secukinumab, ixekizumab, bimekizumab, brodalumab).
20. Prior exposure to biologics that have a potential for or known association with progressive multifocal leukoencephalopathy (ie, natalizumab [Tysabri®], rituximab [Rituxan®], or efalizumab [Raptiva®]).
21. Exposure to TNF-α inhibitors, IL-1, IL-12, IL-23, or IL-12/23 receptor inhibitors within 5 half-lives prior to first dose of study drug.
22. 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
  - 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, PUVA, UVA, UVB]), except for allowable stable dose antibiotics (doxycycline or minocycline)
  - Laser or intense pulse light therapy in anatomic areas of HS lesions

23. 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).

24. 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.
25. 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.
26. Required or is expected to require, opioid analgesics for any reason (excluding tramadol) during the study.
27. History of hypersensitivity or allergy to izokibep or its excipients.
28. Received live vaccination ≤ 12 weeks prior to dosing or scheduled to receive a live vaccine ≤ 12 weeks following the last dose of study drug.
29. Participating in another clinical study or participated in a clinical study involving administration of an investigational medicinal product (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

Laboratory abnormalities and measurements

30. Positive hepatitis B surface antigen (HBsAg) or detected sensitivity on the hepatitis B virus DNA polymerase chain reaction (PCR) qualitative test for hepatitis B core antibodies (HBcAb)/Hepatitis B surface antibodies (HBsAb) positive subjects OR positive Hepatitis C virus antibody test at screening.
31. Laboratory abnormalities at screening:

- Hemoglobin < 9 g/dL
- Platelet count < 100 000/mm^3
- White blood cell count < 3000 cells/mm^3
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) ≥ 2.5 times the upper limit of normal
- Moderate or severe renal impairment (ie, CrCL < 60 mL/min) (Modification of Diet in Renal Disease [MDRD] 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.

32. 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 Exclusions
33. Previously enrolled, randomized to or withdrawn from this study.
34. Active substance abuse (drug or alcohol) within 24 weeks prior to first dose of study drug, as determined by the investigator.
35. 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

Investigator should encourage subject to limit alcohol consumption to < 2 per day, < 7 alcoholic drinks per week. An alcoholic drink is defined as a 6 oz (177 mL) glass of wine, a 1 oz (30 mL) glass of hard liquor (eg, whiskey) or an 8 oz (237 mL) glass of beer.

5.4. Screen Failures

A screen failure occurs when a subject who consents to participate in the clinical study is not subsequently enrolled/randomized to the study. A minimal set of screen failure information will be collected 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 (ie, age, sex), screen failure reason, and any SAE.

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

Subjects 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 case report form (CRF).

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 drug is defined as any investigational drug(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study subject according to the study protocol.

6.1. Study Drug(s) Administered

Table 3. Study Drug(s) Administered

	Investigational drug	Placebo
Drug name	Izokibep	Placebo to izokibep
Pharmacological group	Biologic: IL-17A inhibitor	None
Form	Solution for injection	Solution for injection
Active ingredient per form	CCI [redacted]	Not applicable
Route of administration	Subcutaneous (SC)	Subcutaneous (SC)
Non-active ingredients (excipients)	CCI [redacted]	
Special storage recommendations	Vials are to be stored at 2 to 8°C. The filled syringe must be stored in the refrigerator at 2 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). For further details, refer to Pharmacy Manual.	Can be stored at room temperature (do not store above 25°C). However, given placebo and izokibep will be provided in blinded, matching vials, both should be stored at 2 to 8°C.

6.1.1. Dosage, Administration and Schedule

Study drug (izokibep 160 mg QW, izokibep 160 mg Q2W, or placebo) will be dosed by SC injection as described in Section 6.1.1.1 and Section 6.1.1.2. 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 study site, only authorized investigational site study 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.

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

Please see the Pharmacy Manual for further details on study drug.

6.1.1.1. Part A: Open-label, Single-arm

- Group 0: open-label izokibep 160 mg QW from Day 1/Week 0 to Week 31

6.1.1.2. Part B: Randomized, Double-blind

- Group 1: placebo QW from Day 1/Week 0 to Week 15, then izokibep 160 mg QW from Week 16 to Week 31
- Group 2: placebo Q2W from Day 1/Week 0 to Week 14, then izokibep 160 mg Q2W from Week 16 to Week 30
- Group 3: izokibep 160 mg QW from Day 1/Week 0 to Week 31
- Group 4: izokibep 160 mg Q2W from Day 1/Week 0 to Week 30

6.2. Preparation, Handling, Storage, and Accountability

1. 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.
2. Only subjects enrolled 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.
3. 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).
4. 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 potential sampling error or that could be within range with repeat sampling.

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, 102)
  - 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 =102840**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 102840001, their first subject = 102840001**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, tuberculosis, 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

Once a subject is enrolled, the IXRS will assign the subject to either Part A or Part B. Once Part A is fully enrolled the IXRS will begin assigning subjects to Part B.

6.3.3.1. Treatment Assignment Part A

Part A is a single-arm investigation. Subjects will be assigned to open-label study drug (QW) on Day 1 by IXRS.

6.3.3.2. Treatment Assignment Part B

Part B is a double-blind, randomized investigation. Subjects will be randomized to the study drug (QW or Q2W) on Day 1 by IXRS. Randomization will be based on a schedule generated by the sponsor or sponsor designee before the start of the study and will be centrally executed using 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) but not to the dosing schedule (QW or Q2W). The randomization dates are to be documented in the subject's medical record.

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

Izokibep and matching placebo will be visually indistinguishable to prevent unblinding during preparation or administration of study material.

Subjects assigned to receive placebo will be randomized in a 1:1 ratio to receive placebo administered QW or Q2W. This will allow for blinding of test material, while the treatment schedule (QW or Q2W) will not be blinded from the subject or site personnel, and also will not be blinded from sponsor staff or designee who have access to administration logs.

6.3.4. Site Personnel Access to Individual Treatment Assignments

In Part B, 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 study site for any other reason will be considered a protocol deviation. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a subjects' intervention assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator is strongly encouraged to contact the sponsor to discuss the situation prior to unblinding a subject's intervention assignment unless this could delay emergency treatment for the subject. If a subject's intervention assignment is unblinded, the sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

If an SAE requires an expedited regulatory report to be sent to one or more regulatory agencies, sponsor/designee's safety staff may unblind the study drug assignment for the subject. A copy of the report, identifying the subject's study drug 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(s) 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.

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 trial depends on the subject's individual needs and is left at the physician's discretion.

6.7. Overdose

Excessive dosing (beyond that prescribed in the protocol and including overdose) should be recorded in the CRF. Any SAE or nonserious AE associated with excessive dosing must be followed as any other SAE or nonserious AE. 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, recreational drugs, 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 for HS since 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 TNF-α inhibitors, 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 indexes such as 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 subjects entering the study on oral non-opioid analgesic the dose must be stable for ≥ 5 days. 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 a subject's pain (HS-related or non-HS-related) worsens after Day 1, they may initiate analgesic therapy at any time as follows:

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

- Ibuprofen (at a dose of up to 800 mg po every 6 hours) not to exceed 3.2 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 (Section 10.10). From Week 16 through Week 32, subjects will be required to tell site staff if they took any analgesics within 24 hours of their study-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 a PRN 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.

6.8.2.5. Lesion Intervention

In the event that 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 visit or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same visit. If a 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 he or she must be discontinued from the study intervention.

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

6.8.4. 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 TNF-α inhibitors, 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 6.8.3), methotrexate, cyclosporine, retinoids, and fumaric acid esters
- Prescription topical therapies
- 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 2 months after the last dose of study drug)
- Oral or injectable corticosteroids (except as allowed per Section 6.8.2.5)
- 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.

7. Discontinuation of Study Drug and Subject Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole is 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 the permanent discontinuation of study drug will be documented. If study drug is permanently discontinued, the subject will be encouraged to remain in the study to be evaluated for safety and efficacy. Subjects should continue to complete study assessments as outlined in the SoA where possible, with the exception of study drug administration. Reasons for removal from study drug include any of the following:

- subject request
- safety concern (eg, due to an AE, ineligibility determined, protocol deviation, non-compliance, pregnancy, hepatotoxicity)
- death
- lost to follow-up
- decision by sponsor (other than subject request, safety concern, lost to follow-up)
- protocol-specified reasons:
    - A subject who requires more than 2 lesion interventions within the first 16 weeks of the study must be discontinued from study drug
    - After Week 16, a subject who 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 must be discontinued from study drug

Additionally, subjects experiencing any of the following AEs must be discontinued from study drug, but continued in the study and followed until resolution of the AE:

- Hematologic AE of moderate or severe intensity (refer to Section 10.3.3 for description of intensity assessment)
- Cardiovascular AE of moderate or severe intensity

  Note: Exceptions to this requirement include the following specific cardiovascular events that represent asymptomatic findings discovered as part of testing that may have been done for other reasons most likely unrelated to the drug product or the trial itself. Cardiovascular AEs that do not meet study drug discontinuation criteria include the following AEs related to asymptomatic valvular findings and asymptomatic arrythmia findings:

    - Valvular asymptomatic findings:
        - Aortic valve: Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging
        - Mitral valve disease: Asymptomatic; moderate regurgitation or stenosis by imaging

        - Pulmonary valve disease: Asymptomatic; moderate regurgitation or stenosis by imaging
        - Tricuspid valvular disease: Asymptomatic; moderate regurgitation or stenosis by imaging
    - Arrythmia findings of a non-urgent medical nature:
        - Atrial fibrillation: non-urgent medical intervention indicated
        - Atrial flutter: non-urgent medical intervention indicated
        - Atrioventricular block: non-urgent medical intervention indicated
        - Conduction disorder: non-urgent medical intervention indicated
        - Paroxysmal atrial tachycardia: non-urgent medical intervention indicated
        - Supraventricular tachycardia: non-urgent medical intervention indicated
- AEs of severe intensity in any other organ system

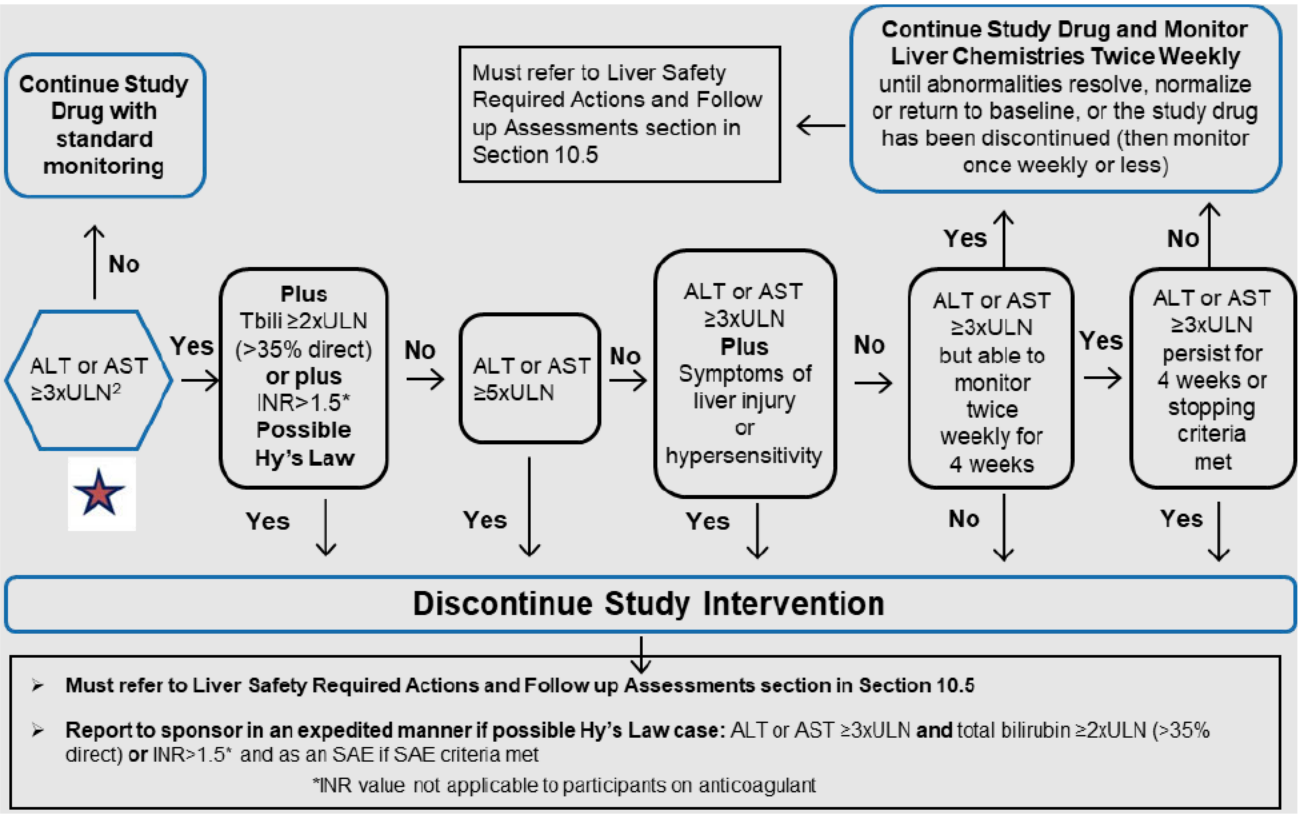
Subjects with newly diagnosed IBD or with IBD flares during the study must:

- Discontinue study drug and be followed-up until resolution of active IBD symptoms
- Be referred, as appropriate, to a healthcare professional treating IBD, such as a gastroenterologist
    - If IBD flares increase in severity or frequency during the study, the investigator should use clinical judgment in deciding whether the subject should continue in the study and contact the medical monitor to confirm the subject's suitability for continued participation in the study.

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 the best interest of the subject.

Phase 2 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm[1]



Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; SAE = serious adverse event; Tbili = total bilirubin; ULN = upper limit of normal.

[1] Liver Safety: Required Actions and Follow-up Assessments can be found in Section 10.5.

[2]If ALT or AST ≥ 3 x ULN, increase monitoring of liver chemistries to twice weekly.

7.1.2. Study Drug Restart or Rechallenge After Liver Stopping Criteria Are 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:

- Sponsor/medical monitor approval **is granted**
- Ethics and/or IRB approval is obtained, if required

NOTE: If study drug was interrupted for suspected study drug-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 Liver Safety: Required Actions and Follow-up Assessments and Study Drug Restart/Rechallenge Guidelines 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 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 he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study 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.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

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. For QW dosing, the time between doses should be no less than 4 days and no more than 10 days. For Q2W dosing, the time between doses should be no less than 11 days and no more than 17 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 assessments are provided in the SoA (Section 1.3). The study site should make every attempt to have the same investigator conduct efficacy assessments throughout the study for each subject.

8.1.1. Lesion Count

The number of inflammatory and non-inflammatory nodules, abscesses, draining and non-draining fistulas, and hypertrophic scars, as well as the physical location (right/left axilla, right/left inframammary, intermammary, right/left buttock, right/left inguino-crural fold, perianal, perineal, other) will be recorded (Section 10.7) at the designated study visits listed in SoA (Section 1.3). 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 one 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, 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 (See Section 3).

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

8.1.1.1. 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, 2016b). The HiSCR 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. HiSCR50, HiSCR75, HiSCR90, and HiSCR100 are defined as at least 50%, 75%, 90%, or 100% reduction respectively from baseline in the total AN count, with no increase from baseline in abscess or draining fistula count.

8.1.1.2. 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 trials setting. The determination of IHS4 requires counting the nodules, abscesses, and draining fistulas/sinus tracts. The IHS4 score (points) = (number of nodules x 1) + (number of abscesses x 2) + (number of draining tunnels [fistulae/sinuses] x 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).

8.1.1.3. 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).

8.1.2. Erythema Score

The erythema score is a scoring system used by the physician to assess the overall degree of erythema in the HS lesions. This assessment uses a 4-point ordinal scale ranging between 0 (no redness) for no erythema and 3 (very red or bright red coloration) for severe erythema. A score of 1 (faint but discernible pink coloration) or 2 (moderate red coloration) indicates a moderate degree of erythema. Refer to Section 10.8.

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 one stage is present in a region, the worst state in each region should be entered.

8.1.4. Hidradenitis Suppurativa-Physician's Global Assessment

The HS-Physician's Global Assessment 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-Physician's Global Assessment 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

8.1.5. Numeric Rating Scale Patient Global Assessment of Skin Pain

The numeric rating scale (NRS) Patient Global Assessment of Skin Pain (Section 10.9) 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.

8.1.6. Dermatology Life Quality Index

Subjects will complete the Dermatology Life Quality Index (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 et al, 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.

8.1.7. 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.

8.1.8. 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.

8.1.9. Hidradenitis Suppurativa Patient Global Impression of Change

Subjects will complete the HS Patient Global Impression of Change (PGIC) (Section 10.11) questionnaire at the designated study visits listed in SoA (Section 1.3). The PGIC consists of one 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 16, when the subject will also be asked about their pain since treatment began during this study.

8.1.10. 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 ≥ 15 and above is considered severe (Snaith and Zigmond, 1994).

8.1.11. 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. Physical Examination

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

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

8.2.2. 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.

8.2.3. Vital Signs

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

8.2.4. Electrocardiograms

Triple 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, QT intervals.

8.2.5. 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 report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the 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.
    a. 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.
    b. All protocol-required laboratory tests, as defined in Section 10.3, must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
    c. 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), then the results must be recorded within source documents.

8.2.6. 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.

8.2.7. Hepatitis Testing

All subjects will be tested for the presence of the hepatitis B virus (HBV) and hepatitis C virus at screening. A positive result for the HBsAg will be exclusionary. Samples negative for HBsAg will be tested for surface antibodies (HBsAb) and core antibodies (HBcAb). If test results are positive for HBcAb or HBsAb, then HBV DNA PCR will be performed and any result that meets or exceeds detection sensitivity will be exclusionary.

8.2.8. 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 another 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.

8.2.9. Home Study Drug Administration Diary

Study-site staff will administer study drug at the first 2 visits. Thereafter, if home dosing is a consideration, the subject or subject's caregiver or designee must administer and demonstrate competency for at least 2 visits prior to being allowed to dose at home. Otherwise, the subject will need to return to the site for all injections. The subject (or caregiver/designee) will complete a diary for every study dose taken outside of the study 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 study 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.

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).

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.

8.3.1. Time Period and Frequency for Collecting AE and SAE 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/designee (see Section 10.3.4).

8.3.2. Method of Detecting AEs and SAEs

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 AEs and SAEs

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 8.3.6) 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 SAEs

- Prompt notification by the investigator to the sponsor or designee 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.

- 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 or designee 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 suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor or designee 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 poststudy 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, he or she 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. 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

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

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

8.4. Pharmacokinetic Assessments

- 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

Not applicable.

8.6. Biomarker Assessments (USA 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 5 years as specified in the future use consent form or other period as per local requirements.
- Biomarker analyses will only be performed on subject samples where future use consent for such analyses has been obtained.

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.
- Anti-drug antibodies (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 8.1.7 Short Form 12 and Section 8.1.8 EQ-5D.

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

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

The primary objective of Part B of this study is to demonstrate that izokibep is superior to placebo in the proportion of subjects achieving HiSCR at Week 16 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 HiSCR at Week 16 among subjects randomly assigned to receive izokibep and placebo, respectively. One set of hypotheses will be tested for each dosing frequency of izokibep.

Analogous statistical hypotheses will be used for the secondary objective of assessing the percentage of subjects who experience a flare through Week 16 and the percentage of subjects who achieve AN count of 0, 1, or 2 at Week 16.

Hypotheses to assess the change in pain score 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 change in Skin Pain NRS from baseline to Week 16.

9.1.1. Multiplicity Adjustment and Type I Error Rate

No alpha-controlled testing will be reported using any data from Part A of the study. Hypotheses tested using data from Part B will be adjusted to control the familywise error rate in the strong sense at $\alpha = 0.050$, two-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 in Part B for the primary efficacy endpoint and the secondary endpoints, all at Week 16, will be carried out in sequential order. The primary endpoint, comparing izokibep dosed QW to placebo dosed QW or Q2W, will be tested first, with significance concluded if $p < 0.0499$. If significant, the primary endpoint, comparing izokibep dosed Q2W to placebo dosed QW or Q2W will be tested next, with significance concluded if $p < 0.0499$.

Testing of secondary endpoints will only be carried out if all prior tests, including both tests of the primary endpoint, first show significance with $p < 0.0499$. As long as all prior tests are significant, testing will proceed in the following order:

- The first secondary endpoint, HiSCR90 at Week 16, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The first secondary endpoint, HiSCR90 at Week 16, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.
- The second secondary endpoint, HiSCR100 at Week 16, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The second secondary endpoint, HiSCR100 at Week 16, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.
- The third secondary endpoint, HiSCR50 at Week 16, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The third secondary endpoint, HiSCR50 at Week 16, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.
- The fourth secondary endpoint, proportion of subjects who experience flare, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The fourth secondary endpoint, proportion of subjects who experience flare, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.
- The fifth secondary endpoint, achieving AN count of 0, 1 or 2 among subjects with baseline Hurley Stage II, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The fifth secondary endpoint, achieving AN count of 0, 1 or 2 among subjects with baseline Hurley Stage II, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.
- The sixth secondary endpoint, change in pain score, comparing izokibep dosed QW to placebo dosed QW or Q2W.
- The sixth secondary endpoint, change in pain score, comparing izokibep dosed Q2W to placebo dosed QW or Q2W.

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

9.2. Analysis Sets

Analysis sets will be created separately for subjects enrolled in Part A and Part B. Hypotheses will be tested using only data from Part B.

Full Analysis Set

Part A

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

Part B

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

For assessment of the third secondary endpoint, the proportion of subjects who achieve AN of 0, 1, or 2 at Week 16, only the subset of subjects in the FAS who have Hurley Stage II at baseline will be included in the assessment. This will be called the FAS for reporting purposes.

Safety Analysis Set

Part A

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

Part B

For assessing the safety objectives, all subjects randomized who receive at least one administration of test material will be included in the summaries and analyses. In the event that a subject receives incorrect study treatment, that subject will be grouped according to treatment received.

9.3. Statistical Analyses

9.3.1. General Considerations

Data from Part A and Part B will be summarized separately.

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. Placebo subjects assigned to receive doses QW or Q2W will be summarized both separately and combined, with hypotheses tested using both placebo dosing frequencies combined.

All hypothesis tests will use only data from Part B and will be reported with two-sided p-values. Comparison of QW dosing to placebo will use only subjects assigned to receive izokibep QW or

placebo; comparison of Q2W dosing to placebo will use only subjects assigned to receive izokibep Q2W or placebo. All CIs will be two-sided with nominal 95% coverage.

Data will be summarized by part and 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.

For testing purposes, subjects randomly assigned to placebo QW and placebo Q2W will be grouped together into a single placebo group for comparison to each dosing regimen of izokibep. This assumes that dosing with placebo QW or Q2W does not affect efficacy, an assumption which will be explored with simple summary statistics. 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.

9.3.2. Primary Endpoint and Estimand

The primary endpoint in Part A 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 8.1.1.1. The primary timepoint for analysis is Week 12 for Part A.

HiSCR75 is defined as meeting all 3 criteria below:

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

Where AN count is abscess count plus inflammatory nodule count, including all abscesses and inflammatory nodules that have previously undergone localized surgical or medical intervention and are no longer present.

The primary endpoint for Part B is HiSCR75, which 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. The primary timepoint for analysis is Week 16 for Part B.

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

The null hypothesis of equal response rates will compare each dosing regimen of izokibep to the combined placebo group. A stratified test of response rates will be used. 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 earlier timepoints when data to calculate the HiSCR are collected will also be presented using the same methodology. P-values from earlier timepoints will be presented for descriptive purposes, not part of the alpha-preserving multiple testing strategy.

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

In Part B, the secondary endpoints are percentage of subjects achieving HiSCR90/100/50 at Week 16, change in pain score, percentage of subjects who experience flare through Week 16 and percentage of subjects with baseline Hurley Stage II who achieved AN count of 0, 1, or 2. The treatment policy strategy will be used to construct estimands for each secondary endpoint.

HiSCR90/100/50 is defined as at least a 90%, 100%, or 50% reduction from baseline in the total AN count with no increase from baseline in abscess or draining fistula count.

The secondary endpoint of percentage of subjects achieving at least a 3-point reduction from baseline in NRS in Patient Global Assessment of Skin Pain at its worst at Week 16 among subjects with baseline NRS ≥ 4 will be analyzed analogously to the primary endpoint. A hybrid estimand will be used, with treatment policy strategy used for most intercurrent events and hypothetical strategy used to account for use of prohibited pain medications. All pain scores after the use of prohibited pain medication will be omitted from the dataset and replaced via non-response imputation. Mean pain from the 7 days prior to an actual visit will be used for analysis, with missing data used at a given visit if fewer than 3 days of observed data are available for that visit. 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 endpoint of percentage of subjects who experience flare will be analyzed analogously to the primary endpoint. Multiple imputation will be used to impute data for subjects with missing data. Subjects with missing AN counts at any scheduled visit (Week 4, Week 8, Week 12 and/or Week 16) will have their AN counts imputed (separately) for each visit with missing data. The imputed counts will be summed and compared to criteria for flare. If the observed or imputed value at any visit meets the definition of flare, the subject will be counted as having a flare; otherwise, the subject will be counted as not having a flare. A total of 100 imputations will be imputed to form the complete data set with a pre-specified seed (3617627) to ensure reproducibility. The final inference on treatment difference is conducted from the multiple datasets using Rubin's combining rules. Other imputation, fully conditional specification method may be implemented if the multiple imputation model does not converge.

The secondary endpoint of 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. Subjects who have missing data at Week 16 or who received an oral antibiotic that could impact HS will be included in the analysis with NRI (did not achieve AN count of 0, 1, or 2). Only subjects with Hurley Stage II at baseline will be included in the hypothesis test for AN count, while other subjects will be summarized, and a p-value reported for descriptive use only.

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. Safety will be reported separately for Parts A and B of the study. In Part B, subjects who received placebo QW and placebo Q2W will be combined for summaries during the placebo-controlled portion of the study. 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 of the primary endpoint 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 first administration of study drug will be listed. All summaries will include only treatment-emergent events. The number of subjects who report one or more AEs, the number who report one or more severe AEs, the number who report one or more SAEs, and the number who report one 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 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

After all subjects in Part A have had the opportunity to complete the Week 8 visit (or discontinued the study early), data at Week 8 will be summarized. The DMC will review the data from Part A only and recommend continuing, stopping, or altering Part B of the study.

No formal interim analysis of data from Part B is planned for purposes of stopping or altering this study. Two summaries of primary endpoint data are planned before the last subject completes the study:

- After the first 105 subjects have had the opportunity to complete the Week 8 visit, the DMC will review unblinded data to make a recommendation on further development activities of izokibep. The DMC will not be empowered to recommend stopping this study or changing the sample size due to a demonstration of positive efficacy. The type I error rate for hypothesis tests at the end of the study will be decreased by 0.0001 to account for this interim summary of unblinded data. The study team and the investigators will remain blinded to these interim results until after the study is completed.
- After all subjects have had an opportunity to complete the Week 16 visit (complete the visit, or complete a subsequent visit, or permanently discontinue the study), the primary endpoint analyses may be conducted. These will be the final analyses for the primary endpoint, so no adjustment of the type I error will be applied. Site staff, and all sponsor staff who interact with site staff, will remain blinded to individual subject treatment assignment until the final subject has completed the final visit.

9.5. Sample Size Determination

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

In Part B, comparisons will have approximately 55 subjects in each izokibep regimen compared to approximately 55 subjects on placebo (QW and Q2W combined). In prior studies of adalimumab in a similar patient population (Kimball, 2016a), HiSCR75 response rates of 10% to 15% were observed with placebo compared with response rates of 25% to 35% with adalimumab. If true response rates with placebo and izokibep are 15% and 40%, respectively, this study will have approximately 80% power to reject the null hypothesis of equal response rates. This calculation was made in SAS® using the POWER procedure on an unstratified test of binomial proportions.

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 international ethical guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations.
- 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.
- Approval for protocols and any substantial amendments to the protocol that requires health authority approval prior to initiation will be obtained except for changes necessary to eliminate an immediate hazard to study subjects.
- The investigator will be responsible for the following:
  - 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the subject and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, 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.
- 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 by the sponsor. 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.
- The subject must be informed that the subject's personal study-related data will be used by the sponsor in accordance with local data protection law. 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 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 regulatory authorities.
- 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. 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 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 will notify all competent data protection authorities of the breach, where required by local regulations. Where feasible and permissible by applicable law, such notification will occur within 72 hours of becoming 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.

- Taking into account 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, identity and access management procedures to restrict physical and logical access to the data, network perimeter and endpoint protection using firewalls and other intrusion detection systems, 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 CRF data from all study 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 CRFs 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 CRF.
- Guidance on completion of CRFs 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 course of 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 CRF 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 CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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 shall 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 clinical trial agreement/site contract will cover additional details regarding publications.
- 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 multi-center studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated.
- 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 4 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4. Protocol-required Safety Laboratory Tests

Laboratory Tests	Parameters			
Hematology	Platelet count Red blood cell (RBC) count Hemoglobin Hematocrit	RBC indices: Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical chemistry[1]	Blood urea nitrogen (BUN)	Potassium	Aspartate aminotransferase (AST)/serum glutamic-oxaloacetic transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT)	Total protein
	Glucose (non-fasting)	Calcium	Alkaline phosphatase[2]	Fasting lipid (total cholesterol, triglycerides & HDL)
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy testing	• Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) at screening[3]			
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) • Serology hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody • Tuberculosis testing: QuantiFERON® test or purified protein derivative (PPD) test o Note: T-SPOT® tuberculosis test may be acceptable if agreed upon with the medical monitor			

Laboratory Tests	Parameters
	• All study-required laboratory tests will be performed by a central laboratory, with the exception of: o Urine pregnancy test o PPD test
Other tests	• C-reactive protein • Pharmacokinetics (PK) • Anti-drug antibody (ADA) • Hemoglobin A1C • HIV • Exploratory biomarkers

NOTES:
[1] 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 and Study Drug Rechallenge Guidelines.
[2] If alkaline phosphatase is elevated, consider fractionating.
[3] After screening, local urine pregnancy testing will be performed unless serum testing is required by local regulation, regulatory agency, or Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Investigators must document their review of each laboratory safety report.

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, 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).
- 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

- 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 significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of study drug dependency or study drug 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 CRF/SAE form.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the sponsor or designee in lieu of completion of the required CRF/SAE form.
- 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, will be 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 Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild**: Awareness of symptoms that are easily tolerated, causing minimal discomfort, and not interfering with everyday activities.
- **Moderate**: Sufficient discomfort is present to cause interference with normal activity.
- **Severe**: Extreme distress, causing significant impairment of functioning or incapacitation; prevents normal everyday activities.

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**: A causal relationship can be excluded, and another documented cause of the AE is most plausible.
- **Related**: 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 make an assessment of 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 in light of 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 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 sponsor or 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 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 in order 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.

10.4. 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 one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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 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 Guidance

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, postovulation 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 and Study Drug Restart/Rechallenge Guidelines

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 FDA 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	Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 5 x upper limit of normal (ULN)
ALT or AST Increase	ALT or AST ≥ 3 x ULN persists for ≥ 4 weeks
Bilirubin[1,2]	ALT or AST ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN (> 35% direct bilirubin)
INR[2]	ALT or AST ≥ 3 x ULN **and** international normalized ratio (INR) > 1.5
Cannot Monitor	ALT or AST ≥ 3 x ULN and cannot be monitored twice weekly for 4 weeks
Symptomatic[3]	ALT or AST ≥ 3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity
Required 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 a serious adverse event (SAE) CRF if the event met the criteria for an SAE.[2] • Perform follow-up assessments as described in the Follow-Up Assessment column. • Monitor the subject until liver chemistry test abnormalities resolve, normalize, or return to baseline.	• Viral hepatitis serology[4] • Obtain blood sample for pharmacokinetic (PK) analysis after the most recent dose[5]. • Obtain serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma-glutamyltransferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin. • Fractionate bilirubin, if total bilirubin ≥ 2 x ULN.

MONITORING:

If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN or INR > 1.5 (with or without symptoms of liver injury or hypersensitivity):

- 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, normalize, or return to baseline.
- A hepatology consultation is recommended.
- Additional monitoring may be done at the investigator's discretion.
- See additional follow-up tests in this section.

If ALT or AST ≥ 3 x ULN AND total bilirubin < 2 x ULN and INR ≤ 1.5 (with or without symptoms of liver injury or hypersensitivity):

- 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, normalize, or return to baseline.
- Additional monitoring may be done at the investigator's discretion.
- Once abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic, frequency of retesting can decrease to once a week or less.
- **Do not restart/rechallenge** subject with study drug unless allowed per protocol and sponsor approval is granted.

- Obtain complete blood count with differential to assess eosinophilia.
- Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the CRF.
- Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications CRF.
- Record alcohol use on the alcohol and nicotine use CRF.

If ALT or AST ≥ 3 x ULN AND total bilirubin ≥ 2 x ULN or INR > 1.5 obtain the following in addition to the assessments listed above:

- Antinuclear antibody, antismooth muscle antibody, Type 1 antiliver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG), or gamma globulins.
- Serum acetaminophen adduct assay, when available, to assess potential acetaminophen contribution to liver injury in 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:
  - In subjects when serology raises the possibility of autoimmune hepatitis (AIH)
  - 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 provide biopsy information.

1. 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.
2. All events of ALT or AST ≥ 3 x ULN **and** total bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT or AST ≥ 3 x 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 if SAE criteria met (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to subjects receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash, or eosinophilia).
4. 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 CRF. If the date or 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
AE	adverse event
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity
$AUC_{0-\tau}$	area under the plasma concentration-time curve over a dosing interval
BID	twice daily
CI	confidence interval
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
COVID-19	coronavirus disease of 2019
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CV%	percent coefficient of variation
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
ECG	electrocardiogram
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
HBV	hepatitis B virus
HBcAb	hepatitis B core antibodies
HBsAb	hepatitis B surface antibodies
HbsAg	hepatitis B surface antigen

Abbreviation	Definition
HiSCR	hidradenitis suppurativa clinical response 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
HiSCR50	HiSCR 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	HiSCR 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	HiSCR 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	HiSCR defined as at least a 100% reduction from baseline in the total abscess and inflammatory nodule count, with no increase from baseline in abscess or draining fistula count
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
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	interleukin
IMP	investigational medicinal product
IRB	Institutional Review Board
IXRS	Interactive Voice/Web Response System
IV	intravenous(ly)
JAK	Janus kinase
MMRM	nonlinear mixed effects model with repeated measures
NOAEL	no observed adverse effect level
NRI	non-response imputation
NRS	numeric rating scale
PASI	Psoriasis Area and Severity Index

Abbreviation	Definition
PCR	polymerase chain reaction
PGIC	Patient Global Impression of Change
PK	pharmacokinetics
PPD	purified protein derivative
PRN	as needed
QW	every week
Q2W	every other week
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus
SC	subcutaneous(ly)
SF-12v2	12-Item Short Form Survey version 2
SoA	Schedule of Activities
$t_{½}$	half-life
TEAE	treatment-emergent adverse events
Th17	IL-17-producing T-helper cells
t_{max}	time to maximum observed concentration
TNF-α	tumor necrosis factor-α
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
WOCBP	women of childbearing potential

10.7. Lesion Count

Lesion counts[a]	Abscess	Non-draining fistula	Draining fistula	Non-inflammatory nodule	Inflammatory nodule	Hypertrophic scar	Longest distance (mm) between 2 relevant lesions[b]	Intervening normal appearance tissue (yes or no)[c]
Left axilla								
Right axilla								
Left sub/inframammary Area								
Right sub/inframammary area								
Intermammary area								
Left buttock								
Right buttock								
Left inguino-crural fold[d]								
Right inguino-crural fold[d]								
Perianal								
Perineal								
Upper back and neck								
Other								
Totals								

[a] Lesion counts are to be recorded every study visit.
[b] If only 1 lesion, record diameter of that single lesion.
[c] Are all lesions in this area clearing and separated by normal-appearing tissues? Answer: yes or no.
[d] Includes the immediate adjacent area.

10.8. Erythema Score

Example

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

Region (to be assessed at every visit)	**Degree of Erythema**
Left axilla	
Right axilla	
Left sub/inframammary area	
Right sub/inframammary area	
Intermammary area	
Left buttock	
Right buttock	
Left inguino-crural fold	
Right inguino-crural fold	
Perianal	
Perineal	
Upper back and neck	
Other	

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

10.9. Numeric Rating Scale Patient Global Assessment of Skin Pain

Example

Please answer the questions below **before you go to bed**. Please mark an "X" in the box (☐) which best describes the severity of your skin pain in the **last 24 hours**.

1. In the last 24 hours, which number best describes your skin pain at its worst due to your HS?	No skin pain										Skin pain as bad as you can imagine
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
2. In the last 24 hours, which number best describes your skin pain on average due to your HS?	No skin pain										Skin pain as bad as you can imagine
	0	1	2	3	4	5	6	7	8	9	10
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

10.10. Daily Subject Analgesic (Pain) Use Diary – Example

Please answer the questions below before you go to bed. Provide your response based on the past 24 hours.

Did you take any pain medication in the past 24 hours? □ Yes □ No

If YES:

Fill in the chart with the information about the pain medication you took. If "Other" write in the name of the pain medication you took.

	Type of Pain Medication Taken (check box)	**Was the Pain Medication for HS?**	**Dose and Unit (example 325 mg pill)**	**Number of Pills Taken (example: 2 pills)**
Pain Medication	□	□ Yes □ No		
Ibuprofen	□	□ Yes □ No		
Acetaminophen	□	□ Yes □ No		
Tramadol	□	□ Yes □ No		
Other pain medication:	□	□ Yes □ No		
Other pain medication:	□	□ Yes □ No		
Other pain medication:	□	□ Yes □ No		

10.11. Hidradenitis Suppurativa Patient Global Impression of Change

Example

1. Since your last visit, how would you rate your pain due to your Hidradenitis Suppurativa (HS)?

- ☐ Very much worse
- ☐ Much worse
- ☐ A little worse
- ☐ No change
- ☐ A little better
- ☐ Much better
- ☐ Very much better

Note, at Week 16 an additional question with the same response options will be as follows: Since the start of study treatment, how would you rate your skin pain due to your Hidradenitis Suppurativa (HS)?

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Approval Task Task Verdict: Approved	PPD

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