TITLE PAGE

Protocol Title: A Phase 2a, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ATI-450 vs Placebo in Patients with Moderate to Severe Hidradenitis Suppurativa (HS)

Protocol Number: ATI-450-HS-201

Version Number: 5.0

Product: ATI-450

Short Title: ATI-450 vs Placebo in Patients with Moderate to Severe Hidradenitis Suppurativa (HS)

Study Phase: 2a

Sponsor Name: Aclaris Therapeutics, Inc

Legal Registered Address:

640 Lee Rd, Ste 200
Wayne, PA 19087, US

Regulatory Agency Identifying Number(s): IND No. 157784

Date of Protocol: 04 August 2022 (Amendment 4, Version 5.0)

Sponsor Signatory

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements. I have read this protocol in its entirety and agree to conduct the study accordingly:

8/4/2022

Date

Aclaris Therapeutics, Inc

Medical Monitor name and contact information can be found in Appendix 2.

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TABLE OF CONTENTS

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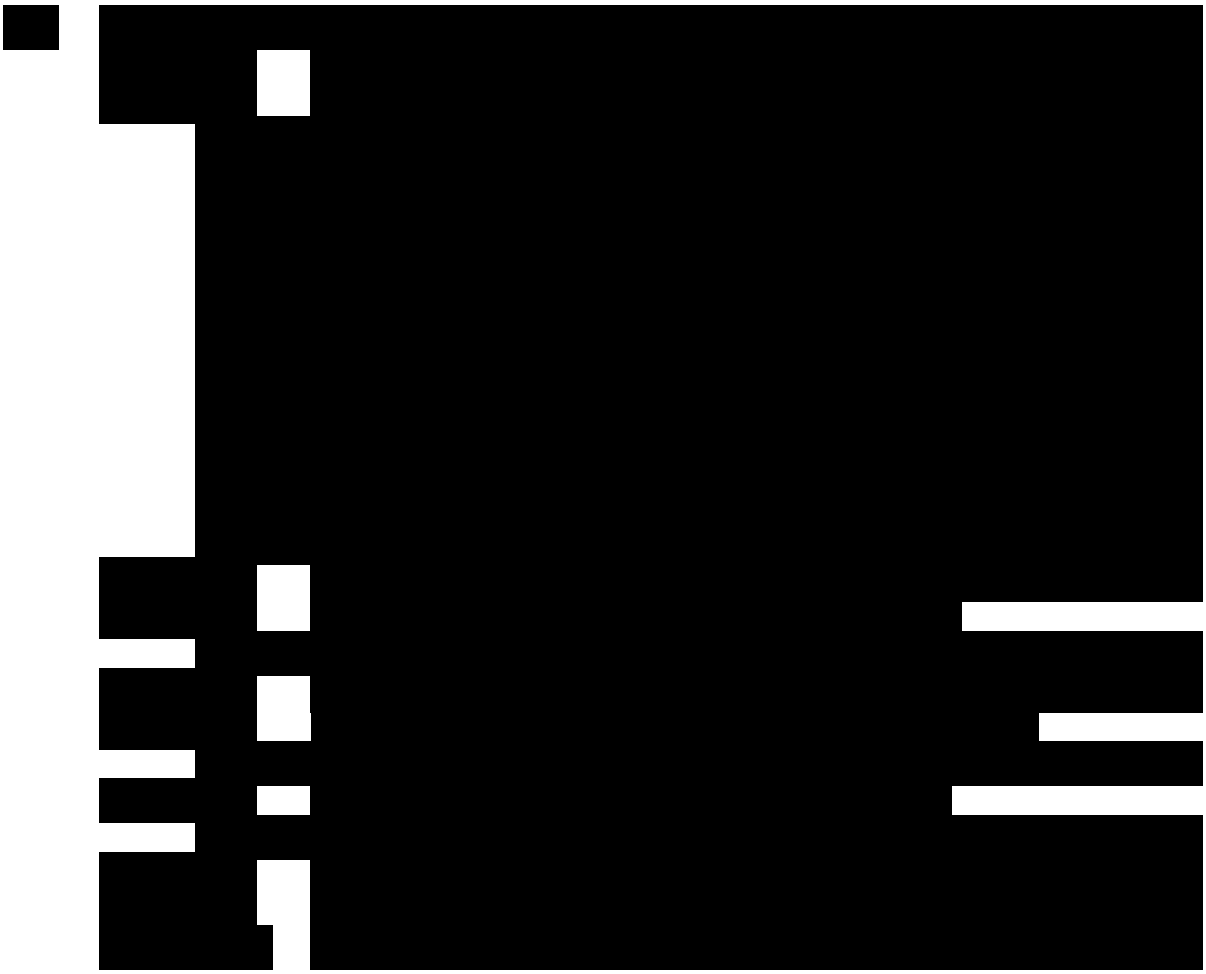


TABLE OF TABLES

TABLE OF FIGURES

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ATI-450 vs Placebo in Patients with Moderate to Severe Hidradenitis Suppurativa (HS).

Short Title: ATI 450 vs Placebo in Patients with Moderate to Severe Hidradenitis Suppurativa (HS)

Rationale:

Hidradenitis suppurativa (HS) is a chronic inflammatory disease primarily affecting apocrine-gland-rich regions of the body such as the axillary and groin areas. The pathophysiology of HS is complex and has not been clearly defined. The primary defect in HS involves occlusion of hair follicles, which leads to dilatation and rupture. The resulting spillage of follicular contents into the surrounding dermis induces a chemotactic response from neutrophils and lymphocytes and inflammation of the hair follicle leads to innate and adaptive immune dysregulation. An upregulation of various cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, IL-8, IL-17, IL-23, and other molecules appears to be important in the pathophysiology of this inflammatory condition.

The study treatment ATI-450 is an orally available, novel, potent, and selective small molecule inhibitor of the p38α mitogen-activated protein kinase (MAPK)/MAPK-activated protein kinase 2 (MK2) inflammatory signaling pathway being developed for treatment of inflammatory disorders. The p38 MAPK pathway offers great potential in the treatment of inflammatory diseases such as hidradenitis suppurativa (HS). By targeting MK2, which is downstream from p38, it is believed that ATI-450 can effectively and safely inhibit pro-inflammatory pathways without substantially impacting other anti-inflammatory pathways. Inhibition of MK2 by ATI-450 has been shown to reduce levels of TNF-α, ILβ, IL6 and IL8. Unlike monoclonal antibody approaches, ATI-450 may inhibit multiple cytokines involved in the pathophysiology of HS. Inhibiting multiple cytokines may deliver good efficacy. This study is being conducted to determine the efficacy, safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of 12 weeks of ATI-450 exposure in patients with moderate to severe HS. This important data will further describe the efficacy and safety of ATI-450 in a relevant patient population.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of ATI-450 in patients with moderate to severe HS	• Change from Baseline in inflammatory nodule/abscess count at Week 12
Secondary	
• To assess the efficacy and safety of ATI-450 in patients with moderate to severe HS	• Percentage of patients achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12 HiSCR is defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule (AN) count, with no increase in abscess or draining fistula counts. • Change from Baseline in International Hidradenitis Suppurativa Severity Score System (IHS-4) over time for the 12-week treatment period • Percentage of patients achieving at least a 30% reduction and at least 1 unit reduction from Baseline in the numerical rating scale (NRS30) in Patient's Global Assessment of Skin Pain at Week 12 among patients with Baseline NRS ≥3. NRS30 is evaluated based on worst skin pain in a 24-hour recall period (maximal daily pain). • Change from Baseline in Hidradenitis Suppurativa-Physician Global Assessment (HS-PGA) over time for the 12-week treatment period • Change from Baseline in Dermatology Life Quality Index (DLQI) over time for the 12-week treatment period The DLQI is a 10-item validated questionnaire used to assess the impact of HS disease symptoms and treatment on quality of life (QoL). It consists of 10 questions evaluating impact of skin diseases on different aspects of a patient's QoL over the prior week, including symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment. • Hurley Stage over time for the 12-week treatment period • Incidence of adverse events (AEs), serious AEs (SAEs), laboratory value abnormalities, electrocardiogram (ECG) abnormalities, vital signs abnormalities
• To assess the PK of ATI-450 in patients with moderate to severe HS	• Trough ATI450 and metabolite (CDD-2164) concentrations at clinic visits. On Day 1, 8, and 85 trough and 2-hour post dose) will be collected.

Exploratory	
• To assess the PD of ATI-450 in patients with moderate to severe HS	[redacted]

Overall Design:

This is a Phase 2a, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety, tolerability, PK, and PD of ATI-450 50 mg twice daily (BID) versus placebo in patients with moderate to severe HS.

- The study will consist of an up to 28-day Screening Period, a 12-week treatment period, and a 30-day follow-up period. The total duration of the study for patients remaining until their final follow-up assessment will be up to 21 weeks.
- The Investigator will obtain signed informed consent from the patient before any study procedures are performed.
- During the Screening Period, each patient will be required to have all assessments performed as outlined in the Schedule of Assessments (SoA) (Table 1).
- Results for all the Screening assessments must be available at the time patient eligibility is reconfirmed prior to randomization and dosing.
- Patients whose eligibility is confirmed at Baseline will be randomized in a 1:1 ratio to receive either ATI-450 tablets (50 mg BID) or matching placebo tablets BID. Study treatments will be administered orally for 12 weeks.
- Patients will attend clinic visits on Days 1, 8, 15, 29, 43, 57, and 85 for safety, efficacy, PK, and PD assessments. The morning dose of study treatment will be administered in the clinic on each study visit day.
- On Day 85 (Week 12), patients will complete the end of study (EOS) assessments. A safety follow-up visit will be conducted 30 days after the last dose of study treatment for patients who completed the treatment period, as well as those who discontinue early.
- The study is randomized and double-blinded to prevent bias in treatment allocation and in the assessment of treatment effect.

Number of Investigators and Study Centers:

Approximately 20 Investigators and study centers in the United States are expected to participate in this study.

Number of Patients:

It is planned to randomize approximately 90 patients, 45 patients per arm (Section 9.2).

Treatment Groups and Duration:

Patients will be randomized to receive ATI-450 or placebo BID for 12 weeks; however, study duration will be up to 21 weeks.

Target Population: Male or nonpregnant, nonbreastfeeding female patients between 18 and 70 years of age, inclusive, at the time of signing the ICF, who have been diagnosed with moderate to severe HS.

Inclusion Criteria

Patients must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and be willing to sign the Institutional Review Board (IRB)-approved patient ICF prior to administration of any study-related procedures.
2. Patient with HS for at least 1 year (365 days) prior to Baseline visit; duration of disease as determined via Investigator review of patient medical history.
3. Patient must have stable HS for at least 60 days prior to Screening visit and at Baseline visit as determined via Investigator review of patient medical history.
4. Total abscesses and/or nodule (AN) count of ≥5 at Baseline visit. Abscesses and nodules must have the following signs of inflammation. (Inflammatory nodules should be raised):
    a. Clinical evidence of erythema and/or warmth.
    b. Clinical evidence of pain/tenderness.
5. HS lesions present in at least 2 distinct anatomical areas at Screening and Baseline. (Bilateral involvement of the same area counts as 2 areas, eg, involvement of right and left axilla.)
6. Draining fistula count of ≤20 at Baseline visit.
7. Male or nonpregnant, nonbreastfeeding female patients between 18 and 70 years of age, inclusive, at the time of signing the ICF.
    a. Heterosexually active female patients who are of childbearing potential must use 2 methods of highly effective contraception, 1 of which must be a physical barrier, for the duration of the study and for 30 days after the last dose (see Appendix 6).
    b. Heterosexually active male patients of childbearing potential with a female partner of childbearing potential must agree to use a condom plus another highly effective form of birth control for the duration of the study and for 90 days after the last dose (Appendix 6Appendix6).
8. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to dosing on Day 1.
9. Screening laboratory evaluations (hematology, chemistry, coagulation, and urinalysis) must fall within the normal range of the central laboratory's reference ranges unless the results have been determined by the Investigator to not be clinically significant.
10. No COVID-19 vaccination or booster within the 4 weeks prior to randomization. Note: COVID vaccination is highly encouraged but not required.

Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Patient has a history of active skin disease other than HS that could interfere with the assessment of HS.
2. Patient has an uncontrolled non-immunoinflammatory disease that may place the patient at increased risk during the study or impact the interpretation of results, eg, previous malignancy, previous venous thromboembolism.
3. History or evidence of active tuberculosis, irrespective of prior or current treatment status; or current or prior untreated latent tuberculosis. Note: Prior latent tuberculosis with completed treatment is not an exclusion.
4. Known hypersensitivity to ATI-450.
5. Patient is an alcoholic, or has a history of alcoholism, alcoholic liver disease, or other chronic liver disease.
6. Active infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.

7. Positive for human immunodeficiency virus (HIV), hepatitis B or C. Note: Patients with hepatitis B surface antibody without the presence of hepatitis B surface antigen will be allowed to participate. Patients with hepatitis C antibody positive can have Hepatitis C viral load tested, if the Hepatitis C virus is undetectable and the patient has been off antivirals for 6 months, he/she may be enrolled in the study.
8. Tests performed at a central laboratory at Screening that meet any of the criteria below (out of range labs may be rechecked once, after consultation with the Medical Monitor, before patient is considered a screen failure):
    a. White blood cell count $<3.0\times10^3$ cells/mm^3.
    b. Absolute neutrophil count $<1.5\times10^3$ cells/mm^3.
    c. Lymphocyte count $<0.5\times10^3$ cells/mm^3.
    d. Platelet count $<100\times10^3$ cells/mm^3.
    e. Hemoglobin <10 g/dL.
    f. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥1.5 × upper limit of normal (ULN).
    g. Total bilirubin level ≥2 × ULN unless patient has been diagnosed with Gilbert syndrome and this is clearly documented.
    h. Estimated glomerular filtration rate (eGFR), <40 mL/min/1.73 m^2 based on Modification of Diet and Renal Disease formula.
9. Any clinically significant laboratory abnormality that would affect interpretation of study data or safety of the patient's participation in the study, per judgment of the Investigator.
10. Clinically significant abnormal findings other than HS from physical examination (PE) conducted at Screening visit (Visit 1) and at Baseline visit (Visit 2) that may affect the interpretation of study data or the safety of the patient's participation in the study, per the judgment of the Investigator.
11. Clinically important history of a medical disorder that would compromise patient safety or data quality, per judgment of the Investigator.
12. Blood pressure levels (in semi-supine position after at least 5 minutes rest): <90 mmHg or >150 mmHg for systolic blood pressure (BP) or <40 mmHg or >90 mmHg for diastolic BP.
13. Patient has experience with >2 biologics, >1 Janus kinase (JAK) inhibitor, or a combination of 1 biologic experience and 1 JAK inhibitor.

[redacted]

[redacted]

15. Are currently receiving corticosteroids at doses greater than 10 mg per day of prednisone (or equivalent) or have been receiving an unstable dosing regimen of corticosteroids within 2 weeks of the Screening visit.
16. Have been using prescription topical therapies for treatment of HS within 14 days prior to Baseline visit.
17. Oral or topical tetracycline class antibiotics for treatment of HS are allowable if patient is on a stable dose for 4 weeks prior to Baseline and willing and able to maintain the stable dose for duration of study.

[redacted]

20. Patients with history of stroke.
21. Significant active cardiac disease, in the past 6 months, that would affect interpretation of study data or the safety of the patient's participation in the study, per judgment of the Investigator. This includes myocardial infarction or unstable angina, acute coronary syndrome, or heart failure with New York Heart Association Class II, III or IV symptoms. In addition, patients with a personal or family history of congenital long QT syndrome, Torsades de Pointes, sustained or symptomatic VT, or unexpected sudden cardiac death.
22. Patients with any of the following Baseline predose ECG findings:
    a. Mean QTcF >450 msec as averaged on triplicate ECG;
    b. ECG or historical evidence of Wolff-Parkinson-White Syndrome (unless ablated);
    c. If atrial fibrillation or flutter is present, the mean ventricular response must be < 90 BPM and the patient must be anticoagulated according to national guidelines; and/or
    d. Any other finding that is considered clinically significant.
23. Any dermatologic surgery or procedure in the past 90 days prior to Screening.
24. Known exposure to an individual with a confirmed, active diagnosis of COVID-19 at any time during the Screening Period.
25. Participated in another ATI-450 clinical study.
26. History of clinically significant drug abuse within 2 years prior to Screening. Note: Marijuana use is allowed if not considered substance abuse by the investigator.

27. Uncontrolled hypokalemia (<3.8mmol/L), or uncontrolled hypomagnesemia (< LLN).

[redacted]

Statistical methods:

Details of all statistical summaries will be provided in the study-specific statistical analysis plan (SAP).

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. Unless otherwise stated, hypothesis tests and corresponding *P* values will be 1-sided with an alpha level of 0.05. No adjustments will be made for multiplicity.

Baseline is defined as the last nonmissing measurement before, or on the date of first administration of, study treatment.

Determination of Sample Size

Ninety (90) randomized patients will provide 90.3% power to demonstrate the superiority of ATI-450 to placebo in the reduction in inflammatory nodules and abscesses at Week 12. This power computation assumes that the reduction in the placebo arm will be on average 2.5 nodules/abscesses and the ATI-450 reduction will be on average 4.75 nodules/abscesses. The assumed standard deviation for the number of nodules/abscesses was assumed to be 3.6. These sample size assumptions were based on the values observed in the adalimumab PIONEER I and PIONEER II Phase 3 trials (Frew et al, 2020). The assumed reduction in nodules/abscesses for ATI-450 was chosen to be slightly less than that shown in the PIONEER I and PIONEER II Phase 3 to account for the potential impact of dropouts on the efficacy.

Interim Analyses

No interim analysis is planned.

Analysis Populations

- The Full Analysis Set (FAS) population will include all patients who have been randomized and administered at least 1 dose of study treatment. The efficacy analyses will be conducted on the FAS population as randomized.
- The Per Protocol (PP) population will include all randomized patients who remain on study treatment, complete assessments for their Day 85 visit, and do not have any major protocol violations.
- The Safety Analysis Set population will include all patients who: are randomly assigned to study treatment, and take at least 1 dose of study treatment. Patients will be analyzed according to the treatment they actually received.

- The PK population will include all patients randomly assigned to study treatment and who take at least 1 dose of study treatment and have at least 1 evaluable PK measurement.
- The PD population will include all patients randomly assigned to study treatment and who take at least 1 dose of study treatment and have at least 1 evaluable PD measurement.

Efficacy Analyses

All efficacy summaries will be conducted on both the FAS and PP populations.

The primary efficacy analysis will be the treatment comparison of the change from Baseline in inflammatory nodules and abscesses at Week 12 in the FAS population. This analysis will be conducted within the context of a Mixed Model Repeated Measures (MMRM). This model will include factors for treatment group, time, and time by treatment interaction as well as a Baseline covariate. Patient identifiers will be included in the model in a manner that allows observations within a given patient over time to be treated as repeated measures. Point estimates and 90% confidence intervals (CIs) for the difference in least square means (LS means) will be provided in addition to the 1-sided *P* values.

Treatment comparisons for all secondary responder endpoints (percentage of patients meeting HiSCR at Week 12, percentage of patients achieving at least 30% reduction from Baseline in NRS30 in PGA Skin Pain, and percentage of patients who experience at least a 25% increase in AN count with a minimum increase of 2 relative to Baseline over the 12-week treatment period) will be conducted using a logistic regression applied to each time point separately. The logistic regression will include a factor for treatment group and a covariate for Baseline, where appropriate. These analyses will be done for both the FAS and PP populations.

Treatment comparisons for all continuous secondary endpoints will be conducted using a MMRM like the one described for the primary endpoint. These analyses will be done for both the FAS and PP populations.

Safety Analyses

The Safety population will be used for the analysis of safety data (AEs, exposure to study treatment, clinical laboratory values, vital signs, and ECG).

Adverse events will be coded with the Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug Global B3 March 2021. Treatment-emergent adverse events (TEAEs) are defined as AEs with an onset date on or after the date of first administration of study treatment and before the date of last administration of study treatment + 30 days. Treatment-emergent adverse events will be presented by system organ class and preferred term in frequency tables. Patients with multiple AEs will be counted only once within each preferred term and system organ class. Key patient information for patients with an AE with an outcome of death, patients with SAEs, and patients with an AE leading to discontinuation of study treatment will be listed.

Laboratory data (hematology, serum chemistry, coagulation, and urinalysis) will be converted to Système International (SI) units for reporting and processing purposes. Absolute values and changes from Baseline will be presented descriptively. Laboratory data outside study specific reference ranges will be listed. Vital signs and ECG parameters will be presented descriptively.

ATI-450 Drug Concentrations and Pharmacokinetic Analyses

Plasma concentrations of ATI-450 and its primary circulating metabolite, CDD-2164, will be summarized by day and sample. Concentration versus time since dose (Days 1, 8, 15, 29, 43, 57, and 85) will be displayed by linear scale.

[redacted]

Handling of Missing Data

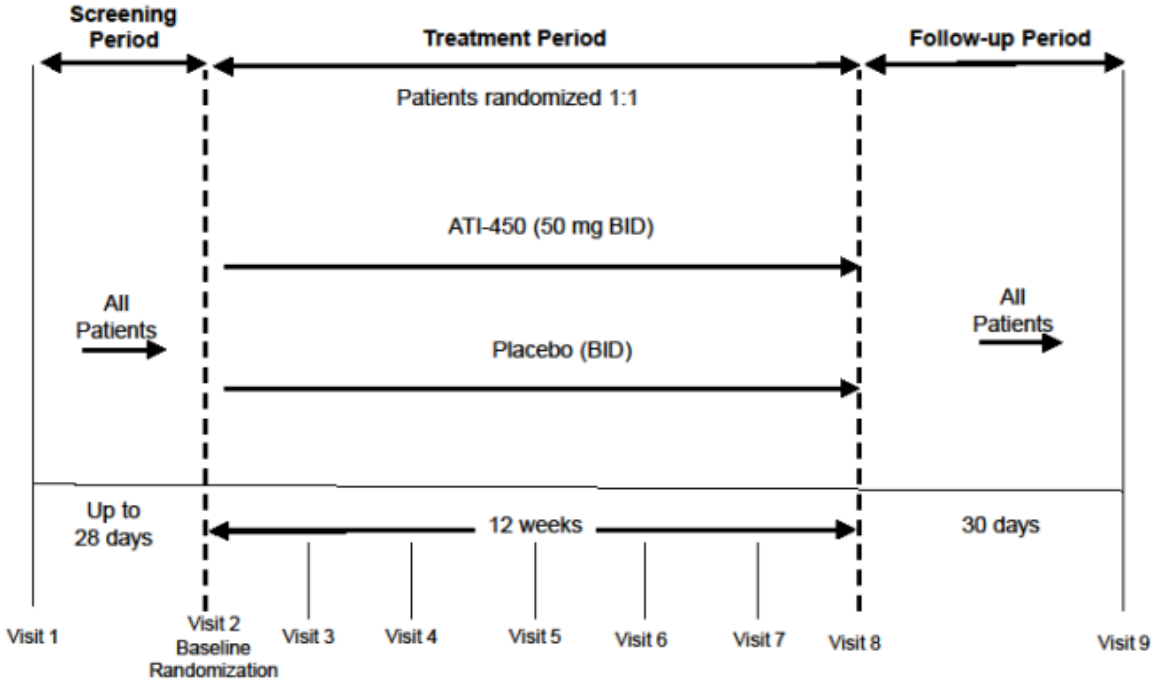
Missing data will not be imputed for the safety summaries, or the efficacy summaries conducted on the PP population. All efficacy analyses conducted on the FAS population will use a last observation carried forward (LOCF) imputation. Additionally, a sensitivity analysis will be conducted for categorical endpoints conducted on the FAS using a non-responder imputation method. Further details regarding the imputation of data that are missing or following intercurrent events will be provided in the SAP.

Data Monitoring Committee:

An independent DSMB will convene to monitor interim safety data. Details regarding DSMB membership, responsibilities, and meeting frequency are outlined in the DSMB Charter.

1.2 Schema

Figure 1 Study Schema



Abbreviations: BID =twice daily

1.3 Schedule of Assessments

Table 1 Schedule of Assessments

Assessment	**Screening Visit 1** **Day -28 to Day -1**	**Baseline Visit 2** **Day 1[j]**	**Visit 3** **Day 8[j]**	**Visit 4** **Day 15**	**Visit 5** **Day 29**	**Visit 6** **Day 43**	**Visit 7** **Day 57**	**Visit 8** **Day 85** **(Week 12/ET)**	**Follow-up Visit 9** **30 days**
Visit Window	NA	NA	±1 day						(+7 days)
Assessments[i]									
Informed Consent	X								
Eligibility Review	X	X							
Randomization		X							
Demographics	X								
Medical History; HS and Other Current Medical Conditions	X								
Lesion Count including AN and draining fistula (tunnels) count	X	X	X	X	X	X	X	X	X
NRS30 – Patient's Global Assessment Skin Pain		X	X	X	X	X	X	X	
DLQI Scale		X			X		X	X	
Hurley Stage Assessment	X	X	X	X	X	X	X	X	X

Assessment	**Screening Visit 1 Day -28 to Day -1**	**Baseline Visit 2 Day 1[j]**	**Visit 3 Day 8[j]**	**Visit 4 Day 15**	**Visit 5 Day 29**	**Visit 6 Day 43**	**Visit 7 Day 57**	**Visit 8 Day 85 (Week 12/ET)**	**Follow-up Visit 9 30 days**
Visit Window	NA	NA	±1 day						(+7 days)
Assessments[i]									
HS-PGA Scale	X	X	X	X	X	X	X	X	X
12-Lead ECG[a]	X	X	X	X	X	X	X	X	
Vital Signs[b]	X	X	X	X	X	X	X	X	X
Body Weight, BMI (derived)	X							X	
Full Physical Exam, Including Height	X								
Targeted Physical Exam		X	X	X	X	X	X	X	X
Lesion Photography (optional)		X			X			X	
Laboratory Assessments: Hematology, Coagulation, Chemistry, Lipids, and Urinalysis	X	X	X	X	X	X	X	X	X
hsCRP	X	X	X	X	X	X	X	X	X
HIV and Hepatitis B & C Screen	X								
SARS-CoV-2 Testing	X	X							
QuantiFERON Gold Test for TB	X								

Assessment	**Screening Visit 1** **Day -28 to Day -1**	**Baseline Visit 2** **Day 1[j]**	**Visit 3** **Day 8[j]**	**Visit 4** **Day 15**	**Visit 5** **Day 29**	**Visit 6** **Day 43**	**Visit 7** **Day 57**	**Visit 8** **Day 85** **(Week 12/ET)**	**Follow-up Visit 9** **30 days**
Visit Window	NA	NA	±1 day						(+7 days)
Assessments[i]									
Serum Pregnancy (WOCBP Only)	X								
Urine Pregnancy (WOCBP Only)		X	X	X	X	X	X	X	X
PK Blood Sampling		X[c]	X[c]	X[d]	X[d]	X[d]	X[d]	X[c]	
[redacted]									
Dispense Study Treatment		X	X	X	X	X	X		
Administration of Morning Dose of Study Treatment in Clinic		X	X	X	X	X	X	X[g]	
Study Treatment Accountability			X	X	X	X	X	X	
Adverse Events[h]	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X

AE=adverse event; AN=abscess and inflammatory nodule count; BMI=body mass index; DLQI=Dermatology Life Quality Index; ECG=electrocardiogram; EOS=end of study; ET=early termination; HIV=human immunodeficiency virus; HS=hidradenitis suppurativa; hsCRP=high sensitivity C-reactive protein; HS-PGA=Physician Global Assessment Scale; mRNA=messenger RNA; NRS30= Numerical Rating Scale for Patient's Global Assessment of Skin Pain; PD=pharmacodynamic; PK=pharmacokinetic; SARS-CoV-2=severe acute respiratory syndrome coronavirus 2; TB=tuberculosis; WOCBP=women of childbearing potential.

a. Triplicate 12-lead ECGs will be performed at least 30 seconds apart, in a supine position, after resting for at least 10 minutes (without external stimulation, e.g., talking, TV, noise) and submitted for central reading. Screening ECGs will be collected prior vital signs and blood samples. On Day 1 and 8, ECGs will be taken predose and 2 hours postdose. Patients not fasting on Day 1 and 8 will have an additional 4 hr postdose ECG. On Days 15, 29, 43, 57, and 85 ECGs will be performed as the last assessment in the clinic (as close to Cmax). See Section 8.2.3 for additional details on collection parameters.
b. Vital signs are to be taken before blood collection for laboratory tests. See Section 8.2.2 for additional details on collection parameters.
c. PK blood sampling times on Days 1, 8, and 85 will occur predose and 2 hours after the morning dose. Patients not fasting on Days 1 and 8 will have an additional PK sample collected at 4 hours postdose. If the patient objects to both blood draws at the 2hr and 4hr timepoint, the 4hr PK sample is more important to collect. Patients must remain in the clinic until 30 minutes after the morning postdose PK blood sampling is completed. See Section 8.5 for additional details on collection parameters.
d. PK blood sampling will occur prior to the morning dose on Days 15, 29, 43, and 57. See Section 8.5 for additional details on collection parameters.
[redacted]
g. The last dose of study treatment will be administered in the clinic on Day 85. The second dose of study treatment is not to be administered on Day 85.
h. Serious AE reporting will start at the time of consent. Any AE that occurs between the time of consent and prior to dosing on Day 1 will be recorded as medical history. Treatment-emergent AEs will be collected following the first dose of study treatment on Day 1 through the Follow-up Visit (30 days after the last administration of study treatment) (Section 5.5).
i. Unscheduled visits are allowed, as deemed necessary by the Investigator, in the event that assessments need to be repeated (eg, lab draws), safety follow-up needs to be conducted, or additional dispensing activities need to occur.
j. Patient should be fasted for visits on Days 1 and 8, defined as 8 hours since last food. A snack is permitted 2 hours after the morning dose.

2.0 INTRODUCTION

2.1 Study Rationale

Hidradenitis suppurativa is a chronic inflammatory disease primarily affecting apocrine-gland-rich regions of the body such as the axillary and groin areas. The pathophysiology of HS is complex and has not been clearly defined. The primary defect in HS involves occlusion of hair follicles, which leads to dilatation and rupture. The resulting spillage of follicular contents into the surrounding dermis induces a chemotactic response from neutrophils and lymphocytes and inflammation of the hair follicle leads to innate and adaptive immune dysregulation. An upregulation of various cytokines, such as TNF-α, IL-1, IL-6, IL-8, IL-17, IL-23, and other molecules appears to be important in the pathophysiology of this inflammatory condition.

The study treatment, ATI-450, is an orally available, novel, potent, and selective small molecule inhibitor of the p38α MAPK/MK2 inflammatory signaling pathway being developed for treatment of inflammatory disorders. The p38 MAPK pathway offers great potential in the treatment of inflammatory diseases such as HS. By targeting MK2, which is downstream from p38, it is believed that ATI-450 can effectively and safely inhibit the inflammatory pathways without substantially impacting anti-inflammatory pathways. [redacted]

This study is being conducted to determine the efficacy, safety, tolerability, PK, and PD of 12 weeks of ATI-450 exposure in patients with moderate to severe HS. This important data will further describe the efficacy and safety of ATI-450 in a relevant patient population.

2.2 Background

Hidradenitis suppurativa, also called acne inversa, is a chronic inflammatory skin disease that affects apocrine gland-bearing skin in the axillae, groin, and under the breasts. It is characterized by persistent or recurrent boil-like nodules and abscesses that culminate in a purulent discharge, sinuses, and scarring.

A retrospective analysis of 48 million unique US patients revealed an overall HS incidence of 0.10% in the sample population, which comprised 47,690 patients with HS (26.2% men and 73.8% women) (Garg et al, 2017).

While anti-TNF-α inhibitor therapy has improved treatment of HS, there remains a need for effective and well tolerated therapies.

The Sponsor is developing ATI-450, an orally available, small molecule inhibitor of the p38α MAPK/MK2 inflammatory signaling pathway. The p38 MAPK signaling pathway has long been a target for therapeutic intervention for inflammatory diseases owing to its involvement in the regulation and the expression of multiple cytokines and other inflammatory signals (Saklatvala, 2004; Schett, 2008). Key inflammatory cytokines driven by this pathway include TNF-α as well as IL-1α, IL-1β, and IL-6. The involvement of these cytokines in a variety of diseases, including rheumatoid arthritis (RA) and HS, has been demonstrated by successful treatment of inflammatory disease with anti-TNF-α monoclonal antibodies, antagonists of the IL-1 receptor, anti-IL-1β monoclonal antibodies, and anti-IL-6 receptor monoclonal antibodies (Ruocco 2009; Patel 2015; Kimball et al 2016; Kullenberg 2016; Broderick 2015; Kanni 2018; Maarouf 2018). However, a drawback of biologics is that they specifically target single cytokine targets in a disease in which multiple cytokines have a pathophysiological role. In addition, biologics require self-administered injections, and many patients prefer oral options. Thus, identification of orally available small molecule therapeutics would add to the available treatment modalities.

Study treatment ATI-450 has a novel mechanism of action in that it targets the high affinity docking interaction between p38α MAPK and MK2 (Wang 2018). Upon binding to the interface created upon formation of this bimolecular complex, ATI-450 blocks MK2 phosphorylation by p38 MAPK and thereby the downstream MK2-mediated inflammatory drive. Study treatment ATI-450 shows low potency for inhibition of p38α phosphorylation/activation of alternate substrates and is selective across the human kinome.

The Sponsor is developing ATI-450 for potential treatment of inflammatory disorders in which anti-TNF-α and anti-IL-1β biotherapeutics have shown themselves to be efficacious. Additional information regarding nonclinical and clinical experience with ATI-450 can be found in the Investigator's Brochure (IB).

2.3 [redacted]

[redacted]

[redacted]

[redacted]

3.0 OBJECTIVES AND ENDPOINTS

Table 2 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of ATI-450 in patients with moderate to severe HS	• Change from Baseline in inflammatory nodule/abscess count at Week 12
Secondary	
• To assess the efficacy, and safety of ATI-450 in patients with moderate to severe HS	• Percentage of patients achieving HiSCR at Week 12. HiSCR is defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule (AN) count, with no increase in abscess or draining fistula counts. • Change from Baseline in IHS-4 over time for the 12-week treatment period. • Percentage of patients achieving at least a 30% reduction and at least 1 unit reduction from Baseline in the numerical rating scale (NRS30) in Patient's Global Assessment of Skin Pain at Week 12 among patients with Baseline NRS ≥3. NRS30 is evaluated based on worst skin pain in a 24-hour recall period (maximal daily pain). • Change from Baseline in Hidradenitis Suppurativa-Physician Global Assessment (HS-PGA) over time for the 12-week treatment period. • Change from Baseline in Dermatology Life Quality Index (DLQI) over time for the 12-week treatment period. The DLQI is a 10-item validated questionnaire used to assess the impact of HS disease symptoms and treatment on quality of life (QoL). It consists of 10 questions evaluating impact of skin diseases on different aspects of a patient's QoL over the prior week, including symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment.

Objectives	**Endpoints**
Secondary (continued)	
	• Change from Baseline in Hurley Stage over time for the 12-week treatment period. • Incidence of adverse events (AEs), serious AEs (SAEs), laboratory value abnormalities, electrocardiogram (ECG) abnormalities, vital signs abnormalities
• To assess the PK of ATI-450 in patients with moderate to severe HS	• Trough ATI-450 and metabolite (CDD-2164) concentrations at clinic visits. On Day 1, 8, and 85 trough and 2-hour post dose will be collected.
Exploratory	
• To assess the pharmacodynamics (PD) of ATI-450 in patients with moderate to severe HS	[redacted]

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 2a, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety, tolerability, PK, and PD of ATI-450 50 mg BID versus placebo in patients with moderate to severe HS.

- The study will consist of an up to 28-day Screening Period, a 12-week treatment period, and a 30-day follow-up period. The total duration of the study for patients remaining until their final follow-up assessment will be up to 21 weeks.
- The Investigator will obtain signed informed consent from the patient before any study procedures are performed.
- During the Screening Period, each patient will be required to have all assessments performed as outlined in the SoA (Table 1).
- Results for all the Screening assessments must be available at the time patient eligibility is reconfirmed prior to randomization and dosing.
- Patients whose eligibility is confirmed at Baseline will be randomized in a 1:1 ratio to receive either ATI-450 tablets (50 mg BID) or matching placebo tablets BID. Study treatments will be administered orally for 12 weeks.
- Patients will attend clinic visits on Days 1, 8, 15, 29, 43, 57, and 85 for safety, efficacy, PK, and PD assessments. The morning dose of study treatment will be administered in the clinic on each study visit day.
- On Day 85 (Week 12), patients will complete the EOS assessments. A safety follow-up visit will be conducted 30 days after the last dose of study treatment for patients who completed the treatment period, as well as those who discontinue early.
- The study is randomized and double-blinded to prevent bias in treatment allocation and in the assessment of treatment effect.

4.2 Scientific Rationale for Study Design

A randomized, double-blind, placebo-controlled study design is a conventional and well-established design to assess efficacy and safety of new treatments in HS.

Sample size justification is provided in Section 9.3.

4.3 [redacted]

[redacted]

4.4 End of Study Definition

A patient is considered to have completed the study if he/she has completed all study visits. For the purposes of this study, the EOS date for an individual patient will be the last date of successful contact for study purposes including nonclinic follow-ups (eg, phone call for patients lost to follow-up, continued follow-up on outstanding AE/SAE, etc).

The end of the study is defined as the date of the last visit or date of last procedure of the last patient in the study.

5.0 STUDY POPULATION

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

5.1 Inclusion Criteria

Patients must meet the following criteria to be eligible for participation in the study:

1. Able to comprehend and be willing to sign the IRB-approved patient ICF prior to administration of any study-related procedures.
2. Patient with HS for at least 1 year (365 days) prior to Baseline visit; duration of disease as determined via Investigator review of patient medical history.
3. Patient must have stable HS for at least 60 days prior to Screening visit and at Baseline visit as determined via Investigator review of patient medical history.
4. Total AN count of ≥5 at Baseline visit. Abscesses and nodules must have the following signs of inflammation. (Inflammatory nodules should be raised):
    a. Clinical evidence of erythema and/or warmth.
    b. Clinical evidence of pain/tenderness.
5. Has HS lesions present in at least 2 distinct anatomical areas at Screening and Baseline. (Bilateral involvement of the same area counts as 2 areas, eg, involvement of right and left axilla.)
6. Draining fistula count of ≤20 at Baseline visit.
7. Male or nonpregnant, nonbreastfeeding female patients between 18 and 70 years of age, inclusive, at the time of signing the ICF.
    a. Heterosexually active female patients who are of childbearing potential must use 2 methods of highly effective contraception, 1 of which must be a physical barrier, for the duration of the study and for 30 days after the last dose (see Appendix 6).
    b. Heterosexually active male patients of childbearing potential with a female partner of childbearing potential must agree to use a condom plus another highly effective form of birth control for the duration of the study and for 90 days after the last dose (see Appendix 6).
8. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test prior to dosing on Day 1.
9. Screening laboratory evaluations (hematology, chemistry, coagulation, and urinalysis) must fall within the normal range of the central laboratory's reference ranges unless the results have been determined by the Investigator to not be clinically significant.
10. No COVID-19 vaccination or booster within the 4 weeks prior to randomization. Note: COVID vaccination is highly encouraged but not required.

5.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for the study:

1. Patient has a history of active skin disease other than HS that could interfere with the assessment of HS.
2. Patient has an uncontrolled non-immunoinflammatory disease that may place the patient at increased risk during the study or impact the interpretation of results, eg, previous malignancy, previous venous thromboembolism.
3. History or evidence of active tuberculosis, irrespective of prior or current treatment status; or current or prior untreated latent tuberculosis. Note: Prior latent tuberculosis with completed treatment is not an exclusion.
4. Known hypersensitivity to ATI-450.
5. Patient is an alcoholic, or has a history of alcoholism, alcoholic liver disease, or other chronic liver disease.
6. Active infection with SARS-CoV-2 virus.
7. Positive for HIV or hepatitis B or C. Note: Patients with hepatitis B surface antibody without the presence of hepatitis B surface antigen will be allowed to participate. Patients with hepatitis C antibody positive can have Hepatitis C viral load tested, if the Hepatitis C virus is undetectable and the patient has been off antivirals for 6 months, he/she may be enrolled in the study.
8. Tests performed at a central laboratory at Screening that meet any of the criteria below (out of range labs may be rechecked once, after consultation with the Medical Monitor, before patient is considered a screen failure):
    a. White blood cell count $<3.0\times10^3$ cells/mm^3.
    b. Absolute neutrophil count $<1.5\times10^3$ cells/mm^3.
    c. Lymphocyte count $<0.5\times10^3$ cells/mm^3.
    d. Platelet count $<100\times10^3$ cells/mm^3.
    e. Hemoglobin <10 g/dL.
    f. Aspartate aminotransferase (AST) or ALT $\geq$1.5 × ULN.
    g. Total bilirubin level $\geq$2 × ULN unless patient has been diagnosed with Gilbert syndrome and this is clearly documented.
    h. Estimated glomerular filtration rate (eGFR), <40 mL/min/1.73 m^2 based on Modification of Diet and Renal Disease formula.
9. Any clinically significant laboratory abnormality that would affect interpretation of study data or safety of the patient's participation in the study, per judgment of the Investigator.

10. Clinically significant abnormal findings other than HS from PE conducted at Screening visit (Visit 1) and at Baseline visit (Visit 2) that may affect the interpretation of study data or the safety of the patient's participation in the study, per the judgment of the Investigator.
11. Clinically important history of a medical disorder that would compromise patient safety or data quality, per judgment of the Investigator.
12. Blood pressure levels (in semi-supine position after at least 5 minutes rest): <90 mmHg or >150 mmHg for systolic BP or <40 mmHg or >90 mmHg for diastolic BP.
13. Patient has experience with >2 biologics, >1 JAK inhibitor, or a combination of 1 biologic experience and 1 JAK inhibitor.

15. Are currently receiving corticosteroids at doses greater than 10 mg per day of prednisone (or equivalent) or have been receiving an unstable dosing regimen of corticosteroids within 2 weeks of the Screening visit.
16. Have been using prescription topical therapies for treatment of HS within 14 days prior to Baseline visit.
17. Oral or topical tetracycline class antibiotics for treatment of HS are allowable if patient is on a stable dose for 4 weeks prior to Baseline and willing and able to maintain the stable dose for duration of study.

[redacted]

20. Patients with history of stroke.
21. Significant active cardiac disease, in the past 6 months, that would affect interpretation of study data or the safety of the patient's participation in the study, per judgment of the Investigator. This includes myocardial infarction or unstable angina, acute coronary syndrome, or heart failure with New York Heart Association Class II, III or IV symptoms. In addition, patients with a personal or family history of congenital long QT syndrome, Torsades de Pointes, sustained or symptomatic VT, or unexpected sudden cardiac death.
22. Patients with any of the following Baseline predose ECG findings:
    a. Mean QTcF >450 msec as averaged on triplicate ECG;
    b. ECG or historical evidence of the Wolff-Parkinson-White Syndrome (unless ablated);
    c. If atrial fibrillation or flutter is present, the mean ventricular response must be < 90 BPM and the patient must be anticoagulated according to national guidelines; and/or
    d. Any other finding that is considered clinically significant.
23. Any dermatologic surgery or procedure in the past 90 days prior to Screening.
24. Known exposure to an individual with a confirmed, active diagnosis of COVID-19 at any time during the Screening Period.
25. Participated in another ATI-450 clinical study.
26. History of clinically significant drug abuse within 2 years prior to Screening. Note: Marijuana use is allowed, if not considered substance abuse by the investigator.
27. Uncontrolled hypokalemia (<3.8mmol/L), or uncontrolled hypomagnesemia (< LLN)

[redacted]

5.3 Lifestyle Considerations

There are no other lifestyle considerations (such as dietary or physical activity restrictions) for this study.

5.4 Screen Failures

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

5.4.1 Retesting During Screening

Laboratory parameters and/or assessments that are included in the Screening procedures (Table 1) may be repeated once during the Screening Period in consultation with the Medical Monitor. Retesting will be allowed when the significance of a laboratory result is unclear, and the retest will help interpretation and decision-making for entry to the study. Retesting will not be undertaken when the laboratory results clearly indicate clinically significant disease that could impact study interpretation or the safety of a study patient during participation.

The most current result prior to randomization is the value by which study inclusion will be assessed, as it represents the patient's most current clinical state.

5.4.2 Rescreening

This study will permit 1 rescreening of a patient who has failed 1 or more inclusion or exclusion criteria. Consultation with the medical monitor will be needed to identify whether rescreening is clinically relevant. If rescreened, the patient must sign a new ICF and the same Patient Number will be assigned.

For patients who are rescreened, consult with the Medical Monitor to confirm which parameters and/or assessments that were collected as part of the original Screening Period procedures may be utilized, if any.

5.5 COVID-19 Guidance

5.5.1 COVID-19 Vaccination and Treatment Guidance

Prior to the Study:

While not a precondition for study participation, it is strongly recommended that patients receive vaccination against COVID-19 prior to enrolling in the study and initiation of study treatment. If possible, the first dose of study treatment should be given at least 4 weeks after completion of the

patient's COVID-19 vaccination regimen (or booster shot, if applicable).

During the Study:

Prior to proceeding with COVID-19 vaccination during the study period, each patient's specific situation should be discussed with and approved by the study medical monitor. Where possible, the timing of vaccination should be planned so that a vaccination is not administered during the study treatment period.

Investigators and patients should consider the schedule of their COVID-19 vaccination (if applicable), including potential booster shots, when planning the timing of their study participation. Where possible, the timing of vaccination should be planned so that a booster vaccination is not administered during the study treatment period. Ideally, administration of a COVID-19 booster vaccine (if applicable) should be given at least 4 weeks prior to the first dose of study treatment.

If unavoidable, vaccination can proceed during the study, but every effort should be made to avoid administration during the final month of the treatment period, if possible. It should be noted that the effect of ATI-450 on the response to COVID-19 vaccination is unknown. The COVID-19 vaccine may lead to AEs (fever, chills, etc.), which will need to be captured and distinguished as related to vaccine versus ATI-450.

Patient's may be treated for COVID-19 infections as needed, including with monoclonal antibody therapy, as long as the treatment is not a prohibited medication per protocol Appendix 5. If a patient is treated with a protocol prohibited medication, then the study drug should be discontinued.

5.5.2 COVID-19 Testing Guidance

At the Screening visit (Visit 1) and Baseline visit (Visit 2) prior to the first dose of study treatment, all patients must have a nasopharyngeal (preferred) or oropharyngeal swab collected to test for the presence of the SARS-CoV-2 virus. The sample will be sent to the study's central lab for analysis by an acceptable diagnostic assay. Patients with positive test results at Visit 1 will be considered screen failures per the exclusion criteria for the study but may be considered for rescreening at a later date following consultation with the study Medical Monitor.

Patients are allowed to dose with study treatment in the interval between sample collection at the Baseline visit and result reporting as long as there is no clinical suspicion of COVID-19 infection or patient recent exposure to an individual with a confirmed, active infection.

If the patient's results are positive for SARS-CoV-2 following sample collection at Visit 2, the patient will need to be notified immediately upon receipt of the results. The patient should be advised to begin self-isolation and self-monitoring procedures according to any applicable local,

state, and/or country-specific health recommendations. Referral to an appropriate health care provider for management of the patient's COVID-19 diagnosis should also be made. The patient's COVID-19 diagnosis will be reported as medical history unless the patient's clinical course progresses such that criterion for SAEs reporting is met (see Appendix 4), in which case, all applicable safety reporting procedures will be followed by the site.

Sites will also have the option to perform an unscheduled test for the SARS-CoV-2 virus at any time during the treatment phase of the study should a patient's clinical presentation necessitate it, in the Investigator's opinion. The same notification and referral procedures, as outlined in the preceding paragraphs, should be followed by the site. However, it is expected that any COVID-19 diagnosis made from a sample collected after the initiation of study treatment administration be reported as an AE per the requirements of Appendix 4 of this protocol.

In the event that a patient tests positive for the SARS-CoV-2 virus at or after Visit 2, the Investigator must consult with the study Medical Monitor to determine if the patient should continue with study medication treatment or discontinue from treatment. Determinations will be made on a case-by-case basis with the intent to minimize any increased risk for the patient.

6.0 STUDY TREATMENT

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

6.1 Study Treatment(s) Administered

Table 3 Study Treatment Details

Study Treatment Name:	ATI-450	Placebo
Dosage Formulation:	Tablet	Tablet
Unit Dose Strength(s)/Dosage Level(s):	50 mg BID	Not applicable
Route of Administration	Oral	Oral
Dosing Instructions:	Take 1 tablet by mouth BID	Take 1 tablet by mouth BID
Packaging and Labeling	[redacted]	[redacted]
Manufacturer	[redacted]	[redacted]

Abbreviation: BID=twice daily

6.2 Preparation/Handling/Storage/Accountability

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

ATI-450 and placebo will be stored under controlled conditions according to the storage requirements described on the label(s). [redacted] The Investigator (or designee) will instruct patients to store the study treatment in accordance with the instructions on the label(s).

Only patients enrolled in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. All study treatments must be stored 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 study center staff.

The Investigator and/or designee is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

The Investigator, a member of the study center staff, or a hospital pharmacist must maintain an adequate record of the receipt and distribution of all study treatment using the Drug Accountability Form. These forms must be available for inspection at any time.

Additional instructions regarding study treatment preparation and handling and the final disposition of unused study treatment can be found in the Pharmacy Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

All patients will be centrally assigned to randomized study treatment using an Interactive Voice/Web Response System (IxRS). Before the study is initiated, access instructions and directions for the IxRS will be provided to each study center.

Study treatment will be dispensed at the study visits summarized in the SoA (Table 1). Refer to the study Pharmacy Manual for specific guidelines concerning dispensing and accountability procedures for study treatment.

Patients will be randomized to study treatment in a 1:1 ratio to ATI-450 50 mg BID or placebo.

This is a double-blind study with limited access to the randomization code. The ATI-450 and placebo tablets will be identical in physical appearance. The treatment each patient will receive will not be disclosed to the Investigator, study center staff, patient, or Sponsor/designee. The treatment codes will be available to a limited number of third-party vendor personnel (IxRS administrative personnel, Clinical Supplies Management personnel, and unblinded biostatistician) for them to support their functions on the study.

The IxRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the study Medical Monitor prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the study Medical Monitor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

6.4 Study Treatment Compliance

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

At each visit, prior to dispensing study treatment, previously dispensed study treatment will be retrieved by the Investigator and compliance assessed both through tablet counting and review of a dosing diary completed by the patient. Patients exhibiting poor compliance as assessed by tablet counts and diary completion should be counseled on the importance of good compliance to the study dosing regimen.

Noncompliance is defined as taking <80% or >120% of study treatment during any evaluation period (visit to visit). See Section 8.4 regarding treatment of ATI-450 overdose.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the patient is receiving at the time of enrollment (within 14 days before the time of enrollment) or receives during the study must be recorded on the eCRF along with:

- Reason for use;
- Dates of administration including start and end dates and times (if available); and
- Dosage information including dose and frequency.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Antibiotic Therapy

Patients are allowed to continue treatment with antibiotics for HS from the tetracycline class if at stable dose. A stable dose is defined as no change for 4 weeks prior to Baseline visit. The patient must be willing and able to maintain stable dose for duration of study. Allowable oral and topical antibiotics from the tetracycline class are: tetracycline, doxycycline, or minocycline.

Antiseptic Use

If previously used prior to entry into the study, patients may continue cleansing HS lesions with their daily antiseptic wash, such as chlorhexidine gluconate, triclosan, benzoyl peroxide, or dilute bleach in bathwater. Use of new antiseptic wash during the study is not permitted.

Wound Care

Concomitant use of wound care dressings on HS wounds is allowed (excluding topical antibiotics and other prohibited medications).

[redacted]

[redacted]

6.5.1 Rescue Medicine

Rescue therapy for HS is not permitted except for the use of acetaminophen (as per label) and nonsteroidal anti-inflammatory drugs to treat breakthrough pain and discomfort during the study. Neither the study center nor the Sponsor will supply rescue medication.

6.6 Dose Modification

No dose modifications are permitted in this study.

6.7 Treatment after the End of the Study

The Sponsor will not provide any additional care to patients after they leave the study because such care should not differ from what is normally expected for patients with HS.

7.0 DISCONTINUATION OF STUDY TREATMENT AND PATIENT DISCONTINUATION/WITHDRAWAL

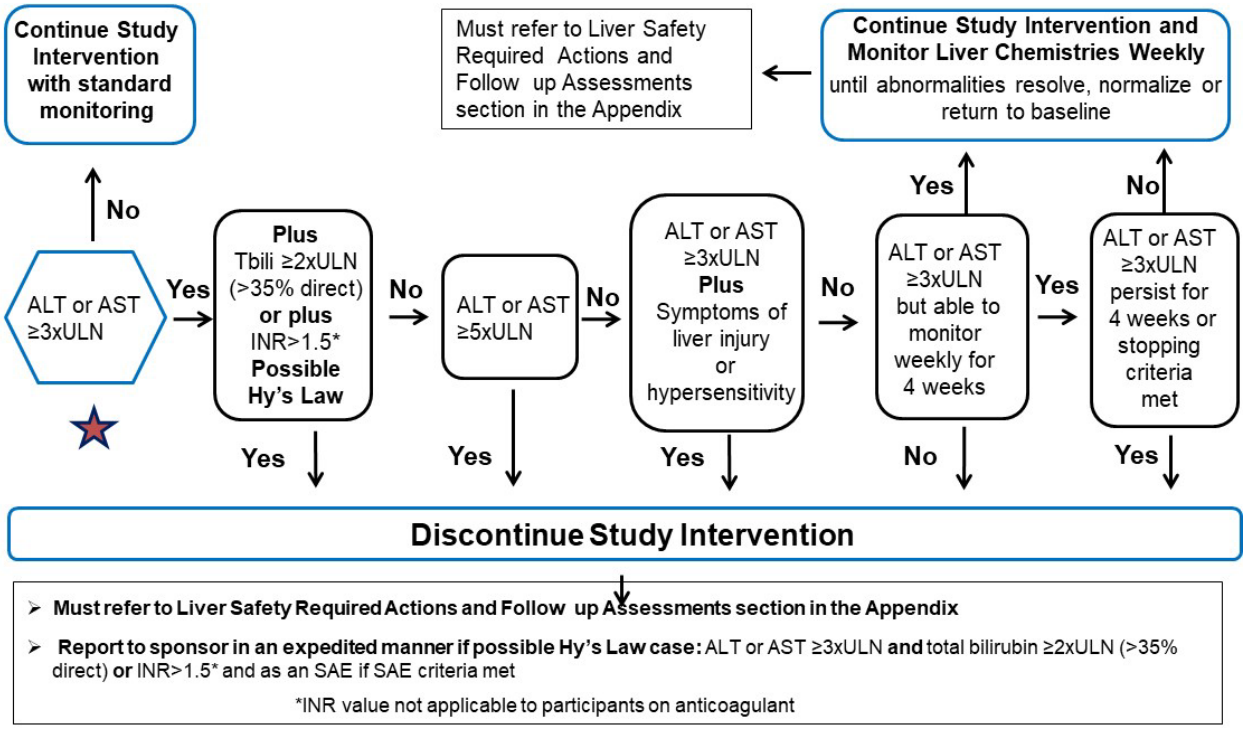
7.1 Discontinuation of Study Treatment

Criteria for discontinuation due to abnormal liver function, neutrophil laboratory values, CK laboratory values, and skin toxicity are outlined below. In the event that a patient discontinues treatment with study treatment prematurely, it is preferred (so as to minimize missing data) that the patient be given the opportunity to complete the remainder of his/her expected study visits per the SoA (Table 1) rather than being discharged from the study in full.

7.1.1 Liver Function

Study intervention will be discontinued for a patient if liver chemistry stopping criteria are met and confirmed upon repeat testing. Samples for confirmation testing should be collected as soon as possible after receipt of initial laboratory results indicative of the need to monitor for stopping criteria. If ALT or AST is ≥5 × ULN, then study treatment should be held while confirming.

Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



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

Note: The red star indicates the starting point.

Liver Safety: Suggested Actions and Follow-up Assessments can be found in Appendix 7.

7.1.2 Neutrophil Laboratory Values

Withdraw study treatment if absolute neutrophil count drops below 500 cells/mm^3 and is maintained below 500 cells/mm^3 on a confirmatory sample.

7.1.3 Creatine Kinase Laboratory Values

Withdraw study treatment if an elevation of CK >5 × ULN is observed on repeat testing without benign explanation (eg, recent exercise) occurs.

7.1.4 Skin Toxicity

Withdraw study treatment in the case of any severe skin reaction which is considered to be related to the study treatment.

If drug is stopped for reasons as described above, restarting the study drug is not allowed.

7.2 Temporary Discontinuation

7.2.1 Unrelated Adverse Events or COVID-19 Diagnosis

If a drug is stopped temporarily due to a clearly unrelated adverse event, for example, treatment of a fracture caused by a motor vehicle accident or COVID-19 infection, dosing may be reinitiated, after discussion with the Medical Monitor, if the temporary discontinuation was shorter than a maximum of 14 days in the total 12-week treatment period. In exceptional circumstances, medical monitor may allow dosing to be resumed with a gap of up to 21 days. In all cases, if the dosing gap is in excess of 21 days, dosing should be discontinued permanently.

In case of **a COVID-19 infection, consult study Medical Monitor to discuss risk/benefit considerations of patient continuing or discontinuing study medication treatment.**

7.2.2 ECG Criterion for Drug Discontinuation

In the event that a study ECG assessment demonstrates either of the bulleted criteria below (upon local review by the Investigator), a PK and lab sample (serum potassium and magnesium levels) should be drawn. The ECG should be repeated within 30 minutes. Patient study treatment dosing should be interrupted until the results of the centrally read cardiologist report are received and the study Medical Monitor should be notified:

- QTcF (average of triplicate set) >500 msec
- Change from Baseline QTcF (average of triplicate set) >60 msec

[redacted]

7.3 Rechallenge

Rechallenge is allowed in only limited circumstances when the drug is temporarily stopped, as noted in Section 7.2. Once the drug is permanently stopped, no rechallenge is allowed.

7.4 Patient Discontinuation/Withdrawal from the Study

All patients will be advised that they are free to withdraw from participation in the study at any time, for any reason, and without prejudice. The Investigator also has the right to withdraw patients from the study at any time for lack of therapeutic effect that is intolerable or otherwise unacceptable to the patient, for intolerable or unacceptable AEs, intercurrent illness, noncompliance, with study procedures, administrative reasons, or in the Investigator's opinion, to protect the patient's best interest. The Sponsor reserves the right to request the withdrawal of a patient due to protocol violations or other reasons.

- Although a patient is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights.
- If the patient withdraws consent, the Investigator must clearly determine and document if the patient is making a full and immediate revocation of consent (eg, no additional data collection may occur) or if the patient is willing to proceed with additional study procedures

to ensure a safe and orderly discharge from the study (eg, completion of Early Termination and EOS Visits).

- If the patient 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 patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.
- If there is a medical reason for withdrawal, the patient should remain under the supervision of the Investigator until satisfactory health has returned.
- See the SoA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.5 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study center.

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

- The study center must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study and the last known contact/assessment will be the date of discontinuation.

8.0 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.
- 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 patients meet all eligibility criteria. The Investigator will maintain a Screening log to record details of all patients screened and to confirm eligibility or record reasons for Screening failure, as applicable.
- Patient Reported Outcomes questionnaires should be completed by patients before study medication administration.
- The site should make every attempt to have the same Investigator complete the below assessments throughout the study for each patient.
- The maximum amount of blood collected from each patient over the duration of the study, not including any extra assessments that may be required, will be specified in the ICF. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Lesion Counts—Abscess, Nodule and Draining Fistulas (tunnels)

The location and extent of HS will be assessed and recorded at the study visits outlined in the SoA (Table 1) by recording the affected anatomic location(s) of the disease, as well as the number of inflammatory and noninflammatory nodules, abscesses, and draining and nondraining fistulas in each of the locations (Appendix 8).

The information regarding location and extent of HS involvement will be used to determine the Hurley Stage and to calculate the HiSCR, the Hidradenitis Suppurativa-Physician's Global Assessment Scale (HS-PGA) and the International Hidradenitis Suppurativa Severity Score System (IHS-4).

The following areas will be evaluated at visits specified in the SoA to assess and record the extent of HS:

• left and right axillae

• left and right inframammary areas

• intermammary area

• left and right buttocks

• left and right inguino-crural folds

• perianal area and perineal area, and

• other (eg, abdominal fold, neck, back).

8.1.1.1 Hidradenitis Suppurativa Lesions:

- Inflammatory lesions: evidence of inflammation (eg, erythema, pain, warmth)
    - Nodule: should be raised, round lesion, can be a pyogenic granuloma-like lesion
    - Abscess: fluid (pus) filled
- Fistula/Tunnel/Sinus Tract: lesion draining to the skin, can be in direct connection with one another or localized closely to one another
    - Draining: if open at skin surface (ulcerated), will sometimes ooze a fluid
    - Nondraining: if not open to the skin surface, will not ooze
- Non-inflammatory lesion:
    - Non-inflammatory nodule: not inflamed or painful

8.1.1.2 Hidradenitis Suppurativa Clinical Response

Hidradenitis Suppurativa Clinical Response is defined as at least a 50% reduction from Baseline in the total AN count, with no increase in abscess and no increase in draining fistula counts relative to Baseline.

The HiSCR is defined by the status of 3 types of lesions (see definitions above):

- Abscesses
- Inflammatory nodules
- Draining fistulas

The definition for response to treatment based on HiSCR relative to Baseline (Day 1, Visit 2) is:

- At least 50% reduction in AN count
- No increase in number of abscesses
- No increase in number of draining fistulas

For this score, patients are defined as achievers or non-achievers. Patient achievers at any scheduled timepoint will have a HiSCR defined as at least a 50% reduction in abscess and inflammatory nodule count (AN count) and no increase in abscesses and no increase in draining fistulas relative to Baseline at that timepoint.

A patient is considered to be a HiSCR achiever only if all 3 criteria above are fulfilled (Kimball et al, 2016b).

The time required for Investigators to complete the HiSCR ranges from 1 to 2 minutes for patients with minimal disease, ie, 5 HS lesions in 2 anatomic locations, up to approximately 30 minutes for patients with multiple lesions in all 12 anatomic locations.

8.1.1.3 International Hidradenitis Suppurativa Severity Score System

The International Hidradenitis Suppurativa Severity (IHS-4) is a validated tool used to assess HS severity. The IHS-4 is calculated based on the clinical signs of HS: inflammatory nodules, abscesses and draining tunnels (fistulas and sinuses). The terms sinus tract and tunnel should be considered as synonyms of fistula (Daxhelet 2020).

The IHS-4 score (points) = (number of nodules multiplied by 1) + (number of abscesses multiplied by 2) + [number of draining tunnels (fistulas/sinuses) multiplied by 4].

A score of 3 or less signifies mild HS, a score of 4-10 signifies moderate HS and a score of 11 or higher signifies severe HS (Zouboulis et al, 2017).

8.1.2 Patient's Global Assessment of Skin Pain

The NRS30 – Patient’s Global Assessment of Skin Pain will be completed daily by patients starting at the Baseline visit through Week 12 as outlined in the SoA (Table 1). On visit days, patients will complete the NRS30 – Patient’s Global Assessment of Skin Pain at the study center prior to administration of the in-clinic morning dose of study treatment. Site personnel will witness the completion of the assessment.

The severity of the patient’s skin pain will be assessed by completion of a numerical rating scale with 0 indicating no pain and 10 indicating the worst pain imaginable in a 24-hour recall period (maximal daily pain) (Kimball et al, 2016). Patients should be instructed to complete the assessment prior to the morning dose of study medication.

This questionnaire will be administered electronically and should take approximately 1 minute to complete.

8.1.3 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a 10-item validated questionnaire used to assess the impact of HS disease symptoms and treatment on QoL. It consists of 10 questions including a single “yes/no” question and 9 multiple choice questions with possible responses of “not at all,”

"a little," "a lot," or "very much." These questions evaluate the impact of skin diseases on different aspects of a patient's QoL over the prior week, including symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment.

Each question is scored using a 4-point scale which ranges from 0-3 based on a patient's response: not at all/not relevant (0), a little (1), a lot (2) and very much (3) (Basra 2015).

Question 7, the single yes/no question is two-part question. The first part can be scored based on a response of "yes" (3) or "no/not relevant." If "no/not relevant" is selected, part two of the question can be scored based on the following responses: not at all (0) little (1), a lot (2).

The total score of the DLQI (range of 0-30) is calculated by adding up the scores from each question. The higher the score, the greater the impact on a patient's quality of life.

This questionnaire will be administered electronically and should take approximately 1 to 3 minutes to complete.

8.1.4 Hidradenitis Suppurativa-Physician's Global Assessment

The HS-PGA scale is a 6-point scale used to assess ranges from clear to very severe (Hidradenitis Suppurativa Trust, 2018). It is used in clinical trials to measure clinical improvement in inflammatory nodules, abscesses and draining fistulas. The 6 stages are based on the presence and numbers of nodules, abscesses, and draining fistulas (Kimball et al, 2012). In the HS-PGA scale, Investigators will rate the counts of nodules (inflammatory and noninflammatory) abscesses and fistulas (both draining and nondraining) and assign a patient to 1 of 6 categories listed below.

Severity	Score	Definition
Clear	0	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodules
Minimal	1	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory nodules
Mild	2	0 abscesses, 0 draining fistulas, and 1 to 4 inflammatory nodules **or** 1 abscess or draining fistula (sum of abscesses and draining fistulas is 1) and 0 inflammatory nodules
Moderate	3	0 abscesses, 0 draining fistulas, and ≥5 inflammatory nodules **or** 1 abscess or draining fistula and ≥1 inflammatory nodule **or** 2 to 5 abscesses or draining fistulas (sum of abscesses and draining fistulas is 2 to 5) and <10 inflammatory nodules
Severe	4	2 to 5 abscesses or draining fistulas and ≥10 inflammatory nodules

Very Severe	5	>5 abscesses or draining fistulas (sum of abscesses and draining fistulas >5)

This questionnaire will be completed electronically by the Investigator and should take approximately 1-3 minutes to complete.

8.1.5 Hurley Staging System

The Hurley Staging System is used to assess and grade the progression of HS by placing patients in 1 of 3 groups or stages: mild (Hurley Stage I), moderate (Hurley Stage II), or severe (Hurley Stage III).

Hurley Stages defined:

- Stage I: Abscess formation, single or multiple, without sinus tracts and scarring
- Stage II: 1 or more widely separated recurrent abscesses with tract formation and scarring

Stage III: Multiple interconnected tracts and abscesses across the entire area, with diffuse or near diffuse involvement

The Investigator will complete the Hurley Staging assessment for each affected anatomical area at each visit specified in the SoA (Table 1). If more than 1 stage is present in an area, the worst stage in each area should be applied.

8.1.6 Lesion Photography

Photographs of identified HS lesions will be taken at each study visit specified in the SoA (Table 1) for patients who consent to it. Sites will be required to submit the patient's Baseline photographs to Canfield Scientific's database. Canfield Scientific will supply all investigational sites with study-specific laptop and camera equipment to photograph each patient's identified target HS lesion treatment areas (at least 1 HS area but up to 2 unique target areas). Details regarding the use of the equipment and how to upload the photographs to the Canfield database will be supplied to the sites in the Photography Manual.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

8.2.1 Physical Examinations

- A complete PE will include, at a minimum, general appearance; skin; eyes; ears, nose, throat; head and neck; heart, chest, and lungs; abdomen; extremities; lymph nodes; musculoskeletal; neurological; and other body systems, if applicable, for describing the status of the patient's health.
- A targeted PE will include, at a minimum, signs of HS.

- Body weight and height (height at Screening only) will also be measured and recorded. Body mass index (BMI) will be calculated electronically in the eCRF. The patient should be dressed in lightweight clothing, without shoes.
- Investigators should pay attention to clinical signs related to previous illnesses. Any new abnormalities or worsening of existing abnormalities should be reported as AEs, as appropriate (see Section 8.3).
- See Section 7.0 for discontinuation criteria based on skin toxicity.

8.2.2 Vital Signs

- Vital signs will be measured prior to dosing and immediately following dosing in a semi-supine position after ≥ 5 minutes' rest without distractions (eg, television, cell phones). Vital signs (to be taken before blood collection for laboratory tests, when applicable) will consist of 1 body temperature measurement, 1 pulse rate measurement, 1 respiratory rate measurement, and 1 systolic and diastolic BP measurements. One repeat will be allowed for any abnormal BP readings.
- Abnormal, clinically significant vital sign results outside of the 1 allowable repeat will be recorded as AEs (see Section 8.3). If known, the underlying etiology for the abnormal clinically significant vital sign will be recorded as an AE rather than the vital sign itself.
- The BP and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.2.3 Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (Table 1) using an ECG machine supplied by the Central ECG Laboratory that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.
- Three individual ECG tracings should be obtained as closely as possible in succession, and completed in less than 4 minutes.
- The ECG tracing should clearly identify the patient, include the date and time of the assessment, and include the signature and date of the person who made the local interpretation; the tracing will be archived at the study site and electronic files sent to the Central ECG Laboratory. Abnormal, clinically significant ECG results will be recorded as AEs (see Section 8.3). If there is noise or other artifacts, they will be repeated. The QTcF intervals should be reviewed based on the automatic read from the ECG machine in real time.
- All ECGs will be transferred and read centrally by a qualified vendor. The ECGs collected at the Baseline visit (prior to randomization) should be assessed locally by the Investigator for confirmation of eligibility, but the final centrally read report will serve as the document of record in the patient's source chart and from the primary ECG database (EXPERT) for the study.

- Triplicate 12-lead ECGs will be performed at least 30 seconds apart, in a supine position, resting for at least 10 minutes (without external stimulation, e.g., talking, TV, noise) and submitted for central reading. Screening ECGs will be collected prior vital signs and blood samples. On Day 1 and 8, ECGs will be taken predose and 2 hours postdose. Patients not fasting on Day 1 and 8 will have an additional 4 hr postdose ECG. On Days 15, 29, 43, 57, and 85 ECGs will be performed as the last assessment in the clinic.

8.2.4 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA (Table 1) for the timing and frequency.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE Section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

See Section 7.0 for discontinuation criteria based on abnormal liver function tests, neutrophil values, CK values, or positive SARS-CoV-2 test.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days (+7 days) after the last dose of study treatment should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Medical Monitor notified.
- All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the Laboratory Manual and the SoA (Table 1).
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.
- Serum potassium levels < 3.8 mmol/L will be treated and repeated as will serum magnesium levels < LLN.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Any AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the patient to discontinue study treatment or the study (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected at the time points specified in the SoA (Table 1). Serious AE reporting will start at the time of consent. Any AE that occurs between the time of consent and prior to dosing on Day 1 will be recorded as medical history. All TEAEs will be collected following the first dose of study treatment on Day 1 through the Follow-up Visit (30 days after the last administration of study treatment).

All SAEs will be recorded and reported to the Sponsor/designee within 24 hours, as indicated in Appendix 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 AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor/designee.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 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 nonleading verbal questioning of the patient 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 patient at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (AESIs) (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up up to database lock (as defined in Section 7.5). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor/designee of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of patients and the safety of a study treatment under clinical investigation are met.

The Sponsor and/or designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor and/or designee will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

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 and/or designee will review and then file it along with the IB, and will also notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

All patients are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (see Sections 5.1 and 5.2, respectively).

Serum pregnancy testing will be performed only for women of childbearing potential (WOCBP) at Screening (Day -28 to Day -1); the result must be negative for the patient to be eligible. A urine pregnancy test will be performed only for WOCBP on Day 1 (prior to dosing) and at every subsequent study visit through the follow-up visit (Visit 9). The serum pregnancy tests will be analyzed by the central laboratory, and the urine pregnancy tests will be analyzed locally.

- Details of pregnancies in female patients and, if indicated, female partners of male patients will be collected after the start of study treatment and until 30 days (ie, 1 menstrual cycle) after the last dose of study treatment.
- If a pregnancy is reported, the Investigator should inform the Sponsor/designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 6.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

The following AEs will be classified as AESI in this study:

8.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable. Further information on general AE/SAE considerations is given in Appendix 4.

8.4 Treatment of Overdose

For this study, any dose of >3 tablets of ATI-450/placebo per day OR 2 tablets of ATI-450/placebo taken at any single dosing time point (eg, morning dose, evening dose) will be considered an overdose. The dose of ATI-450 used in this study is based on doses previously studied in Phase 1, and plasma exposure is unlikely to exceed previously studied levels if patients adhere to dosing instructions. Given the blinded nature of the study, the above recommendations make the assumption that each blinded tablet contains 50 mg of ATI-450.

The Sponsor does not recommend specific treatment for an overdose.

In the event of suspected or confirmed overdose, the Investigator should:

- Undertake any supportive measures, as per Investigator judgment.
- Contact the Medical Monitor immediately.
- Closely monitor the patient for any AE/SAE and/or laboratory abnormalities until the risk is considered to be resolved as agreed with the Medical Monitor.
- Obtain a plasma sample for PK analysis and any other relevant interventions or assessments, if requested by the Medical Monitor (determined on a case-by-case basis).
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient. Treatment of confirmed or suspected overdose with ATI-450 should consist of clinically appropriate supportive measures.

Any overdose associated with clinical symptoms will be recorded as an AE or SAE, as appropriate. Details of any signs or symptoms and their management should be recorded, including details of any treatments administered for the overdose. All overdoses with clinical symptoms meeting the SAE criteria must be reported as described in Section 8.3.4.

8.5 Pharmacokinetics

Up to twelve (12) venous blood samples of approximately 2 mL each will be collected for measurement of plasma concentrations of ATI-450 and its primary circulating metabolite, CDD-2164, as specified in the SoA (Table 1). Instructions for the collection and handling of biological samples will be provided by the Sponsor/designee. The actual date and time (24-hour

clock time) of each sample will be recorded. The date and time of study treatment administration will also be recorded.

A PK sample will be collected if ECG withdrawal criteria are met, see Section 7.1.1.

Samples will be used to evaluate the PK of ATI-450. Each plasma sample will be divided into 2 aliquots (1 each for primary analysis and back-up). Samples collected for analyses of ATI-450, CDD-2164 and other metabolite/enantiomer plasma concentrations 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. Patient confidentiality will be maintained.

At visits during which blood samples for the determination of PK of ATI-450 will be taken, 1 sample of sufficient volume can be used. Every effort will be taken to collect the blood samples as close as possible to the scheduled time points, but a window of ±10 minutes is permitted for each blood draw. In instances where different assessments are due at the same time point, they will be performed such that the blood samples for PK analyses will be drawn at the correct time (as long as patient safety is not compromised).

Drug concentration information that may unblind the study will not be reported to study centers or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the trial master file and Investigator site file but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

If a patient refuses blood collection for PK analysis, this will not be considered a protocol violation as the PK analysis is a secondary objective.

Details regarding the processing and shipment of all blood samples can be found in the Laboratory Manual.

8.6 [redacted]

[redacted]

8.7 Genetics

Genetics are not evaluated in this study.

8.8 Biomarkers

Biomarkers, other than the pharmacodynamic markers, are not evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters will not be evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary statistical hypothesis to be tested in this study is the hypothesis that the ATI-450 treatment group is superior to placebo for the treatment of HS based upon the 12-week change from Baseline in inflammatory nodules and abscesses versus the null hypothesis of no difference. This hypothesis will be conducted using a one-sided testing procedure with an alpha level of 0.05. No adjustment for multiplicity will be made.

Secondary superiority hypotheses will be tested on the secondary efficacy endpoints to gather supportive evidence for the primary hypothesis. These secondary assessments will have the same null and alternative hypotheses as the primary and will be tested using a one-sided procedure with an alpha level of 0.05.

9.2 Sample Size Determination

Ninety (90) randomized patients will provide 90.3% power to demonstrate the superiority of ATI-450 to placebo in the reduction in inflammatory nodules and abscesses at Week 12. This power computation assumes that the reduction in the placebo arm will be on average 2.5 nodules/abscesses and the ATI-450 reduction will be on average 4.75 nodules/abscesses. The assumed standard deviation for the number of nodules/abscesses was assumed to be 3.6. These

sample size assumptions were based on the values observed in the adalimumab PIONEER I and PIONEER II Phase 3 trials (Frew et al, 2020). The assumed reduction in nodules/abscesses for ATI-450 was chosen to be slightly less than that shown in the PIONEER I and PIONEER II Phase 3 in order to account for the potential impact of dropouts on the efficacy.

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 4 are defined.

Table 4 Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	All patients who have been randomized and administered at least 1 dose of study treatment. The efficacy analyses will be conducted on the FAS population as randomized.
Per Protocol (PP)	All randomized patients who remain on study treatment, complete their assessments for their Day 85 visit, with no major protocol violations.
Safety Analysis Set	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment. Patients will be analyzed according to the treatment they actually received.
Pharmacokinetic (PK)	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment and have at least 1 evaluable PK measurement
Pharmacodynamic (PD)	All patients randomly assigned to study treatment and who take at least 1 dose of study treatment and have at least 1 evaluable PD measurement

9.4 Statistical Analyses

Details of all statistical summaries will be provided in the study-specific SAP.

All data will be presented by treatment group. Descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum) will be provided for continuous variables, and counts and percentages will be presented for categorical variables. Unless otherwise stated, hypothesis tests and corresponding *P* values will be 1-sided with an alpha level of 0.05. No adjustments will be made for multiplicity.

Baseline is defined as the last nonmissing measurement before, or on the date of first administration of study treatment.

9.4.1 Efficacy Analyses

Table 5 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	All efficacy summaries will be conducted on both the FAS and PP populations. The primary efficacy analysis will be the treatment comparison of the change from Baseline in inflammatory nodules and abscesses at Week 12 in the FAS population. This analysis will be conducted within the context of a Mixed Model Repeated Measures (MMRM). This model will include factors for treatment group, time, and time by treatment interaction as well as a Baseline covariate. Patient identifiers will be included in the model in a manner that allows observations within a given patient over time to be treated as repeated measures. Point estimates and 90% confidence intervals (CI) for the difference in least square means (LS means) will be provided in addition to the 1-sided *P* values.
Secondary	Treatment comparisons for all secondary responder endpoints (percentage of patients meeting HiSCR at Week 12, percentage of patients achieving at least 30% reduction from Baseline in NRS30-PGA Skin Pain, and percentage of patients who experience at least a 25% increase in AN count with a minimum increase of 2 relative to Baseline over the 12-week treatment period) will be conducted using a logistic regression applied to each time point separately. The logistic regression will include a factor for treatment group and a covariate for Baseline, where appropriate. These analyses will be done for both the FAS and PP populations. Treatment comparisons for all continuous secondary endpoints will be conducted using a MMRM like the 1 described for the primary endpoint. These analyses will be done for both the FAS and PP populations.
Exploratory	Will be described in the SAP finalized before database lock.

Abbreviations: AN=abscess and inflammatory nodule; FAS=Full Analysis Set; HiSCR=Hidradenitis Suppurativa Clinical Response; NRS30-PGA=Patient's Global Assessment; PP=Per Protocol; SAP=Statistical Analysis Plan.

9.4.2 Safety Analyses

The Safety population will be used for the analysis of safety data (AEs, exposure to study treatment, clinical laboratory values, vital signs, and ECG).

Adverse events will be coded with MedDRA and WHODrug Global B3 March 2021. The TEAEs are defined as AEs with an onset date on or after the date of first administration of study treatment and before the date of last administration of study treatment +30 days. Treatment-emergent adverse events will be presented by system organ class and preferred term in frequency tables. Patients with multiple AEs will be counted only once within each preferred term and system organ class. Key patient information for patients with an AE with an outcome of death, patients with SAEs, and patients with an AE leading to discontinuation of study treatment will be listed.

Laboratory data (hematology, serum chemistry, coagulation, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from Baseline will be presented descriptively. Laboratory data outside study specific reference ranges will be listed. Vital signs and ECG parameters will be presented descriptively.

9.4.3 Other Analyses

9.4.3.1 ATI-450 Drug Concentrations and Pharmacokinetic Analyses

All PK analyses will be performed using the PK Population. Plasma concentrations of ATI-450 and its primary circulating metabolite, CDD-2164, will be summarized by day and sample time. Concentration versus time since dose (Days 1, 8, 15, 29, 43, 57, and 85) will be displayed by linear scale. Population PK modeling and related exposure response modeling may be explored, as appropriate.

9.4.3.2 [redacted]

[redacted]

9.4.4 Missing Data

Missing data will not be imputed for the safety summaries, or the efficacy summaries conducted on the PP population. All efficacy analyses conducted on the FAS population will use a LOCF analysis. Additionally, a sensitivity analysis will be conducted for categorical endpoints conducted on the FAS using the non-responder imputation method. Further details regarding the imputation of data that are missing or following intercurrent events will be provided in the SAP.

9.5 Interim Analyses

No interim analysis for efficacy is planned.

9.6 Data Monitoring Committee

An independent DSMB will convene to monitor interim safety data. The DSMB is responsible for reviewing and evaluating unblinded safety data at regularly scheduled meetings. The Committee may also meet in ad hoc meetings at its discretion as needed in response to events occurring in the study. Details regarding DSMB membership, responsibilities, and meeting frequency are outlined in the DSMB Charter.

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