PROTOCOL

Protocol Amendment 2.0

TITLE PAGE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan in Subjects with Moderate to Severe Hidradenitis Suppurativa
Protocol Number:	CL016_168
Investigational Product:	Avacopan (formerly CCX168)
Indication:	Treatment of subjects with Hidradenitis Suppurativa
Sponsor:	ChemoCentryx, Inc.
Development Phase:	2
IND number	139933
EudraCT number	2018-002351-15
Sponsor's Responsible Medical Officer:	PPD ChemoCentryx, Inc. PPD
Sponsor Signatory:	PPD
Original:	**19 October 2018**
Amendment 1.0:	**19 March 2019**
Amendment 2.0:	**31 July 2019**

This study will be conducted according to the principles of Good Clinical Practice as described in International Conference on Harmonization guidelines, including the archiving of essential documents.

INVESTIGATOR SIGNATORY PAGE

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I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by ChemoCentryx, Inc.
- Not to implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and written approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
- That I am thoroughly familiar with the appropriate use of the investigational drug(s), as described in this protocol, and any other information provided by the Sponsor including, but not limited to the following: the current version of the Investigator's Brochure prepared by ChemoCentryx, Inc. and approved product label, if applicable.
- That I am aware of and will comply with current International Conference on Harmonisation (ICH)/Food and Drug Administration (FDA) good clinical practices (GCP) guidelines and all regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the investigational drug(s) and their study-related duties and function as described in the protocol.

_____ _____
Principal Investigator Date

_____
Printed Name

Address*_____

_____

Phone Number* _____

* If the address or phone number needs to be changed during the course of the study, this will be done by the Investigator, with written notification to the Sponsor, and will not require (a) protocol amendment(s).

SPONSOR CONTACT INFORMATION

Protocol Number: CL016_168

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan in Subjects with Moderate to Severe Hidradenitis Suppurativa

Medical Officer	PPD Vice President Clinical Development and Translational Medicine ChemoCentryx, Inc. PPD
Clinical Operations Manager	PPD ChemoCentryx, Inc. PPD

SPONSOR SIGNATURE FOR APPROVAL

Protocol Number: CL016_168

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan in Subjects with Moderate to Severe Hidradenitis Suppurativa

PPD

Vice President, Clinical Development
and Translational Medicine

PPD

Date

PROTOCOL AMENDMENT 2.0: SUMMARY OF CHANGES

1. The protocol Title Page was updated with the new amendment number and date.
2. Collection of the Dermatology Life Quality Index (DLQI) and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) scores were updated throughout the document.
3. Period 1 has been defined to refer to the blinded, placebo-controlled 12-week treatment period. Period 2 has been defined to refer to the 24-week, active treatment period.
4. Scars have been updated to include the term "hypertrophic" where appropriate throughout the document.
5. SYNOPSIS - Secondary and Other Objectives and Section 2.2 Secondary Objectives and Other Objectives have been updated to prioritize the objectives.
6. SYNOPSIS - Secondary Efficacy Endpoints and Section 8.5.2 Secondary Endpoints have been updated to prioritize four main secondary efficacy endpoints. All other previous secondary efficacy endpoints were relocated to SYNOPSIS - Other Efficacy Endpoints and Section 8.5.3 Other Endpoints.
7. SYNOPSIS - Other Efficacy Endpoints and Section 8.5.3 Other Endpoints have been added.
8. SYNOPSIS - Study Interventions/Methodology and Section 4.4 Removal of Subjects from Therapy have been updated to include details on discontinuation of study medication due to inadequate or worsening response during the 24-week active treatment period.
9. SYNOPSIS - Study Interventions/Methodology and Section 3.1 Stratification and Randomization have been updated to state that not more than 20% of enrolled subjects will be on allowed concomitant antibiotic therapy.
10. SYNOPSIS - Criteria for Inclusion and Section 4.1 Inclusion Criteria have been updated to indicate the requirement of subjects to have at least 5 inflammatory nodules and abscesses at Screening in Inclusion #5 and to clarify contraception methods in Inclusion #7.
11. SYNOPSIS - Criteria for Exclusion and Section 4.2 Exclusion Criteria have been updated to clarify medicines with potential therapeutic impact on HS in Exclusion #9.
12. STUDY SCHEMA has been updated to clarify the two treatment periods.
13. TIME AND EVENTS TABLE has been updated:
    a. To add a urine pregnancy test for women of childbearing potential on Day 1;
    b. To add collection of DLQI and WPAI:SHP scores (in Patient-Reported Outcomes) and Health-Economic Information;
    c. To clarify the collection of AEs at Screening;
    d. To clarify the maximum number of days allowed to exceed the Screening period;
    e. To update PK blood sample collection for timepoints up to 3 hours following dosing;
    f. To add study procedures to Week 24 and 32 visits;
    g. To add exploratory biomarker plasma sample collection at Day 1, Week 12, and Week 36 or Early Termination visits;

h. To add optional photography to all visits.

14. LIST OF ABBREVIATIONS AND ACRONYMS has been updated to include missing acronyms.
15. Section 5.7 Concomitant Therapy and Restrictions has been updated to clarify concomitant use of treatments with potential impact on HS including systemic antibiotics, antiseptics, analgesics, wound care, and lesion intervention methods.
16. Section 6 STUDY PROCEDURES has been updated to harmonize study procedures with Time and Events Table in Sections 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 6.10, 6.11, 6.12, 6.13 and 6.14.
17. Section 7.1.1 Location and Extent of Hidradenitis Suppurativa Assessment has been updated to specify that the same Investigator should assess the lesions at each visit to assure consistency.
18. Section 7.1.7 Health-Economic Information has been added.
19. Section 7.2.3.3 Adverse Events of Special Interest (AESI) has been added.
20. Section 7.2.4 Serious Adverse Event Reporting has been updated to include the new email contact for Serious Adverse Event reporting.
21. Section 7.4 Exploratory Biomarker Assessments has been added to allow collection of plasma blood samples for biomarker assessments.
22. Section 7.5 Photographic Assessments has been updated to specify the different uses of the photographs.
23. Section 8.1 Timing of Analyses has been updated to describe the primary and final analyses.
24. Section 8.4.1 Modified Intent-to-Treat Population has been updated to define the modified intent-to-treat populations.
25. Section 8.4.3 Safety Population has been updated to define the safety populations.
26. Section 8.8.1 General Approach has been updated to clarify on the non-responder and missing data analyses.
27. Section 8.8.2 Analysis of Primary Efficacy Endpoint has been updated.
28. Section 8.8.3 Analysis of Secondary and Other Efficacy Endpoints in Period 1 and Section 8.8.4 Analysis of Secondary and Other Efficacy Endpoints in Period 2 have been added.
29. Section 8.8.12 Covariates and Subgroups has been updated to include new variables for the analysis of the efficacy endpoints.
30. Section 8.9 Interim Analyses has been updated to include a potential futility analysis.

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LIST OF TABLES

STUDY SYNOPSIS

Name of Sponsor	**Name of Active Ingredient**	**Study Number:**
ChemoCentryx, Inc.	Avacopan (formerly CCX168)	CL016_168

Title

A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Phase 2 Study to Evaluate the Safety and Efficacy of Avacopan in Subjects with Moderate to Severe Hidradenitis Suppurativa

Study centers

Multi-centers

Study period	**Phase of development**
29 months	Phase 2

Background

Hidradenitis suppurativa (HS), also called acne inversa, is a chronic inflammatory skin disease characterized by inflammatory nodule, abscess, sinus and fistula formation, and scarring of the skin, most commonly in apocrine gland rich areas such as the axilla, inframammary area, inguinal area, perineum, and perianal area. Therapy for subjects with HS includes local and systemic antibiotics, pain medication, and anti-TNF-α agents such as adalimumab. Acitretin is used in early stage disease. Other drugs such as cyclosporin A, dapsone, and isotretinoin have been used with limited success.

Studies have shown that HS is a neutrophil-driven disease, and that complement activation with the production of terminal fragment C5a may be important in the pathogenesis of the disease. The C5a-C5aR signaling axis is essential in mediating neutrophil activation and migration. Avacopan, an orally administered selective C5a receptor (C5aR) inhibitor, was shown to be effective and safe in a Phase 2 study in subjects with anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) and is being tested in a Phase 3 clinical trial in subjects with AAV. Since avacopan selectively blocks the C5aR, it has the potential to be an effective therapy for subjects with HS. Hence, the clinical hypothesis of this trial is to test whether avacopan is effective in treating subjects with moderate to severe HS.

Study Description

The study is a randomized, double-blind, placebo-controlled, three-group Phase 2 trial in approximately 390 subjects with moderate to severe hidradenitis suppurativa (Hurley Stage II or III). Subjects will be randomized 1:1:1 to a treatment of 10 mg avacopan twice daily, 30 mg avacopan twice daily or placebo for 12 weeks. Other systemic treatments for HS including anti-TNF-α treatments are prohibited. Stable antibiotic therapy with doxycycline or minocycline is allowed as specified in the protocol. Subjects treated with 10 mg or 30 mg avacopan twice daily during the blinded, placebo-controlled 12-week treatment period (Period 1) will be followed by

an additional 24-week, active treatment period (Period 2) during which they will continue to receive the same dose regimen, either 10 mg or 30 mg avacopan twice daily. Subjects on placebo who complete Period 1 will be re-randomized 1:1 to receive 10 mg or 30 mg avacopan twice daily in Period 2. During Period 2 the treatment assignment to 10 mg or 30 mg twice daily will not be disclosed to the subject, study site personnel or the Sponsor. Thereafter, all subjects will be followed without study drug for 8 weeks before they exit the study.

Objectives

Primary Objectives:

1. Evaluation of the efficacy of avacopan compared to placebo in subjects with Hurley Stage II or III hidradenitis suppurativa (HS) based on subjects achieving a Hidradenitis Suppurativa Clinical Response (HiSCR) after 12 weeks of treatment. HiSCR is defined as at least a 50% reduction in abscess and inflammatory nodule count and no increase in abscess count and no increase in draining fistula count at Week 12 relative to baseline.
2. Evaluation of the safety of avacopan compared to placebo in these subjects based on the adverse event incidence, changes from baseline in laboratory parameters, and vital signs.

Secondary and Other Objectives:

1. Evaluation of the efficacy of avacopan compared to placebo in these subjects include:
    a. The subject's global assessment of skin pain numeric rating scale (NRS),
    b. The modified Sartorius score, and
    c. Achieving an AN count of 0, 1, or 2.
2. Assessment of patient-reported outcomes including health-related quality-of-life changes based on the Short Form-36 version 2 (SF-36 v2), the EuroQOL-5D-5L (EQ-5D-5L), the Hidradenitis Suppurativa Quality of Life (HiSQOL) Index, the Dermatology Life Quality Index (DLQI), and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) with avacopan compared to placebo.
3. Evaluation of the pharmacokinetic profile of avacopan in subjects with HS.
4. Evaluation of the safety and efficacy of avacopan treatment from Day 1 by each timepoint up to Week 44 in subjects with HS.
5. Evaluation of the efficacy of avacopan compared to placebo in these subjects include:
    a. The Sartorius score, International HS Severity Scoring System (IHS4) score, HS Physician Global Assessment (HS-PGA),
    b. Proportion of subjects who experienced flare, who experienced loss of response during Period 2, who received oral antibiotic rescue therapy or lesion intervention, and who received disallowed opioid pain therapy, and
    c. The duration of flare in days.
6. Evaluation of health-economic information.

Endpoints

Endpoints will be evaluated by treatment group.

Primary Efficacy Endpoint

The proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12. A response is defined as a reduction of at least 50% in abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline.

Secondary Efficacy Endpoints:

1. Reduction of IHS4 score relative to baseline at Week 12;
2. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Day 1 in the subject's global assessment of skin pain (NRS30) in subjects with a Day 1 NRS of at least 3, evaluated at Week 12; weekly averages of daily pain will be calculated based on subjects' daily diary recording of the worst pain experienced in the previous 24 hours;
3. Change from Day 1 to Week 12 in the modified Sartorius score to quantify the severity change of HS;
4. Proportion of subjects with baseline Hurley Stage II who achieved an abscess and inflammatory nodule count of 0, 1, or 2 at Week 12.

Other Efficacy Endpoints:

The following efficacy endpoints will be analyzed from Day 1 to each timepoint up to Week 44, where applicable:

1. Proportion of subjects achieving HiSCR;
2. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Day 1 in the subject's global assessment of skin pain (NRS30), in subjects with a Day 1 NRS of at least 3;
3. Proportion of subjects with baseline Hurley Stage II who achieved an abscess and inflammatory nodule count of 0, 1, or 2;
4. Change from Day 1 in inflammatory nodule count, abscess count, draining fistula count, and total AN count;
5. Change from Day 1 in the Sartorius score, modified Sartorius score, IHS4 score, and HS-PGA to quantify the severity change of HS;
6. Change from Day 1 in patient-reported outcomes: SF-36 v2, EQ-5D-5L, HiSQOL and DLQI;
7. Proportion of subjects who experienced flare, defined by at least a 25% increase in AN counts with a minimum increase of 2 AN lesions relative to Day 1;
8. Duration of flare in days (calculated from the day when flare is observed to the day prior to the observation that flare is no longer present; of note, there could be multiple periods that flares are observed, in which case, the total days from the multiple periods will be used);
9. Proportion of subjects who experience at least 25% increase in draining fistula counts with a minimum increase of 2 draining fistula counts relative to Day 1;

10. During Period 2, Proportion of subjects with a loss of response, (LOR) defined as loss of at least 50% of AN count improvement achieved from Period 1;
11. Time to LOR during Period 2;
12. Proportion of subjects who received oral antibiotic rescue therapy;
13. Proportion of subjects who start disallowed opioid pain therapy;
14. Proportion of subjects who undergo lesion intervention due to HS;
15. Number of lesion interventions due to HS;
16. Health-economic information:
    a. WPAI:SHP: Change from Day 1 to each timepoint during Period 1and Change from Week 12 to each timepoint during Period 2 and including the follow-up period;
    b. Hospitalizations (cumulative): Number of Hospitalizations total and due to HS, Number of days hospitalized, Number of days missed from work;
    c. Emergency or Urgent Care visits (cumulative): Number of visits total and due to HS, Number of days (or hours where applicable) missed from work;
    d. Lesion interventions for HS: Number of days (or hours where applicable) missed from work due to HS lesion interventions.

Safety endpoints:

1. Subject incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events;
2. Change from Day 1 and shifts from Day 1 in all safety laboratory parameters;
3. Change from Day 1 in vital signs and significant changes in physical examination abnormalities.

Number of Subjects/Sample Size Assumptions:

The study will enroll approximately 390 subjects. The proportion of subjects in the placebo control group achieving a HiSCR at Week 12 is estimated to be approximately 30%. The attrition rate throughout the trial is estimated to be approximately 7%. A sample size of approximately 130 subjects per treatment group (390 in total) at a Type I error rate of two-sided $\alpha = 0.05$ provides approximately 90% power to detect a 20% superiority of avacopan compared to the placebo control group in HiSCR at Week 12, assuming an HiSCR at Week 12 of 50% in the avacopan group.

Study Interventions/Methodology

Eligible adult subjects (at least 18 years of age) with moderate to severe hidradenitis suppurativa (Hurley Stage II or III) as specified by the eligibility criteria are allowed to enter the study.

In Period 1, subjects will be randomized 1:1:1 to receive 10 mg avacopan twice daily, 30 mg avacopan twice daily or matching placebo for 12 weeks in a double-blind, placebo-controlled manner.

To obtain balance across treatment groups, a stratified randomization scheme will be implemented. The stratification factors and strata within each factor are listed below. Eligible subjects will be randomized with equal chance (i.e., 1:1:1) to one of the three treatment groups within each stratum based on a non-dynamic, list-based blocked randomization scheme.

1. Hurley Stage (Stage II vs. III):
    a. Stage II disease: one or more widely separated recurrent abscesses with tract formation and scars, or
    b. Stage III disease: multiple interconnected tracts and abscesses across an entire area, with diffuse or near diffuse involvement.
2. Concomitant antibiotic therapy (Yes vs. No)
    a. Concomitantly treated with doxycycline or minocycline as the only allowed antibiotic treatment for HS, or
    b. No concomitant antibiotic therapy.
3. Anti-TNF-α treatment (Treatment naïve vs. Previous treatment):
    a. Did not previously receive anti-TNF-α drug such as adalimumab or infliximab (anti-TNF-α drug naïve), or
    b. Previously (but no longer) received an anti-TNF-α drug and
        - completed anti-TNF-α treatment but may have relapsed, or
        - was intolerant to anti-TNF-α treatment, or
        - previously failed to respond or inadequately responded to anti-TNF-α treatment.

Not more than 20% of subjects will be in stratum 2a.

Subjects will be screened for eligibility based on the stage of the disease and their health status. The Screening period will be up to 28 days. The primary efficacy analysis can occur when the last enrolled subject has completed the Week 12 visit. After Period 1, all subjects will continue into Period 2 with an additional 24-week treatment with either 10 mg or 30 mg avacopan twice daily. The treatment assignment to 10 mg or 30 mg twice daily will not be disclosed to the subject, study site personnel or the Sponsor. Thereafter, all subjects will be followed for 8 weeks.

All subjects will visit the study center during the 28-day Screening period, and, if eligible, on Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 44 of the study. Study drug will be dispensed at the study site and subjects will take the first dose of study drug, i.e., avacopan or matching placebo, while at the study center. Following the first dose, subjects will take study drug twice daily which will continue for 12 weeks (84 days). Thereafter, all subjects will take avacopan study drug for 24 weeks (168 days), after which all subjects will be followed for 8 weeks (56 days) without taking study medication. Study procedures at each visit day are detailed in the Time and Events Table.

Subjects will be discontinued from the study when all the Study Week 44 visit procedures have been completed.

Subjects who experience a flare of HS or need HS lesion intervention during the study will be treated by the Investigator as outlined in Section 5.7 Concomitant Therapy and Restrictions. These subjects will be requested to remain in the study and to complete all study procedures if

possible. During this time, subjects may continue to receive the study drug if deemed clinically feasible by the Investigator as described in Section 5.7.

Discontinuation of study medication due to inadequate or worsening response in Period 2: Unless prohibited for safety reasons, deemed inappropriate by the Investigator, or subject withdraws consent, all subjects are allowed to enter Period 2. Subjects in Period 2 will discontinue taking study medication if at two consecutive protocol-specified visits ≥14 days apart, the AN count increases by more than 50% compared to the AN count at Week 12. However, these subjects will be requested to remain in the study and to complete all study procedures if possible.

Criteria for Inclusion

1. Aged at least 18 years of age;
2. Clinical diagnosis of HS (Hurley Stage II or III), confirmed by a dermatologist, for at least 6 months prior to Screening. Hurley Stage II disease is defined as having one or more widely separated recurrent abscesses with tract formation and scars; Stage III disease is defined as having multiple interconnected tracts and abscesses across an entire anatomical area, with diffuse or near diffuse involvement.
3. HS lesions are present in at least 2 distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), one of which is Hurley Stage II or Hurley Stage III;
4. Inadequate or loss of response to a systemic course of antibiotics of 90 days. However, a subject who has completed less than 90 days of antibiotic treatment may be allowed into the study upon discussion with the Medical Monitor if: 1) the subject has demonstrated intolerance to or contraindication for antibiotics to treat HS, or 2) it was determined by the Investigator that an antibiotic course of at least 28 days to treat HS did not benefit the subject and a continued antibiotic therapy would therefore not be indicated.

   Inadequate or loss of response is defined if the following was observed despite antibiotic treatment:

   a. Progression of Hurley Stage (i.e., the Hurley Stage of at least one affected anatomic region progressed from I→II, II→III, or I→III);
   b. Subject required at least one intervention (e.g., incision and drainage or intralesional injection of corticosteroid);
   c. Subject experienced pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or acetaminophen);
   d. Subject experienced pain requiring opioids, including tramadol;
   e. Subject experienced drainage interfering with activities of daily living (e.g., requires multiple dressing changes and/or changes of clothes daily);
   f. Subject experienced an increase in the number of anatomic regions affected by HS;
   g. Subject experienced at least one new abscess or one new draining fistula.
5. Must have at least 5 inflammatory nodules or abscesses at Screening;
6. Must agree to use a topical antiseptic daily over the course of the study; topical antiseptics may include but are not limited to chlorhexidine, triclosan, benzoyl peroxide, or diluted bleach in bath water;

7. Female subjects of childbearing potential may participate if adequate contraception is used during the study and for at least three months after study completion. Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception where inhibition of ovulation is the primary mode of action [oral, injectable, or implantable], intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true [absolute] sexual abstinence, i.e., in line with the preferred and usual lifestyle of the subject). Male subjects with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception as defined above is used during the study and for at least three months after study completion. In addition, a barrier method (i.e., condom, cervical cap, or diaphragm) must be used during intercourse between a male study subject and a female partner of childbearing potential;
8. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol;
9. Judged by the Investigator to be otherwise fit for the study, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Subjects with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to compromise subject participation in the study, may be entered into the study.

Criteria for Exclusion

1. Pregnant or breast-feeding;
2. Any other skin disease that may interfere with the assessment of HS, such as a viral or fungal skin infection;
3. Rapidly progressive, expanding HS within 30 days prior to Screening;
4. More than 20 draining fistulae at Screening;
5. Any anti-TNF-α treatment for HS or for other conditions prior to Day 1 visit will be prohibited. Exception: Subjects who were previously treated with an anti-TNF-α drug and discontinued treatment >12 weeks prior to Day 1 visit are allowed for enrollment;
6. Systemic antibiotics are generally excluded. Exception: subjects on systemic antibiotic treatment with doxycycline or minocycline who have been on a stable dose for at least 28 days prior to Day 1. After a pre-specified percentage of subjects on these permissible antibiotic treatments have been enrolled, no further enrollment of such subjects will be allowed;
7. Topical antibiotics use within 14 days prior to Day 1;
8. Have started a topical prescription medicine for HS within 14 days prior to Screening or is anticipated to start during the screening period. Topical prescription medicine for HS other than topical antibiotics that was started >14 days prior to Screening is allowed;

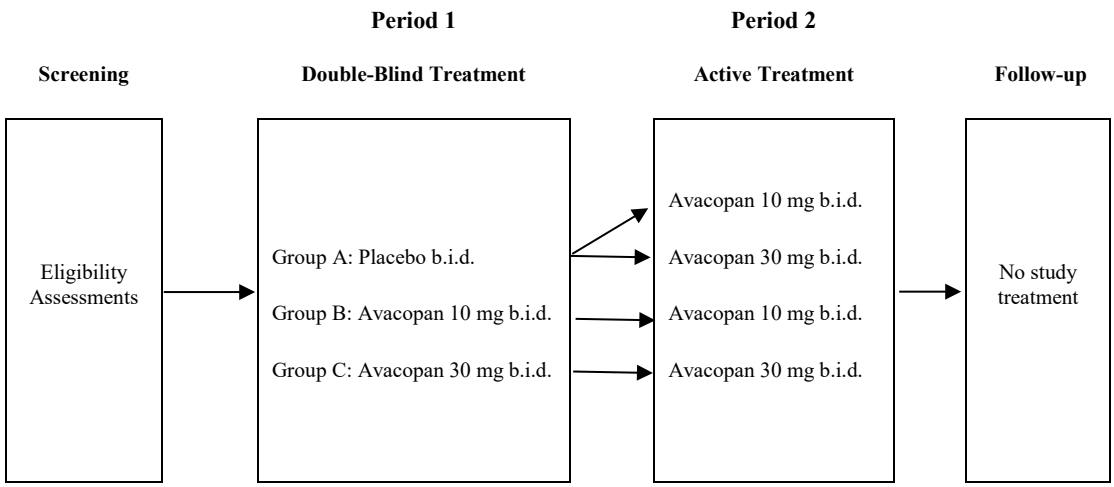
9. With the exception of permissible antibiotic treatment regimens, have received a systemic medicine for HS or with a potential therapeutic impact on HS, including systemic antibiotic therapy, biologics and other systemic therapies such as methotrexate, cyclosporine, retinoids, and fumaric acid esters, etc., within a minimum of 30 days or 5 half-lives (whichever is longer) after taking the last dose;
10. Have received within 14 days prior to Day 1 visit or is expected to require during the study oral or transdermal opioid analgesics (except for tramadol) for any reason; non-opioid analgesics are allowed if the subject is on a stable dose for at least 14 days prior to the Day 1 visit ("as needed" dosing is not considered to be a stable dose);
11. Currently taking a strong inducer of the cytochrome P450 3A4 (CYP3A4) enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort;
12. Any of the following within 12 weeks prior to Screening: symptomatic congestive heart failure requiring prescription medication, unstable angina (unless successfully treated with stent or bypass surgery), clinically significant cardiac arrhythmia, myocardial infarction or stroke;
13. History or presence of any form of cancer within the 5 years prior to Screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
14. Evidence of tuberculosis based on interferon γ release assay (IGRA);
15. HBV, HCV, or HIV viral screening test done at Screening or within 6 weeks prior to screening showing evidence of active or chronic viral infection;
16. Received a live vaccine within 4 weeks prior to Screening;
17. WBC count less than 3500/μL, or neutrophil count less than 1500/μL, or lymphocyte count less than 500/μL before start of dosing;
18. Evidence of hepatic disease: AST, ALT, alkaline phosphatase, or bilirubin >3 times the upper limit of normal before the start of dosing;
19. Clinically significant abnormal electrocardiogram (ECG) during Screening which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation;
20. Known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including gelatin, polyethylene glycol, or macrogolglycerol hydroxystearate [EP, European Pharmacopoeia (EP)] known also as polyoxyl 40 hydrogenated castor oil [NF, National Formulary]) or Cremophor® RH 40;
21. Participated in any clinical study of an investigational product within 30 days prior to Screening or within 5 half-lives after taking the last dose;
22. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

Study Drug, Dose, and Mode of Administration

Study subjects will receive active avacopan or placebo capsules as study drug. The study drug consists of hard gelatin capsules containing 10 mg avacopan or placebo administered orally. Avacopan and placebo bottles and capsules will be identical in appearance.

Subjects will be asked to take 3 capsules of study drug orally with water and preferably with food every morning, and 3 capsules with water and preferably with food in the evening approximately 12 hours after the morning dose, as instructed. Study drug will be taken for 36 weeks (252 days) continuously.

STUDY SCHEMA



Duration	≤ 28 days	84 days (12 weeks)	168 days (24 weeks)	56 days (8 weeks)
Study Visits	One or more visits to complete screening procedures	Day 1 and, Weeks 2, 4, 8 and 12	Weeks 16, 20, 24, 28, 32, 36	Week 44

TIME AND EVENTS TABLE

	Screening		Period 1 Double-Blind Treatment					Period 2 Active Treatment						Follow-up
Study Week[1]	**≤4 weeks[1]**			**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**44**
Study Day[1]	**≤28 days[1]**		**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**309**
		-7 days												
Informed consent	X													
Review inclusion/exclusion criteria	X													
Demographics, medical history, prior treatments	X													
Physical examination[2]	X		X[3]	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X		X[3]	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test for women of childbearing potential	X		X		X	X	X	X	X	X	X	X	X	
Urine pregnancy test for women of childbearing potential			X[3]											
HIV, HBV, HCV testing	X													
Screening for tuberculosis[4]	X													
12-Lead ECG	X						X							X
Serum chemistry incl. Liver Function Tests, Hematology	X		X[3]	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X		X[3]		X	X	X	X	X	X	X	X	X	X
Biomarker plasma sample collection[15]			X[15]				X						X	
Stratification and randomization			X				X[10]							
Record location and number of HS inflammatory nodules, abscesses, fistulae, and scars	X		X[3]	X	X	X	X	X	X	X	X	X	X	X
Record Hurley Stage	X													
Subject global assessment of skin pain daily diary recording[5]		X[3]→	→	→	→	→	→	→	→	→	→	→	→	→X

	Screening		Period 1 Double-Blind Treatment					Period 2 Active Treatment						Follow-up
Study Week[1]	**≤4 weeks[1]**			**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**44**
Study Day[1]	**≤28 days[1]**		**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**309**
		-7 days												
Record items for the Sartorius and modified Sartorius scores calculation[6]			X[3]	X	X	X	X	X	X	X	X	X	X	X
Photograph selected lesions[12]			X[12]	X	X[12]	X	X[12]	X[12]	X	X	X[12]	X	X[12]	X
Record IHS4 score[7]			X[3]	X	X	X	X	X	X	X	X	X	X	X
HS-PGA[14]			X[3]	X	X	X	X	X	X	X	X	X	X	X
SF-36 v2 and EQ-5D-5L Patient-Reported Outcomes[8]			X[3]		X		X	X			X		X	X
HiSQOL Index[8] Health-Economic Information[13]			X[3] X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensing			X[3]				X			X				
Study drug compliance			X	X	X	X	X	X	X	X	X	X	X	
Study drug accountability[11]							X[11]			X[11]			X[11]	
PK plasma sample collection[9]			X	X	X	X	X	X	X		X		X	X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X
Adverse event assessment	X		X	X	X	X	X	X	X	X	X	X	X	X

[1]Screening period may be exceeded by up to 3 days. Week 1 through 36 visits may occur within a ± 2-day window. The Week 44 visit may occur within a ± 4-day window.

[2]Physical examination will include body weight measurements. Height will be measured only at Screening.

[3]These procedures must be performed before taking the first dose of blinded study drug (avacopan or placebo).

[4]Screening for tuberculosis: see exclusion criteria for specifics.

[5]Subjects will record the maximum severity pain on a numeric rating scale from 0 (no skin pain) to 10 (skin pain as bad as can be imagined) in a daily diary from one week prior to Day 1 through the Week 44 visit.

[6]Twelve body areas will be evaluated to calculate the Sartorius and modified Sartorius scores: left and right axillae, left and right inframammary areas, intermammary area, left and right buttocks, left and right inguino-crural folds, perianal area, perineal area, and other. The presence of nodules, abscesses, fistulae, scars, and other findings will be recorded. The longest distance between two lesions and whether lesions are separated by normal skin will be recorded.

[7]IHS4 score (points) = (number of nodules multiplied by 1) + (number of abscesses multiplied by 2) + [number of draining tunnels (fistulae/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.

[8]"Patient-reported outcomes" (PROs) include the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI-SHP questionnaires. The SF-36 v2 and EQ-5D-5L instruments are widely accepted global non-disease-specific tools to measure changes in subjects' health-related quality of life. The HiSQOL index (an HS-specific instrument) and DLQI instruments are designed to measure the impact of HS or skin disease on subjects' quality of life. The WPAI:SHP assesses the effect of general and specific health conditions on productivity losses.

[9] PK blood sample will be collected prior to the morning dose on Day 1 and at 0.5, 1, 2, and 3 (+/- 5 minutes) hours following dosing. Single PK samples will be collected pre-dosing at the subsequent visits as indicated. The date and time of the PK sample collection will be recorded. The date and time of the last dose of study drug prior to the PK sample collection will also be recorded. On study visit days when PK samples are collected, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples. PK will be performed in up to 150 subjects participating in the study. The Sponsor will continuously assess the number of subjects enrolled in the PK group. If at any point during enrollment, the number of PK subjects is below the required number, PK samples will be considered mandatory for the remaining subjects to be enrolled in the study. Additional consenting will be requested from subject for collection of PK samples.

[10] Subjects on placebo who complete the blinded, placebo-controlled 12-week period (Period 1) will be re-randomized 1:1 to receive 10 mg or 30 mg avacopan twice daily during the 24-week active treatment period (Period 2).

[11] At Week 12, 24, and 36 visits, full drug accountability will be conducted on returned study drug.

[12] If consented, photography will be used for the purpose of publications and lesion assessment comparison. If feasible, it is recommended that photographs be taken at every visit.

[13] Health-economic information include hospitalizations, emergency or urgent care visits, and lesion interventions due to HS. The WPAI:SHP questionnaire administration will follow the Patient-Reported Outcomes schedule.

[14] HS-PGA is an ordinal scale specific to HS that categorizes subjects into clear, minimal, mild, moderate, severe, or very severe disease.

[15] Biomarker plasma sample will be collected at Day 1, Week 12, and Week 36 or Early Termination visits in subjects who consented and at study sites adequately equipped to perform the collection. For Day 1, the biomarker sample collection must be done before the subject takes the first dose of study drug.

LIST OF ABBREVIATIONS AND ACRONYMS

AAV	ANCA-associated vasculitis
AE	adverse event
AESI	adverse event of special interest
aHUS	atypical hemolytic uremic syndrome
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule (count)
ANA	antinuclear antibodies
ANC	absolute neutrophil count
ANCA	anti-neutrophil cytoplasmic autoantibody
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AT	Aminotransferase
ATC	Anatomic Therapeutic Chemistry
AUC	area under the plasma concentration-time curve
b.i.d.	twice daily
BVAS	Birmingham Vasculitis Activity Score
C3	complement component 3
C3a	complement component 3a fragment
C4a	complement component 4a fragment
C5a	complement component 5a fragment
C5aR	receptor for C5a
C5b-9	membrane attack complex or terminal complement complex
CA	competent authority
C_{max}	maximum (maximal) plasma concentration
C_{min}	minimum plasma concentration
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	clinical research organization
CSR	clinical study report
CYP3A4	cytochrome P450 3A4
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EIA	enzyme immunoassay
EP	European Pharmacopoeia
EQ-5D-5L	EuroQuality of Life-5 Domains-5 Levels
FDA	Food and Drug Administration
g	Gram
GCP	Good Clinical Practice
HBV	hepatitis B virus

HCV	hepatitis C virus
hERG	potassium channel encoded by the human ether-à-gogo related gene
HiSCR	hidradenitis suppurativa clinical response
HiSQOL	Hidradenitis Suppurativa Quality of Life
HIV	human immunodeficiency virus
HS	hidradenitis suppurativa
HS-PGA	Hidradenitis Suppurativa-Physician Global Assessment
ICH	International Conference on Harmonisation
IC_{50}	concentration associated with 50% inhibition
Ig	Immunoglobulin
IgAN	immunoglobulin A nephropathy
IGRA	interferon γ release assay
IHS4	International HS Severity Scoring System
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent-to-treat
IV	intravenous(ly)
kDa	Kilodalton
kg	Kilogram
LOCF	last observation carried forward
LOR	loss of response
MAC	membrane attack complex
MCP-1	monocyte chemoattractant protein-1, also known as CCL2
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mITT	modified intent-to-treat
mL	Milliliter
MPO	myeloperoxidase
MSS	modified Sartorius score
N	Number
NF	National Formulary
NRI	Non-Responder Imputation
NRS	numeric rating scale
NRS30	proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from baseline in the subject's global assessment of skin pain on a numeric rating scale
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PP	Per-protocol
PRO	patient-reported outcome
PT	prothrombin time
QA	quality assurance
QC	quality control
QT/QTc	Q-T interval on ECG; corrected Q-T interval

RBC	red blood cell(s)
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SD	standard deviation
SEM	standard error of the mean
SF-36 v2	Short Form-36 version 2.0
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TBili	total bilirubin
TCC	terminal complement complex, also known as membrane attack complex
ULN	upper limit of normal
WBC	white blood cell
WHODD	World Health Organization Drug Dictionary
WPAI:SHP	Work Productivity and Activity Impairment Questionnaire: Specific Health Problem

1. INTRODUCTION

1.1. Complement and Avacopan

The activation of the complement pathway generates biologically active fragments of complement proteins, e.g., C3a, C4a and C5a anaphylatoxins, and the C5b-9 membrane attack complex (MAC) or terminal complement complex (TCC), all of which mediate inflammatory responses by inducing leukocyte chemotaxis, activating macrophages, neutrophils, platelets, mast cells and endothelial cells and by increasing vascular permeability, cytolysis, and tissue injury.

C5a is one of the most potent pro-inflammatory mediators of the complement system, being at least 100 times more potent than C3a. This 12 to 14.5 kD polypeptide, along with a C5b fragment, is produced by enzymatic cleavage of a C5 precursor during activation of any of the 3 complement pathways. C5a induces expression of adhesion molecules and chemotactic migration of neutrophils, eosinophils, basophils, and monocytes. It also mediates inflammatory reactions by causing smooth muscle contraction, increasing vascular permeability, inducing basophil and mast cell degranulation, and inducing release of lysosomal proteases and oxidative free radicals. The anaphylactic and chemotactic effects of C5a are mediated through its interaction with the C5aR, a G protein-coupled receptor expressed on human neutrophils, monocytes, basophils, eosinophils, renal glomerular tissues, and lung smooth muscle and endothelial cells.

Avacopan (formerly CCX168) is an orally administered, small molecule, selective inhibitor of the complement 5a receptor (C5aR).

As measured in vitro, avacopan functionally inhibits C5a-mediated chemotaxis, displaces [^{125}I]-C5a from human C5aR, and inhibits C5a-mediated increase in cytoplasmic calcium levels with a potency (IC_{50}) of 0.2 to 0.9 nM in buffer (Bekker et al, 2016).

Avacopan was also evaluated for its ability to inhibit the C5a-mediated chemotaxis of neutrophils in freshly isolated human whole blood. Avacopan produced 50% inhibition (IC_{50}) of C5a-mediation neutrophil migration in this assay at a concentration of 1.7 nM; 90% inhibition (A_{10} value) occurred at an avacopan concentration of 15.4 nM. Avacopan also inhibits C5aR in cynomolgus monkeys and hamsters with potencies similar to that observed with human whole blood. However, avacopan possesses moderate potency for rabbit C5aR (IC_{50} ~ 1.4 µM) and lacks affinity for mouse, rat, or dog C5aR (IC_{50} >10 µM).

The efficacy of avacopan was assessed using genetically-modified mice where the mouse C5aR coding region was substituted for the human C5aR coding region. In these studies, intravenous injection of mouse anti-myeloperoxidase (anti-MPO) IgG into the human C5aR knock-in mice caused glomerulonephritis in a manner mimicking anti-neutrophil cytoplasmic autoantibody (ANCA) disease in humans. At daily oral doses of 30 mg/kg avacopan, a marked inhibition of anti-MPO induced glomerulonephritis was documented histologically, as assessed by the number of necrotic and crescent-containing glomeruli. These results were consistent with reduced protein, leukocytes, and red blood cells in the urine, and reduced serum blood urea nitrogen and creatinine in mice receiving avacopan (Xiao et al, 2014).

1.2. Previous Clinical Studies

Five Phase 1 studies and four Phase 2 studies with avacopan have previously been completed. Avacopan was generally well tolerated in these studies. A Phase 3 study in subjects with AAV previously completed enrollment but follow up is ongoing and the study remains blinded. Another Phase 2 study in subjects with C3 glomerulopathy is currently enrolling and is also blinded.

Results from a mass balance study (CL004_168) showed that avacopan was mostly metabolized in the liver; in vitro metabolism studies showed that avacopan was primarily metabolized through cytochrome P450 3A4 (CYP3A4).

Avacopan did not show evidence of a detrimental effect on QT/QTc based on results from an intensive ECG study (CL007_168).

Co-administration of the strong CYP3A4 enzyme inducer rifampicin in study CL008_168 resulted in an approximately 93% reduction of systemic exposure of avacopan, which may result in a loss of efficacy of avacopan. Therefore, the use of strong CYP3A4 enzyme inducers with avacopan is an exclusion criterion for this study. Co-administration of the strong CYP3A4 enzyme inhibitor itraconazole resulted in a 119% increase of systemic exposure of avacopan. Concomitant use of avacopan with strong CYP3A4 enzyme inhibitors should be used with caution.

Two Phase 2 clinical trials in 109 subjects with ANCA-associated vasculitis (AAV) were conducted. The first study in 67 subjects (CL002_168) included three dose groups: 30 mg avacopan twice daily plus low dose prednisone (20 mg/day), 30 mg avacopan twice daily plus no prednisone, and placebo plus full dose prednisone (60 mg/day). All subjects received either IV cyclophosphamide or rituximab as standard of care treatment. Avacopan, alone or with low dose prednisone, was associated with a rapid onset of action based on improvements in a global disease activity index (the Birmingham Vasculitis Activity Score, BVAS), and improvements in renal parameters such as albuminuria, and health-related quality of life measurements over a 12-week treatment period (Jayne et al, 2017). The steady state mean avacopan plasma concentration was approximately 204 ng/mL in these subjects, corresponding to >95% projected inhibition of the C5aR in the circulation. Avacopan also showed a favorable safety profile in this study.

The second study in 42 subjects (CL003_168) included three dose groups: 10 mg avacopan twice daily plus full dose prednisone (60 mg), 30 mg avacopan twice daily plus full dose prednisone, and placebo plus full dose prednisone. All subjects received either IV cyclophosphamide or rituximab as standard of care treatment. Avacopan appeared to be safe when added on top of full dose prednisone plus cyclophosphamide or rituximab, and the efficacy data support 30 mg avacopan twice daily as the therapeutic dose in AAV. Refer to the Investigator's Brochure for more details.

An open-label Phase 2 clinical trial in 7 subjects with IgA nephropathy (IgAN) has been conducted (CL005_168). Results showed that avacopan therapy was associated with improvement in proteinuria over a 12-week treatment period; 3 of 7 subjects showed approximately 50% decrease in either urinary protein:creatinine ratio (UPCR) or albumin:creatinine ratio (UACR). An open-label Phase 2 clinical trial in 6 subjects with atypical hemolytic uremic syndrome (aHUS) was conducted (CL006_168). Results showed that serum

collected from subjects dosed with avacopan caused a mean percent reduction of 82% in thrombus size compared to baseline in an ex vivo assay.

A Phase 2 clinical trial with a target enrollment of approximately 88 subjects with C3 glomerulopathy is ongoing (CL011_168). The study remains blinded.

A Phase 3 clinical trial with a target enrollment of approximately 300 subjects with AAV previously completed enrollment and follow up is ongoing (ADVOCATE, CL010_168). In this study in subjects with AAV, avacopan (or placebo) is compared with standard of care glucocorticoids as added medications to background therapy of either rituximab or cyclophosphamide followed by azathioprine. The study remains blinded.

The Reference Safety Information section of the Investigator's Brochure has been updated to include the potential risk of urticaria, angioedema, and of hepatotoxicity, and to state that general gastrointestinal adverse events (e.g., nausea, diarrhea) observed in Phase 2 AAV studies have been observed in the ongoing Phase 3 CL010_168 study at approximately the same frequency and severity. Further, as a result of the DMC review of safety data from all completed and ongoing studies of avacopan, the frequency of monitoring of hematology has been increased to monthly and rules for pausing administration of blinded study drug have been modified.

A benefit and risk assessment of avacopan is presented in Section 11; detailed information about non-clinical and clinical trials with avacopan is presented in the Investigator's Brochure. Results from nonclinical and clinical studies conducted to date showed a positive risk-benefit profile of avacopan in treatment of subjects with HS (Section 11).

1.3. Rationale for the Study

Hidradenitis suppurativa (HS), also called acne inversa, is a chronic inflammatory skin disease characterized by inflammatory nodule, abscess, sinus and fistula formation, and scarring of the skin, most commonly in apocrine gland rich areas such as the axilla, inframammary area, inguinal area, perineum, and perianal area. In its moderate and severe forms, HS is debilitating and causes significant discomfort, pain, anxiety and depression, as well as impairment of quality of life. The exact cause of HS has not been identified, although genetic defects in the gene encoding for gamma-secretase have been described in subjects with HS. Potential target proteins include Notch, E-cadherin, and nicastrin. Notch plays an important role in hair follicle development, and a defect in Notch may lead to formation of epidermal cysts, dysregulation of normal T-cell mediated immune responses, and suppression of Toll-like receptor-4-induced pro-inflammatory macrophage mediated cytokine responses (Radtke et al, 2010; Wang et al, 2010). Smoking and obesity have been associated with HS (Prens and Deckers, 2015).

Therapy for subjects with HS includes local and systemic antibiotics, pain medication, and anti-TNF-α agents such as adalimumab. Acitretin is used in early stage disease. Other drugs such as cyclosporin A, dapsone, and isotretinoin have been used with limited success (Napolitano et al, 2017). In more advanced cases, a multifaceted approach may be adopted, where surgical therapy is used to remove the chronic components of HS which are not expected to respond to medical therapy (e.g., scarring, fistulas, and sinus tracts), and long-term systemic medical therapy is used to treat the acute or sub-chronic manifestations of HS (e.g., abscesses and inflammatory nodules).

Studies have shown that HS is a neutrophil-driven disease, and that complement activation with the production of terminal fragment C5a may be important in the pathogenesis of the disease (Kanni et al, 2018). The C5a-C5aR signaling axis is essential in mediating neutrophil activation and migration. Recently it is has been reported that circulating C5a and C5b-9 levels were significantly greater in HS patients, further adding to the relevance of C5a-C5aR an important mechanistic contributor to the disease process. More importantly, plasma from HS patients activates neutrophils (CD11b upregulation) ex vivo, and this activation can be blocked by a neutralizing antibody against C5a (IFX-1; Kanni T, et al. 2018), suggesting that C5a may be a critical factor in driving neutrophil activation and infiltration in the diseased tissue in HS patients. An anti-C5a agent, IFX-1, has shown efficacy in a Phase 2 study, suggesting a role for C5a blocking agents in the treatment of HS (Guo et al, 2017).

Avacopan, an orally administered, C5a receptor (C5aR) selective agent, was shown to be effective and safe in a Phase 2 study in subjects with AAV (Jayne et al, 2017) and is being tested in a Phase 3 clinical trial in subjects with AAV. Since HS is a neutrophil-driven disease and avacopan selectively blocks the C5aR, the activation of which leads to neutrophil attraction, avacopan has the potential to be an effective therapy for patients with HS. Hence, the clinical hypothesis of this trial is to test whether avacopan is effective in treating patients with moderate to severe HS.

This clinical trial will be conducted in compliance with the protocol, good clinical practice (GCP), and applicable regulatory requirements.

2. OBJECTIVES

2.1. Primary Objectives

The primary objectives of this study include:

1. Evaluation of the efficacy of avacopan compared to placebo in subjects with Hurley Stage II or III hidradenitis suppurativa (HS) based on subjects achieving a Hidradenitis Suppurativa Clinical Response (HiSCR) after 12 weeks of treatment. HiSCR is defined as at least a 50% reduction in abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count at Week 12 relative to baseline.
2. Evaluation of the safety of avacopan compared to placebo in these subjects based on the adverse event incidence, changes from baseline in laboratory parameters, and vital signs.

2.2. Secondary and Other Objectives

The secondary and other objectives of this study include:

1. Evaluation of the efficacy of avacopan compared to placebo in these subjects include:
    a. The subject's global assessment of skin pain numeric rating scale (NRS),
    b. The modified Sartorius score, and
    c. Achieving an AN count of 0, 1, or 2.
2. Assessment of patient-reported outcomes including health-related quality-of-life changes based on the Short Form-36 version 2 (SF-36 v2), the EuroQOL-5D-5L (EQ-5D-5L), the

Hidradenitis Suppurativa Quality of Life (HiSQOL) Index, the Dermatology Life Quality Index (DLQI), and the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP) with avacopan compared to placebo.

3. Evaluation of the pharmacokinetic profile of avacopan in subjects with HS.
4. Evaluation of the safety and efficacy of avacopan treatment from Day 1 by each timepoint up to Week 44 in subjects with HS.
5. Evaluation of the efficacy of avacopan compared to placebo in these subjects include:
    a. The Sartorius score, International HS Severity Scoring System (IHS4) score, HS Physician Global Assessment (HS-PGA),
    b. Proportion of subjects who experienced flare, who experienced loss of response during Period 2, who received oral antibiotic rescue therapy or lesion intervention, and who received disallowed opioid pain therapy, and
    c. The duration of flare in days.
6. Evaluation of health-economic information.

3. STUDY DESIGN

The study is a randomized, double-blind, placebo-controlled, three-group Phase 2 trial in approximately 390 subjects with moderate to severe hidradenitis suppurativa (Hurley Stage II or III). Subjects will be randomized 1:1:1 to a treatment of 10 mg avacopan twice daily, 30 mg avacopan twice daily or placebo for 12 weeks. Other systemic treatments for HS including anti-TNF-α treatments are prohibited. Stable antibiotic therapy with doxycycline or minocycline is allowed as specified in the protocol. Subjects treated with 10 mg or 30 mg twice daily during the blinded, placebo-controlled 12-week treatment period (Period 1) will be followed by an additional 24-week, active treatment period (Period 2) during which they will continue to receive the same dose regimen, either 10 mg or 30 mg avacopan twice daily. Subjects on placebo who complete Period 1 will be re-randomized 1:1 to receive 10 mg or 30 mg avacopan twice daily in Period 2. During Period 2 the treatment assignment to 10 mg or 30 mg twice daily will not be disclosed to the subject, study site personnel or the Sponsor. Thereafter, all subjects will be followed for 8 weeks without study drug before they exit the study.

To obtain balance across treatment groups, a stratified randomization scheme will be implemented. The stratification factors and strata within each factor are listed below.

3.1. Stratification and Randomization

1. Hurley Stage (Stage II vs. III)
    a. Stage II disease: one or more widely separated recurrent abscesses with tract formation and scars, or
    b. Stage III disease: multiple interconnected tracts and abscesses across an entire area, with diffuse or near diffuse involvement.
2. Concomitant antibiotic therapy (Yes vs. No)

a. Concomitantly treated with doxycycline or minocycline as the only allowed antibiotic treatment for HS, or
b. No concomitant antibiotic therapy.

3. Anti-TNF-α treatment (Treatment naïve vs. Previous treatment):
    a. Did not previously receive anti-TNF-α drug such as adalimumab or infliximab (anti-TNF-α drug naïve), or
    b. Previously (but no longer) received an anti-TNF-α drug and
        - completed anti-TNF-α treatment but may have relapsed, or
        - was intolerant to anti-TNF-α treatment, or
        - previously failed to respond or inadequately responded to anti-TNF-α treatment.

Not more than 20% of subjects will be in stratum 2a as described above.

Eligible subjects will be randomized with equal chance (i.e., 1:1:1) to one of the three treatment groups within each stratum based on a non-dynamic, list-based blocked randomization scheme.

1) Placebo twice daily

2) Avacopan 10 mg twice daily

3) Avacopan 30 mg twice daily

3.2. Study Treatments

Treatments for each group are shown in Table 1.

The treatment period is 36 weeks (252 days), followed by an 8-week (56 days) follow-up period without taking study medication. Subjects will be randomized 1:1:1 to receive placebo, 10 mg avacopan or 30 mg avacopan b.i.d. for the blinded, placebo-controlled treatment for the first 12 weeks (Period 1). Subjects randomized to 10 mg and 30 mg avacopan in Period 1 will continue with the same drug regimen during the next 24-week active drug treatment period (Period 2). Subjects randomized to placebo in Period 1 will be re-randomized to receive either 10 mg or 30 mg avacopan b.i.d. in Period 2. Study treatment-group specific drug kits will be dispensed at relevant study visits. Detailed information about the study drug kits, dispensation and accountability is available in the Study Pharmacy Manual.

Study drug will be taken as described in Section 5.2.

Table 1: Avacopan/Placebo Treatment for the Three Study Groups

	Period 1 (12-Week Placebo-Controlled Treatment)	**Period 2 (24-Week Active Drug Treatment)**
Group A Placebo	Kit # 1	Re-randomized 50% to Kit # 2 50% to Kit # 3
Group B 10 mg Avacopan	Kit # 2	Kit # 2
Group C 30 mg Avacopan	Kit # 3	Kit # 3

3.3. Study Flow

Subjects will be screened for eligibility based on the stage of the disease and their health status. The Screening period will be up to 28 days. The primary efficacy analysis can occur when the last enrolled subject has completed the Week 12 visit. After the blinded, placebo-controlled 12-week treatment period, all subjects will continue with a 24-week active treatment with 10 mg avacopan twice daily or 30 mg avacopan twice daily. After Week 36, all subjects will be followed for 8 weeks without receiving study medication.

All subjects will visit the study center during the 28-day Screening period, and, if eligible, on Day 1 and Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, and 44 of the study. Study drug will be dispensed at the study site and subjects will take the first dose of study drug, i.e., avacopan or matching placebo, while at the study center. Preferably, on visit days subject should take their dose while on-site. Following the first dose, subjects will take study drug twice daily, which will continue for 12 weeks (84 days). Thereafter, all subjects will take avacopan study drug for 24 weeks (168 days), after which they will be followed for 8 weeks (56 days) without taking study drug. Study procedures at each visit day are detailed in the Time and Events Table.

Subjects will exit the study when all the Study Week 44 visit procedures have been completed.

Subjects who experience a flare of HS during the study will be treated by the Investigator, which may include a maximum 1-week course of antibiotic rescue treatment with doxycycline or minocycline or intralesional Kenalog® rescue injections (triamcinolone acetonide, 10 mg total maximum per subject within a period no longer than 1 week). These subjects will be requested to remain in the study and to complete all study procedures if possible. During this time, subjects may continue to receive the study drug, if deemed clinically feasible by the Investigator.

3.4. Scientific Rationale for Study Design

The aim of this study is to determine whether avacopan is effective in subjects with moderate to severe hidradenitis suppurativa. The placebo-controlled study design allows evaluation of whether or not avacopan treatment will yield superior efficacy compared to placebo. A certain

proportion of subjects will be allowed to have concomitant treatment for HS with doxycycline or minocycline.

There is well-documented precedence of placebo-controlled trials in HS as previous adalimumab Phase 2 and 3 studies were conducted as placebo-controlled studies.

3.5. Rationale for Dose Selection

Single doses of 1 mg up to 100 mg avacopan were studied in a Phase 1 study (CL001_168) in 48 healthy volunteers. Once daily doses of 1, 3, and 10 mg avacopan, and twice daily doses of 30 mg and 50 mg for up to 7 days were studied in the multiple dose period of the study.

Doses from 3 mg up to 100 mg twice daily for 7 days were tested in 16 healthy volunteers in Phase 1 study CL007_168, and 30 mg (single dose and twice daily doses for 17 days) in 32 healthy volunteers in Phase 1 study CL008_168. Further, 64 healthy Japanese and Caucasian male subjects were tested in both fed and fasted states at doses up to 100 mg/day (CCX1101). All these avacopan doses were found to be safe in these studies.

A dose of 30 mg avacopan twice daily given for 12 weeks was studied in clinical trial CL002_168 in subjects with AAV. This dose regimen was shown to be effective and well tolerated in study CL002_168. Doses of 10 mg and 30 mg avacopan twice daily given for 12 weeks were studied in clinical trial CL003_168 in subjects with AAV and found to be well tolerated. Refer to the Investigator's Brochure for details.

A dose of 30 mg avacopan twice daily is being studied in a Phase 3 clinical trial in AAV (CL010_168).

A dose of 30 mg avacopan twice daily has been selected for this study in HS based on experience with this dose regimen in subjects with AAV. This dose regimen is lower than the maximum dose regimen of 100 mg twice daily tested in study CL007_168. A dose regimen of 30 mg avacopan twice daily provides a trough (C_{min}) plasma avacopan concentration of approximately 204 ng/mL; this concentration was shown to provide at least 95% C5aR blockade of blood neutrophils continuously throughout the day based on ex vivo C5a-induced CD11b upregulation assays conducted in whole blood samples obtained from subjects in Phase 1 clinical trial CL001_168. This level of C5aR coverage is deemed appropriate to achieve optimal pharmacology.

A dose of 10 mg avacopan twice daily has been selected to determine the lower dose range that could still elicit significant clinical effects. It is anticipated that both avacopan dose regimens would be well tolerated in subjects with HS. At steady state, plasma levels for the 10 mg twice daily dose regimen result in at least 90% C5aR inhibition on blood neutrophils continuously throughout the day.

Based on the favorable safety profile observed in the long-term toxicology studies (26 weeks in rats and 44 weeks in cynomolgus monkeys; see Investigator's Brochure), and on the safety and tolerability results from the clinical trials conducted to date, 10 mg and 30 mg avacopan twice daily are considered appropriate doses to test in this clinical trial.

4. STUDY POPULATION

Eligible adult subjects (at least 18 years of age) with moderate to severe hidradenitis suppurativa (Hurley Stage II or III) on standard-of-care therapy as specified by the inclusion and exclusion criteria, are allowed to enter the study.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria in order to enter the study:

1. Aged at least 18 years of age;
2. Clinical diagnosis of HS (Hurley Stage II or III), confirmed by a dermatologist, for at least 6 months prior to Screening. Hurley Stage II disease is defined as having one or more widely separated recurrent abscesses with tract formation and scars; Stage III disease is defined as having multiple interconnected tracts and abscesses across an entire anatomical area with diffuse or near diffuse involvement;
3. HS lesions are present in at least 2 distinct anatomic areas (e.g., left and right axilla; or left axilla and left inguino-crural fold), one of which is Hurley Stage II or Hurley Stage III;
4. Inadequate or loss of response to a systemic course of antibiotics of 90 days. However, a subject who has completed less than 90 days of antibiotic treatment may be allowed into the study upon discussion with the Medical Monitor if: 1) the subject has demonstrated intolerance to or contraindication for antibiotics to treat HS, or 2) it was determined by the Investigator that an antibiotic course of at least 28 days to treat HS did not benefit the subject and a continued antibiotic therapy would therefore not be indicated.

   Inadequate or loss of response is defined if the following was observed despite antibiotic treatment:

   a. Progression of Hurley Stage (i.e., the Hurley Stage of at least one affected anatomic region progressed from I→II, II→III, or I→III);
   b. Subject required at least one intervention (e.g., incision and drainage or intralesional injection of corticosteroid);
   c. Subject experienced pain interfering with activities of daily living, with unsatisfactory relief from over-the-counter analgesics (e.g., ibuprofen or acetaminophen);
   d. Subject experienced pain requiring opioids, including tramadol;
   e. Subject experienced drainage interfering with activities of daily living (e.g., requires multiple dressing changes and/or changes of clothes daily);
   f. Subject experienced an increase in the number of anatomic regions affected by HS;
   g. Subject experienced at least one new abscess or one new draining fistula.
5. Must have at least 5 inflammatory nodules or abscesses at Screening;
6. Must agree to use a topical antiseptic daily over the course of the study; topical antiseptics may include but are not limited to chlorhexidine, triclosan, benzoyl peroxide, or diluted bleach in bath water;
7. Female subjects of childbearing potential may participate if adequate contraception is used during the study and for at least three months after study completion. Adequate contraception is defined as resulting in a failure rate of less than 1% per year (combined estrogen and

progestogen [oral, intravaginal, or transdermal], or progestogen-only hormonal contraception where inhibition of ovulation is the primary mode of action [oral, injectable, or implantable], intra-uterine device, intra-uterine hormone releasing system, bilateral tubal occlusion, vasectomized partner, or true [absolute] sexual abstinence, i.e., in line with the preferred and usual lifestyle of the subject). Male subjects with partners of childbearing potential may participate in the study if they had a vasectomy at least 6 months prior to randomization or if adequate contraception as defined above is used by their female partners of childbearing potential during the study and for at least three months after study completion. In addition, a barrier method (i.e., condom, cervical cap, or diaphragm) must be used during intercourse between a male study subject and a female partner of childbearing potential;

8. Willing and able to give written Informed Consent and to comply with the requirements of the study protocol;
9. Judged by the Investigator to be otherwise fit for the study, based on medical history, physical examination (including electrocardiogram [ECG]), and clinical laboratory assessments. Subjects with clinical laboratory values that are outside of normal limits (other than those specified in the Exclusion Criteria) and/or with other abnormal clinical findings that are judged by the Investigator not to compromise subject participation in the study may be entered into the study.

4.2. Exclusion Criteria

Subjects will be excluded from study participation if any of the following criteria are met:

1. Pregnant or breast-feeding;
2. Any other skin disease that may interfere with the assessment of HS, such as a viral or fungal skin infection;
3. Rapidly progressive, expanding HS within 30 days prior to Screening;
4. More than 20 draining fistulae at Screening;
5. Any anti-TNF-α treatment for HS or for other conditions prior to Day 1 visit will be prohibited. Exception: subjects who were previously treated with an anti-TNF-α drug and discontinued treatment >12 weeks prior to Day 1 visit are allowed for enrollment;
6. Systemic antibiotics are generally excluded. Exception: subjects on systemic antibiotic treatment with doxycycline or minocycline who have been on a stable dose for at least 28 days prior to Day 1. After a pre-specified percentage of subjects on these permissible antibiotic treatments have been enrolled, no further enrollment of such subjects will be allowed;
7. Topical antibiotics use within 14 days prior to Day 1;
8. Have started a topical prescription medicine for HS within 14 days prior to Screening or is anticipated to start during the Screening period. Topical prescription medicine for HS other than topical antibiotics that was started >14 days prior to Screening is allowed;
9. With the exception of permissible antibiotic treatment regimens, have received a systemic medicine for HS or with a potential therapeutic impact on HS, including systemic antibiotic therapy, biologics and other systemic therapies such as methotrexate, cyclosporine, retinoids,

and fumaric acid esters, etc., within a minimum of 30 days or 5 half-lives (whichever is longer) after taking the last dose;

10. Have received within 14 days prior to the Day 1 visit, or is expected to require during the study, oral or transdermal opioid analgesics (except for tramadol) for any reason; non-opioid analgesics are allowed if the subject is on a stable dose for at least 14 days prior to the Day 1 visit ("as needed" dosing is not considered to be a stable dose);
11. Currently taking a strong inducer of the cytochrome P450 3A4 (CYP3A4) enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin, or St. John's wort;
12. Any of the following within 12 weeks prior to Screening: symptomatic congestive heart failure requiring prescription medication, unstable angina (unless successfully treated with stent or bypass surgery), clinically significant cardiac arrhythmia, myocardial infarction or stroke;
13. History or presence of any form of cancer within the 5 years prior to Screening, with the exception of excised basal cell or squamous cell carcinoma of the skin, or carcinoma in situ such as cervical or breast carcinoma in situ that has been excised or resected completely and is without evidence of local recurrence or metastasis;
14. Evidence of tuberculosis based on interferon γ release assay (IGRA);
15. HBV, HCV, or HIV viral screening test done at Screening or within 6 weeks prior to Screening showing evidence of active or chronic viral infection;
16. Received a live vaccine within 4 weeks prior to Screening;
17. WBC count less than 3500/µL, or neutrophil count less than 1500/µL, or lymphocyte count less than 500/µL before start of dosing;
18. Evidence of hepatic disease: AST, ALT, alkaline phosphatase, or bilirubin >3 times the upper limit of normal before the start of dosing;
19. Clinically significant abnormal electrocardiogram (ECG) during Screening which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation;
20. Known hypersensitivity to avacopan or inactive ingredients of the avacopan capsules (including gelatin, polyethylene glycol, or macrogolglycerol hydroxystearate [EP] known also as polyoxyl 40 hydrogenated castor oil [NF] or Cremophor® RH 40);
21. Participated in any clinical study of an investigational product within 30 days prior to Screening or within 5 half-lives after taking the last dose;
22. History or presence of any medical condition or disease which, in the opinion of the Investigator, may place the subject at unacceptable risk for study participation.

4.3. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently randomized to receive a study intervention or dosed with any study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, 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 serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) may potentially be rescreened. These cases need to be discussed with the Medical Monitor.

4.4. Removal of Subjects from Therapy

Investigators must clearly distinguish between discontinuation of study drug treatment and withdrawal from the study. Subjects who discontinue study drug treatment or who initiate medication changes (including those prohibited by the protocol) will not be automatically withdrawn from the study but all efforts must be made to continue to follow the subjects for all regularly scheduled visits. All safety and efficacy assessments should be completed.

Investigators must take appropriate measures to make sure that subjects are motivated to comply with all requirements of the protocol in order to minimize the amount of missing data, including subjects who discontinue study treatment early or initiate medication changes (including those prohibited by the protocol). If subjects are not followed, they should complete all safety and efficacy assessments required for the Early Termination visit. Investigators and their staff must take measures to actively maintain contact with their subjects in the study, such as telephone calls, texts, or emails between visits, and offers for transportation support to visit the study site.

Subjects may be withdrawn from the study for only one of the following reasons:

1. Subject withdrawal of consent to contribute additional outcome information;
2. Subject non-compliance with dosing or diary completion;
3. Loss to follow-up.

Subjects may discontinue study drug treatment for any of the following reasons:

1. Subject withdrawal of consent;
2. The Investigator may discontinue study drug treatment if, in his/her clinical judgment, it is in the best interest of the subject;
3. The Sponsor may request discontinuation of study drug treatment for safety reasons. If a subject develops any of the following lab abnormalities:

If a subject develops ALT or AST >3x ULN, additional testing should be performed immediately and repeated in one week to assay for total and fractionated serum bilirubin concentration, serum albumin concentration, and prothrombin time or INR, in addition to repeat transaminase (ALT, AST) testing. In addition, if a subject develops Grade 3 or greater increased hepatic transaminases (>5 times the upper limit of normal), or if a subject develops Grade 2 or greater increased transaminases (>3 times the upper limit of normal) with elevation of bilirubin to >2 times the upper limit of normal, dosing with study drug must be paused in this subject.

Study medication must be permanently discontinued (FDA Guidance 2009) if any of the following markers of hepatic injury and/or impaired liver synthetic function are observed, and cannot be attributed to a reversible etiology unrelated to study medication (e.g., cholelithiasis):

- ALT or AST >8x ULN

- ALT or AST >5x ULN for more than 2 weeks
- ALT or AST >3x ULN and (Total Bilirubin >2x ULN or INR >1.5)
- ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

If a subject develops Grade 3 or greater leukopenia (WBC count <2 x 10^9/L) or neutropenia (<1 x 10^9/L), or Grade 4 lymphopenia (<0.2 x 10^9/L), then study drug (avacopan or placebo) must be paused in this subject. In addition, if a subject develops Grade 2 leukopenia (WBC count <3 x 10^9/L, but ≥2 x 10^9/L), the subject must be followed closely for infection and for further significant reduction (reduction by an additional 0.5 x 10^9/L or more, or to <2 x 10^9/L) in WBC count; if either occurs, then study drug must be paused in this subject. Study drug may be resumed only if the abnormal value returns to normal and the Investigator deems resumption to be appropriate.

If a subject develops Grade 3 or worse CPK increase (>5 times the upper limit of normal), dosing with study drug must be paused in this subject. Study drug may be resumed only if the CPK returns to normal levels.

Discontinuation of study medication due to inadequate or worsening response in Period 2: Unless prohibited for safety reasons, deemed inappropriate by the Investigator, or subject withdraws consent, all subjects are allowed to enter Period 2. Subjects in Period 2 will discontinue taking study medication if at two consecutive protocol-specified visits ≥14 days apart, the AN count increases by more than 50% compared to the AN count at Week 12. However, these subjects will be requested to remain in the study and to complete all study procedures if possible. In the event of early withdrawal from the study, the tests and evaluations listed for the Early Termination visit in Section 6.14 will be performed, whenever possible. Data collected at this visit will be designated as an "Early Termination" visit in the electronic data capture (EDC) system. The Sponsor should be notified of all study drug treatment and study withdrawals in a timely manner.

5. STUDY DRUG/TREATMENT

5.1. Product Characteristics

The study drug consists of hard gelatin capsules containing 10 mg avacopan or placebo administered orally. Avacopan and placebo bottles and capsules will be identical in appearance. The capsules are manufactured under current good manufacturing practice.

5.2. Doses and Regimens

Subjects will be asked to take 3 capsules of study drug orally with water and preferably with food every morning, and 3 capsules with water and preferably with food in the evening approximately 12 hours after the morning dose, as instructed. Study drug will be taken for 36 weeks (252 days) continuously. Study drug will be dispensed as outlined in the Time and Events Table.

Subjects will be asked to bring all bottles of study drug, whether empty or not, to the study center at each study visit for study drug compliance/accountability check.

If a subject misses a dose, the missed dose should be taken as soon as possible. If it is close to the time for their next dose (within 3 hours), the missed dose should not be taken and the next dose should be taken at the regular time.

On study visit days it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit.

5.3. Drug Supply

5.3.1. Packaging and Labeling

Study drug will be packaged in treatment assignment-specific kits and provided to the study sites for dispensing. Capsules containing 10 mg avacopan and/or identical placebo capsules will be packaged in plastic bottles with child-resistant screw caps. Each kit will include 3 bottles. Each bottle will contain 180 capsules with a label including, at minimum, the study number, bottle number, dosing instructions, storage instructions, and Sponsor name and address.

5.3.2. Storage

Study drug, both avacopan and placebo, capsules should be stored according to label instructions. Access should be restricted to pharmacy staff or to the designated responsible member of the Investigator's staff, and to the study monitor.

5.4. Blinding

This study is double-blind. Blinding of the study will be achieved by the following measures:

1. The study drug kits, bottles and capsule appearance for avacopan and placebo will be identical;
2. Limited access to the randomization code: Sponsor personnel, study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers involved in data analysis of the study will remain blinded to treatment assignment for the duration of the study;
3. While laboratory personnel conducting the PK assays will not be blinded to treatment assignment, unblinded avacopan plasma concentration results will not be shared with the study site personnel or study staff who have direct contact with study sites during the study;
4. Data that could potentially be unblinding, i.e., WBC and neutrophil count data within the normal range (i.e., values outside the normal range will be made available for safety monitoring) will not be made available to study site personnel, study subjects, personnel responsible for study monitoring, and biostatisticians and data managers during the study unless required for safety monitoring. Investigators, however, will be provided with safety laboratory data reports, flagging abnormally high and low values to make informed decisions regarding subject care.

Treatment assignments for individual subjects in the blinded portion of the study will remain blinded to the study team, Investigators, and subjects until after the study database has been

cleaned and locked. Designated study staff will be provided with instructions regarding how to unblind an individual subject's treatment assignment if it becomes medically necessary. An individual subject treatment assignment may be unblinded only in the case of an adverse event that requires knowledge of the study drug received by the subject in order to provide appropriate treatment or management of the adverse event. The study monitor and Sponsor should be consulted or notified as soon as possible in the event that unblinding of an individual subject's treatment assignment occurs prior to study completion.

When the last subject has completed the double-blind treatment period, an unblinded analysis of the double-blind treatment period will be conducted. All data collected in the double-blind treatment period will be cleaned and locked before the analysis. To maintain the blinding of treatment assignment in the active treatment period, the Sponsor will designate a contract research organization (CRO) to conduct the analysis. The analysis results will be communicated to the Sponsor with aggregated data only (i.e., by treatment group without disclosing treatment assignment for individual subjects). In the event it becomes necessary to identify the treatment assignment for an individual subject for safety analysis, the treatment assignment can be disclosed on an individual basis. If occurred, these events will be documented.

An external data monitoring committee (DMC) will be constituted for the study (see Section 10.1.6). The DMC members will review data periodically over the course of the study in an unblinded manner. The membership and the primary responsibilities of the DMC will be defined in a charter that will also provide procedures for data review, documentation, and communication of recommendations.

5.5. Drug Accountability

The Investigator or designee is responsible for maintaining complete accountability including dates and quantities of study product(s) received, accurate inventory on an ongoing basis as well as dispensation and returned medication records. Periodically throughout the study, a Sponsor representative, usually the study monitor, will verify and inventory the used, unused, and partially used study drug. The Investigator or designee must retain all unused and/or expired study supplies until the study monitor has confirmed the accountability data.

With Sponsor approval following drug accountability, unused study drug can be destroyed per site SOP or policy. Unused study drug may also be returned to the Sponsor or its designee for destruction with appropriate documentation. The documentation of such disposition/destruction should be maintained in the pharmacy files to be reviewed by a Sponsor representative.

At the termination of the study, a final drug accountability review and reconciliation must be performed and any discrepancies must be investigated and their resolution documented.

Please refer to the Study Pharmacy Manual for further instruction regarding study drug receiving, handling, storage and return/destruction.

5.6. Treatment Compliance

The avacopan and placebo capsules will be self-administered by participating study subjects. The first dose of study drug on Day 1 will be taken in the presence of study site personnel. Subjects will be provided with dosing instructions at the start of the study and will be encouraged by study site personnel to take the study drug according to the instructions for the duration of the

study. The study drug dispensed will be checked and a capsule count will be done at Weeks 12, 24, and 36 of any remaining avacopan or placebo capsules returned. This information will be recorded and entered into the EDC system. The study subjects will be required to maintain a record of daily drug administration in a daily diary.

Avacopan plasma concentration measurements over the course of the study may also be used to assess subject compliance. Any events of non-compliance to the protocol will be documented in the study records.

5.7. Concomitant Therapy and Restrictions

No new treatment for HS (other than the study drug) may be introduced during the study period with the exceptions as outlined below.

All concomitant medications taken during the course of the study must be recorded meticulously on the concomitant medication pages in the EDC.

Anti- TNF-α Therapy, Systemic or Other Treatments with Potential Impact on HS: Concomitant anti-TNF-α treatment during the trial is prohibited. Subjects who were previously treated with any anti-TNF-α drug and discontinued treatment >12 weeks prior to Day 1 visit would be allowed for enrollment.

Anti-TNF-α agents comprise five different FDA-approved drugs: adalimumab (Humira®), infliximab (Remicade®), entanercept (Enbrel®), golimumab (Simponi®), and certolizumab (Cimzia®). Of these anti-TNF-α agents, adalimumab, golimumab, and certolizumab share the longest mean terminal half-lives of 14 days as specified in their respective prescribing information labels. Subjects entering the trial need to be anti-TNF-α treatment-naïve or must have discontinued anti-TNF-α treatment for at least 12 weeks (which provides a washout period of over 5 times the half-life of any anti-TNF-α agent).

With the exception of permissible antibiotic treatment regimens, systemic or other treatments with a potential therapeutic impact on HS, including systemic antibiotic therapy, biologics and other systemic therapies such as methotrexate, cyclosporine, retinoids, and fumaric acid esters, etc., are prohibited.

Antibiotic Therapy: Concomitant use of oral antibiotic therapy for treatment of HS is generally not allowed. Systemic antibiotics (doxycycline or minocycline only) for the treatment of HS are permissible only for those subjects whose randomization was appropriately stratified for antibiotic use (see Section 3.1 Stratification and Randomization). During the study, the dose(s) of these drugs for the treatment of HS may not be increased. A systemic antibiotic must not be started for the treatment of HS during the course of the trial (treatment for a condition other than HS is allowed). However, the Investigators will be allowed to reduce the dose(s) or discontinue these ongoing antibiotic treatments during the study. Any dose changes in these treatments during the study must be recorded in the EDC system.

Antibiotic rescue medication may be initiated at Week 4 or Week 8, if a subject experiences an increase in their AN count such that the total count is greater than or equal to 150% of their baseline AN count. For example, if a subject has a baseline (= Day 1) AN count of 15, antibiotic rescue therapy may be allowed with a minimum AN count of 23 (1.5 x 15 = 22.5) at Week 4 or 8.

Subjects who qualify may initiate treatment with minocycline or doxycyline up to 100 mg b.i.d. The dosing regimen must remain stable throughout study participation. Rescue antibiotic therapy must be captured in the source document and on the appropriate eCRF.

***Antiseptic Therapy**:* All subjects must use a topical antiseptic daily over the course of the study; topical antiseptics may include but are not limited to chlorhexidine, triclosan, benzoyl peroxide, or dilute bleach in bath water.

***Wound Care**:* Concomitant use of wound care dressings on HS wounds is allowed.

***Lesion Intervention**:* In the event that an acutely painful lesion occurs that requires an immediate intervention, physicians will have the option to perform protocol-allowed interventions. All study visit evaluations must occur before any interventions are performed. Any lesion that undergoes an intervention will be documented in the source. The site will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention, and must account for it in the source and on the appropriate eCRF.

Lesions that receive lesion interventions will be reported as adverse events.

Only two types of interventions are allowed: injection with intralesional triamcinolone acetonide suspension (intralesional Kenalog® rescue injections, i.e., triamcinolone acetonide, 10 mg total maximum per subject within a period no longer than 1 week) and incision and drainage.

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

Subjects should continue using any allowed ongoing oral and topical therapies during the study.

During Period 1, a total of two protocol-allowed interventions are permissible. An intervention can occur on maximally two different lesions at the same visit or on the same lesion at two different study visits. The same lesion cannot be treated two times at the same visit. If a subject requires more than two interventions within the first 12 weeks, then they must discontinue taking study medication. However, these subjects will be requested to remain in the study and to complete all study procedures if possible.

During Period 2, maximally two interventions every 4 weeks are permitted. An intervention can occur on two different lesions at the same visit or on the same lesion at two different study visits. Within each 4-week period, the same type of intervention cannot be used two times on the same lesion. If a subject requires more than two interventions within a 4-week period or has two of the same interventions on the same lesion within that period, the subject must discontinue taking study medication. However, these subjects will be requested to remain in the study and to complete all study procedures if possible.

***Analgesic Therapy**:* Subjects may receive non-opioid analgesics and also tramadol during the study. Any dose changes need to be recorded in the EDC. Oral and transdermal opioid analgesics (except for tramadol) for any reason are disallowed.

***CYP3A4 Metabolism**:* Drugs that are strong inducers of the CYP3A4 enzyme, such as carbamazepine, phenobarbital, phenytoin, rifampin or St. John's wort are prohibited during the study because these drugs may substantially reduce the plasma concentrations of avacopan and reduce its effectiveness.

Substances that are strong inhibitors of CYP3A4, such as boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole, and grapefruit juice should be avoided during the study, because these may modestly increase (~2-fold) the plasma concentrations of avacopan. However, these are not absolutely contra-indicated. If these must be used concomitantly with avacopan, subjects should be monitored carefully for any untoward side effects.

All concomitant medications taken during the course of the study must be recorded meticulously on the concomitant medication pages in the EDC.

6. STUDY PROCEDURES

6.1. Screening and Enrollment

Informed consent must be obtained prior to performance of any study-specific tests or evaluations. Screening should occur within 28 days and not exceed 31 days prior to randomization. Subjects will undergo the following evaluations to determine their eligibility for study participation:

- Recording of demographic data and relevant medical history in the EDC;
- Recording of all prior medications and treatments for HS from diagnosis to Screening in the EDC;
- Recording of all other concomitant medications on the Screening day(s) in the EDC, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- A physical examination will be performed (see Section 7.2.1); body weight and height will be measured;
- Vital signs will be obtained as detailed in Section 7.2.1; temperature, sitting blood pressure, and heart rate will be measured after at least 3 minutes of rest;
- Serum pregnancy test (in women of childbearing potential);
- Virology assessments as detailed in Section 7.2.2, unless done within 6 weeks prior to Screening;
- Tuberculosis exclusion based on interferon γ release assay (IGRA);
- 12-lead ECG to exclude any clinically significant findings;
- Serum chemistry and hematology tests according to Section 7.2.2;
- A urine sample will be collected for urinalysis (see Section 7.2.2);
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars and the Hurley Stage of HS will be recorded;
- Any pre-treatment adverse events (occurring during the Screening visit) will be recorded.

Results from certain tests that have been performed prior to Screening may be used to determine study eligibility if these tests were performed as part of the practice of medicine and were done whether or not study entry was contemplated, such as for diagnosis or treatment of the subject's condition. Results from the prior tests must be recorded in the EDC.

After all Screening procedures have been completed and the subject satisfies all eligibility criteria:

- The study schedule will be discussed with the subject and the schedule will be provided to the subject to ensure compliance with the study visits.
- Subjects will be issued a daily diary on Day -7 along with instructions on how to record skin pain in the daily diary and will be asked to start recording their skin pain starting that day (one week prior to the Day 1 visit).

6.2. Study Day 1

If eligible for the study, the subject will visit the study center on Day 1. The following procedures will be performed before taking the first dose of study drug:

- Stratification and randomization in the IRT system;
- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Urine pregnancy test (in women of childbearing potential);
- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements;
- Biomarker plasma sample will be collected (see Section 7.4);
- The date and time of collection of the PK sample will be recorded;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Lesions will be selected and baseline photography will be completed;
- Items for the Sartorius and modified Sartorius scores will be collected (see Section 7.1.2);
- IHS4 score will be calculated (see Section 7.1.3);
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms;
- Compliance with daily recording of skin pain in daily diary starting one week prior to Day 1 will be checked and retraining provided, if necessary;
- Any pre-treatment adverse events (from time of the Screening visit) will be recorded.

Thereafter, the following procedures will be performed:

- Study drug will be provided to the subject with dosing instructions (see Section 5.2);
- The subject will be asked to take the first dose of study drug while at the study center;
- The time of the dosing of study drug will be recorded;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any post-dosing adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 2 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug, as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit, and
  - Continue taking all their other concomitant medications as usual.

6.3. Study Week 2 (Day 15)

The Study Week 2 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for shipment to the central laboratory for serum chemistry, hematology, and PK measurements; the date and time of collection of the PK sample will be recorded;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- If the subject has not yet taken the morning dose of study drug for this day, the subject will be asked to take the dose;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of skin pain and drug dosing in diaries will be checked and re-training provided if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;

- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- The study site personnel will make sure the subject is taking the study drug as instructed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 4 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit, and
  - Continue taking all their other concomitant medications as usual.

6.4. Study Week 4 (Day 29)

The Study Week 4 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- If the subject has not yet taken the morning dose of study drug for this day, the subject will be asked to take the dose;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of skin pain and study drug dosing in diaries will be checked and retraining provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;

- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms;
- The study site personnel will make sure the subject is taking the study drug as instructed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 8 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and
  - Continue taking all their other concomitant medications as usual.

6.5. Study Week 8 (Day 57)

The Study Week 8 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- If the subject has not yet taken the morning dose of study drug for this day, the subject will be asked to take the dose;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;

- Compliance with daily recording of pain and study drug dosing in diaries will be checked and retraining provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- The study site personnel will make sure the subject is taking the study drug as instructed and that the subject has adequate study drug for dosing until the following visit;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug administration in daily diary;
  - Come to the study center for the Week 12 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and
  - Continue taking all their other concomitant medications as usual.

6.6. Study Week 12 (Day 85)

The Study Week 12 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- Biomarker plasma sample will be collected;
- A 12-lead ECG will be taken to exclude any clinically significant findings;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- If the subject has not yet taken the morning dose of study drug for this day, the subject will be asked to take the dose;

- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of pain in diaries will be checked and re-training provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms;
- Drug accountability will be performed; the returned bottles of study drug will be checked to make sure the subject is taking the study drug as instructed;
- Study drug will be dispensed. Note: At this visit, subjects who were assigned to placebo arm will be re-randomized to receive 10 mg or 30 mg avacopan twice a day;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 16 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and
  - Continue taking all their other concomitant medications as usual.

6.7. Study Week 16 (Day 113)

The Study Week 16 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;

- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- If the subject has not yet taken the morning dose of study drug for this day, the subject will be asked to take the dose;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of pain and study drug dosing in diaries will be checked and re-training provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms;
- The study site personnel will make sure the subject is taking the study drug as instructed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 20 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and
  - Continue taking all their other concomitant medications as usual.

6.8. Study Week 20 (Day 141)

The Study Week 20 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- If the subject has not yet taken the morning dose of study drug for this day, the subject will be asked to take the dose;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of pain in diaries will be checked and re-training provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- The study site personnel will make sure the subject is taking the study drug as instructed and that the subject has adequate study drug for dosing until the following visit;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 24 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and
  - Continue taking all their other concomitant medications as usual.

6.9. Study Week 24 (Day 169)

The Study Week 24 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, and serum pregnancy test (in women of childbearing potential);
- Drug accountability will be performed; the returned bottles of study drug will be checked to make sure the subject is taking the study drug as instructed;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of pain in diary will be checked and re-training provided, if necessary;
- Study drug will be dispensed;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 28 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and
  - Continue taking all other concomitant medications as usual.

6.10. Study Week 28 (Day 197)

The Study Week 28 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- If the subject has not yet taken the morning dose of study drug for this day, the subject will be asked to take the dose;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of pain and study drug dosing in diaries will be checked and re-training provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms;
- The study site personnel will make sure the subject is taking the study drug as instructed;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 32 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;

- Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and
- Continue taking all their other concomitant medications as usual.

6.11. Study Week 32 (Day 225)

The Study Week 32 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, and serum pregnancy test (in women of childbearing potential);
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of pain in dairy will be checked and re-training provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- The study site personnel will make sure the subject is taking the study drug as instructed and that the subject has adequate study drug for dosing until the following visit;
- Study personnel will record health-economic information;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain and study drug dosing in daily diary;
  - Come to the study center for the Week 36 study visit;
  - Store the study drug in a cool and dry place according to label instructions for the duration of the study;
  - Take the study drug as instructed. On study visit days, it is preferable that the subjects take the morning dose of study drug at the site following the collection of PK samples, if applicable to that visit; and

- Continue taking all their other concomitant medications as usual.

6.12. Study Week 36 (Day 253)

The Study Week 36 visit must occur within ± 2 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- Blood samples will be collected for serum chemistry, hematology, serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- Biomarker plasma sample will be collected;
- The date and time of the last dose of study drug prior to collection of the PK sample will be recorded;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Compliance with daily recording of pain and study drug dosing in diaries will be checked and re-training provided, if necessary;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms;
- Drug accountability will be performed on the returned bottle(s) of study drug;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will be reminded to:
  - Record severity of skin pain in daily diary;
  - Come to the study center for the Week 44 study visit; and
  - Continue taking all their other concomitant medications as usual.

6.13. Study Week 44 (Day 309)

The Study Week 44 (follow-up) visit must occur within ± 4 days of the scheduled date. During this visit, the following study procedures will be performed:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be taken to exclude any clinically significant findings;
- Blood samples will be collected for serum chemistry, hematology and PK measurements; the date and time of collection of the PK sample will be recorded;
- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Items for the Sartorius and modified Sartorius scores will be collected;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms;
- The completed daily diary will be collected;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded;
- After all study procedures have been completed, the subject will exit the study.

6.14. Early Termination Visit

If a subject will be withdrawn early from the study, the following termination procedures must be completed whenever possible:

- A physical examination including body weight;
- Vital signs (temperature, sitting blood pressure, heart rate) after at least 3 minutes of rest;
- A 12-lead ECG will be taken to exclude any clinically significant findings;
- Blood samples for serum chemistry, hematology, and serum pregnancy test (in women of childbearing potential), and PK measurements; the date and time of collection of the PK sample will be recorded;
- Biomarker plasma sample will be collected;

- A urine sample will be collected for urinalysis;
- The anatomic location and number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars will be recorded;
- Follow-up photography of lesions will be completed;
- Items for the Sartorius and modified Sartorius scores will be collected if the prior visit where this assessment was made was more than 2 weeks before;
- IHS4 score will be calculated;
- The Investigator will complete the HS-PGA, if the prior visit where these assessments were made was more than 2 weeks before;
- Study personnel will record health-economic information;
- Subjects will be asked to complete the SF-36 v2, EQ-5D-5L, HiSQOL, DLQI, and WPAI:SHP forms, if the prior visit where these assessments were made was more than 2 weeks before;
- Drug accountability will be performed on the returned bottles of study drug;
- Completed daily diary will be collected;
- Any changes in concomitant medication use will be recorded, including alcohol intake, recreational drug use, non-prescription medications, herbal preparations or special diets;
- Any adverse events will be recorded.

7. STUDY ASSESSMENTS

7.1. Efficacy Assessments

7.1.1. Location and Extent of Hidradenitis Suppurativa Assessment

The location and extent of HS will be assessed at visits in the Time and Events Table by recording the anatomic location(s) of the disease, as well as the number of HS inflammatory nodules, abscesses, fistulae, and hypertrophic scars in each of the locations in the EDC. All study Investigators will receive study specific training to assess HS lesions.

The same Investigator should assess the lesions at each visit to assure consistency. Study sites should schedule all visits for the same subject such that the same Investigator is available to assess the lesions of that subject.

The information regarding location and extent of HS involvement will be used to determine the Hurley Stage and also to calculate the HiSCR at post-baseline visits. The HiSCR will be calculated programmatically in the EDC.

7.1.2. Sartorius and Modified Sartorius Scores

Twelve body areas will be evaluated at visits specified in the Time and Events Table to calculate the Sartorius and modified Sartorius scores:

- 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 (specify).

A score of 4 indicates the least severe disease, and higher scores indicate increasingly severe disease. There is no upper limit in the score (Sartorius et al, 2003; Sartorius et al, 2009).

The presence of nodules, abscesses, fistulae, hypertrophic scars, and other findings will be recorded in the EDC. The longest distance between two lesions and whether lesions are separated by normal skin will also be recorded.

7.1.3. International Hidradenitis Suppurativa Severity Score System

The International Hidradenitis Suppurativa Severity Score (IHS4) is simple to calculate and has been validated with the use of existing physician-derived outcomes such as HS-PGA, Hurley classification, MSS or Expert Opinion classification) and patient-reported outcome measure (DLQI). IHS4 score (points) = (number of nodules multiplied by 1) + (number of abscesses multiplied by 2) + [number of draining tunnels (fistulae/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.

7.1.4. Hidradenitis Suppurativa-Physician Global Assessment (HS-PGA)

The HS-PGA is an ordinal scale specific to HS that categorizes subjects into clear, minimal, mild, moderate, severe, or very severe disease, and it was used successfully in a phase 2 interventional clinical trial. A recently developed six stage PGA was defined as follows (Kimball et al, 2012):

- Clear: no inflammatory or non-inflammatory nodules
- Minimal: Only the presence of non-inflammatory nodules
- Mild: Less than 5 inflammatory nodules or 1 abscess or draining fistula and no inflammatory nodules
- Moderate: Less than 5 inflammatory nodules or one abscess or draining fistula and one or more inflammatory nodules or 2–5 abscesses or draining fistulae and less than ten inflammatory nodules
- Severe: 2–5 abscesses or draining fistulae and ten or more inflammatory nodules
- Very severe: More than 5 abscesses or draining fistulae

7.1.5. Global Assessment of Skin Pain

Subjects will record the maximum severity pain on a numeric rating scale from 0 (no skin pain) to 10 (skin pain as bad as can be imagined) in a daily diary from one week prior to Day 1 through the Week 44 visit.

The weekly average of the maximum severity pain for visits designated in the Time and Events Table will be calculated programmatically.

7.1.6. Health-Related Quality of Life Assessments

The SF-36 v2 and EQ-5D-5L instruments are widely accepted global non-disease-specific tools to measure changes in subjects' health-related quality of life. The HiSQOL index (an HS-specific instrument) and DLQI instruments are designed to measure the impact of HS or skin disease on subjects' quality of life. Forms for these instruments will be completed by study subjects at visits specified in the Time and Events Table. Proven translations will be used for non-English speaking subjects, whenever possible.

Study site personnel will facilitate completion of the questionnaires by the subjects, but will not complete the forms for the subjects. The administrator will establish a rapport with the subject, emphasize the importance of completing the form, and serve to answer questions and address concerns. Subjects should complete the questionnaires before seeing the Investigator at the visit.

7.1.7. Health-Economic Information

The WPAI:SHP (https://www.cdisc.org/foundational/qrs) assesses the effect of general and specific health conditions on productivity losses. Scores are calculated for four areas: percent work time missed due to HS, percent impairment while working due to HS, percent overall work impairment due to HS, and percent activity impairment due to HS. Forms for this instrument will be completed by study subjects at visits specified in the Time and Events Table to measure changes from baseline in work productivity and activity impairment.

Other health-economic information will be recorded by the study personnel on the appropriate CRFs such as details on Hospitalizations (i.e., Number of Hospitalizations total and due to HS, Number of days hospitalized, Number of days missed from work), Emergency or Urgent Care visit (i.e., Number of visits total and due to HS, Number of days (or hours where applicable) missed from work), Lesion interventions for HS (i.e., Number of days (or hours where applicable) missed from work due to HS lesion interventions).

7.2. Safety Assessments

7.2.1. Physical Examinations and Vital Signs

A physical examination (including evaluation of general appearance/mental status, head, eyes, ears, nose, throat, and the following body systems: dermatologic, cardiovascular, respiratory, gastrointestinal, musculoskeletal and neurologic) will be performed at visits indicated in the Time and Events Table. Findings must be recorded in the source documents.

Any new or worsening findings upon physical examination need to be recorded as adverse events.

Body weight will be measured as part of the physical examinations. Height needs to be recorded only at Screening. BMI will be calculated in the EDC from the body weight and height measurements.

Vital signs and 12-Lead ECG will be measured during Screening and on each scheduled study day as indicated in the Time and Events Table. Sitting blood pressure, pulse rate, and body temperature will be measured. All vital signs assessments will be performed after the subject has rested for at least three minutes.

7.2.2. Clinical Safety Laboratory Assessments

The following tests will be performed at the visits identified in the Time and Events Table.

- Hematology: At the central laboratory hemoglobin, hematocrit, RBC count, WBC count with differential, platelet count, mean cell hemoglobin, mean cell hemoglobin concentration, mean corpuscular volume;
- Serum Chemistry: At the central laboratory, liver panel (total and fractionated bilirubin, lactate dehydrogenase, aspartate aminotransferase [AST], alanine aminotransferase [ALT]), renal panel (blood urea nitrogen, creatinine), creatine phosphokinase (CPK), albumin, sodium, potassium, magnesium, bicarbonate, chloride, calcium, inorganic phosphorus, glucose, total protein, alkaline phosphatase, total cholesterol, uric acid, serum amylase, and serum lipase;
- Coagulation: PT and INR will be performed only if ALT and/or AST >3x ULN;
- Urinalysis: At the central laboratory, nitrite, blood, and protein, will be tested. If positive, microscopy will be performed;
- Virology (measured only at Screening and may be measured at the local laboratory): hepatitis B surface antigen, hepatitis C antibodies, HIV 1 and 2 antibodies; virology tests done within 6 weeks prior to Screening are acceptable for eligibility assessment; results from prior virology tests performed at the local laboratory must be recorded in the EDC system;
- TB screen: Interferon γ release assay (IGRA) through the central laboratory.

7.2.3. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An adverse event could therefore be any unfavorable and/or unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of the drug, whether or not considered related to the drug. This definition includes intercurrent illnesses or injuries and exacerbation of pre-existing conditions.

An unexpected adverse event is an adverse event that is not identified in nature, severity, or frequency in the current Investigator's Brochure, or that is of greater severity than expected based on the information in the Reference Safety Information listing within the Investigator's Brochure.

All adverse events occurring in subjects who have been randomized to treatment will be recorded in the EDC system and will be reported in accordance with regulatory requirements. Adverse events reported prior to commencement of administration of study drug will be considered pre-treatment events.

All adverse events will be monitored until resolution or, if the adverse event is determined to be chronic, until a cause is identified. If an adverse event remains unresolved at the conclusion of the study, a clinical assessment will be made by the Investigator and the Sponsor's Medical Monitor to determine whether continued follow-up of the adverse event is warranted.

7.2.3.1. Adverse Event Severity Assessment

The severity of each adverse event will be determined by the Investigator using the following scale:

- Mild (Grade 1): no limitation of usual activities
- Moderate (Grade 2): some limitation of usual activities
- Severe (Grade 3): inability to carry out usual activities
- Life-threatening (Grade 4): an immediate risk of death
- Death (Grade 5)

7.2.3.2. Causality Assessment

The relationship of study drug to an adverse event will be determined by the Investigator and Sponsor based on the following definitions:

- Probably Not Related: the adverse event was more likely explained by causes other than study drug.
- Possibly Related: there is evidence for a reasonable possibility that study drug administration caused the adverse event.

7.2.3.3. Adverse Events of Special Interest (AESI)

The following findings, as defined below, must be reported as AEs and will be considered adverse events of interest (AESI):

Infections:

For medically important infections, the organisms involved in the infection need to be determined whenever possible and be documented in the EDC. All local and national vaccination recommendations should be followed.

Hepatic Transaminase Elevation:

- Grade 3 or greater increased ALT or AST (>5 times the upper limit of normal)
- Grade 2 or greater increased ALT or AST (>3 times the upper limit of normal) *with* elevation of bilirubin to >2 times the upper limit of normal or INR >1.5

Neutropenia, Lymphopenia, and Leuokopenia:

- Grade 3 or greater neutropenia (<1 x 10^9/L)
- Grade 4 lymphopenia (<0.2 x 10^9/L)
- Grade 3 or greater leukopenia (WBC count <2 x 10^9/L)

Creatine Phosphokinase Elevation:

- Grade 3 or greater CPK increase (>5 times the upper limit of dosing)

Hypersensitivity Reactions:

- urticaria
- angioedema

Malignancies:

- Any malignancies will be reported as AEs.

HS Lesion Interventions:

- Lesion interventions as described in Section 5.7 will be recorded as AE.

7.2.3.4. Serious Adverse Events

A serious adverse event (SAE) is defined as any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (i.e., the subject was, in the opinion of the Investigator, at immediate risk of death from the event as it occurred);
- Requires or prolongs hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect;
- Is an important and significant medical event that, based on appropriate medical judgment, may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the other outcomes defining serious.

Elective surgery already known during Screening to occur in the course of the study, and elective hospitalizations for convenience of the subject which are clearly unrelated to any medical condition, and agreed upon between the Investigator and the subject prior to randomization, will not have to be reported as SAEs.

7.2.3.5. SARs and SUSARs

A serious adverse reaction (SAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug caused the event.

A suspected unexpected serious adverse reaction (SUSAR) is defined as an SAE for which there is at least a reasonable possibility that the study drug caused the event, and the SAE is ”unexpected”, i.e., not described in terms of nature, severity, or frequency in the Reference Safety Information within the current Investigator’s Brochure.

”Reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the adverse event. Within the reporting requirements, the following examples illustrate the types of evidence that would suggest a causal relationship:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Events related to the underlying disease, such as relapses or worsening of disease will not be considered as SUSARs, unless there is a reasonable possibility that avacopan use was associated with these events.

7.2.3.6. Laboratory Abnormalities

Safety laboratory tests are performed frequently over the course of the study. Laboratory reports with abnormal findings will be reviewed by the Investigator. The Medical Monitor will review notably abnormal laboratory results according to the Safety Monitoring Plan. The Investigator will be advised to follow subjects with notably high liver panel tests closely and to take appropriate steps, such as potentially discontinuing study drug, in case the abnormalities persist.

Please see Section 4.4 for guidance on laboratory abnormalities (white blood cell count, neutrophil count, lymphocyte count, AST or ALT and other lab abnormalities of impaired liver function or hepatic toxicity, CPK increase) that would prompt pausing or permanently discontinuing study drug.

7.2.3.7. Pregnancies

Any pregnancies that occur in female subjects or partners of male study subjects must be reported to the Safety team within 24 hours of awareness as indicated in Section 7.2.4. All pregnancies must be followed up until conclusion and the outcome of the pregnancy reported within 24 hours of awareness to the Safety team as indicated in Section 7.2.4.

7.2.4. Serious Adverse Event Reporting

Any serious adverse event occurring from Screening through the end of the follow-up period, whether or not considered study related, will be reported immediately (within 24 hours) to the Safety team. Reporting is done by completing the SAE form in the EDC system. If it is not possible to access the EDC system, the Investigator will send an email to the clinical safety mailbox (see information below) of the Clinical Research Organization (CRO) or call their regional SAE hotline and fax the completed SAE report form within 24 hours of awareness.

Contact details are as follows:

CRO Clinical Safety e-mail: PPD

CRO SAE hotline: PPD

CRO Facsimile: PPD

Any medication or other therapeutic measures used to treat the event, in addition to the outcome of the adverse event, will be recorded in the EDC system.

Follow-Up Reports:

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., subject discharge summary or autopsy reports) to the CRO Clinical Safety team via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

The Sponsor or its representatives will report all SUSARs to national health authorities and central ethics committees in an expedited manner in accordance with Clinical Trial Directive, Articles 16 and 17, ICH Guideline E2A and ENTR CT3 on the reporting of all SUSARs. Investigators will forward any safety communication as applicable to their local ethics committees.

7.3. Pharmacokinetic Assessments

Concentrations of avacopan (and metabolites) will be determined in plasma according to the schedule in the Time and Events Table. The date and time of the last dose of study drug prior to the sample collections must be recorded in the EDC system. The date and time of the PK sample collection must also be recorded.

Total plasma concentrations of avacopan (and metabolites) will be determined using validated analytical methods.

7.4. Exploratory Biomarker Assessments

Subjects who consented will have their plasma collected for biomarker assessments including for example complement fragments inflammatory chemokine and cytokines. The collection will occur according to the schedule in the Time and Events Table.

7.5. Photographic Assessments

Photographs of affected skin and lesions will be taken to document the changes in visual appearance and severity over the course of study treatment in subjects who consented.

Investigators will use these photographs to compare their current and prior lesion assessments. In rare cases, the Investigator may use an anonymized photograph to consult with the study team to assure accuracy and consistency of the assessments.

In selected cases, anonymized photographs may be used to communicate potential treatment effects in a publication.

7.6. Study Completion and Withdrawal

The Week 44 visit will be the last study say for all subjects. Procedures for this day will be completed per the Time and Events Table. Each subject's condition will be evaluated by the Investigator at the end of the clinical trial and subjects will be returned to standard of care medical treatment, at the Investigator's discretion. For early withdrawals from the study, the procedures for the Early Termination visit will be performed, when possible (see Section 6.14).

8. STATISTICAL CONSIDERATIONS

8.1. Timing of Analyses

Primary Analysis: This study consists of a 12-week placebo-controlled, double-blind treatment period (Period 1), followed by a 24-week active treatment period (Period 2). When the last subject has completed or dropped out of Period 1, an unblinded analysis of the data collected from Period 1 can be conducted.

To maintain the blinding of treatment assignment in Period 2, the analysis results will be conducted by a CRO and only aggregated results by treatment will be available to the Sponsor. Treatment assignment for individual subjects will not be disclosed to the subject, study site personnel at the site, or the Sponsor until the end of the study.

Final Analysis: When all subjects have completed all of the Week 44 assessments or the last subject has dropped out of Period 2, a final analysis will be conducted on all data collected in the study.

8.2. Statistical Hypotheses

The primary efficacy objective is to evaluate the efficacy of avacopan compared to placebo in subjects with Hurley Stage II or III HS based on subjects achieving a Hidradenitis Suppurativa Clinical Response (HiSCR) after 12 weeks of treatment. To address this objective, the following hypotheses will be tested using the data collected from Period 1 after the last subject has completed Period 1:

- The null hypothesis (H_0) is that the avacopan group is not different from the placebo control group when comparing the HiSCR rate at Week 12.
- The alternative hypothesis (H_1) is that the avacopan group is different from the placebo control group when comparing the HiSCR rate at Week 12.

To address the multiplicity issue with two dose groups, a fixed hierarchical testing sequence will be employed. The hypothesis testing will test the avacopan 30 mg vs. placebo first. If the test is significant at the $\alpha = 0.05$ level, the avacopan 10 mg vs. placebo will be tested at the $\alpha = 0.05$ level. If the test of avacopan 30 mg vs. placebo is not significant at the $\alpha = 0.05$ level, the avacopan 10 mg vs. placebo will be tested as an exploratory analysis.

8.3. Sample Size Determination

The study will enroll approximately 390 subjects. In two Phase 3 clinical trials with adalimumab (PIONEER I and II; Kimball et al, 2016a), the proportions of subjects in the placebo control group achieving a HiSCR at Week 12 were 26.0% and 27.6%, respectively. Hence, if the control group only receives placebo, one may assume a HiSCR at Week 12 of approximately 30%. The average HiSCR at Week 12 in the adalimumab groups in PIONEER I and II were 41.8% and 58.9%, respectively with an average of approximately 50% (Kimball et al, 2016a). The attrition rate throughout the trial is estimated to be approximately 7%. A sample size of approximately 130 subjects per treatment group (390 in total) at a Type I error rate of $\alpha = 0.05$ (two-sided) provides approximately 90% power to detect a 20% superiority of avacopan compared to the placebo control group in HiSCR at Week 12, assuming an HiSCR at Week 12 of 50% in the avacopan group.

8.4. Analysis Populations

8.4.1. Modified Intent-to-Treat Population

For the purposes of efficacy data analysis, the Modified Intent-to-Treat (mITT) population will be used. This population will include all subjects who are randomized and received at least one dose of study drug. The efficacy population will be analyzed according to the treatment group each subject is randomized to. The mITT population will be the primary analysis population for the efficacy analysis.

The mITT populations are defined for the two treatment periods as the following:

- The mITT1 Population in Period 1 is defined as all subjects who are randomized at baseline and have received at least one dose of study drug during Period 1.
- The mITT2 Population in Period 2 is defined as all subjects who have received at least one dose of study drug during Period 2.

8.4.2. Per-Protocol Population

The Per-Protocol (PP) population will consist of all randomized subjects who receive at least one dose of study drug and do not have protocol deviations that could significantly affect the interpretation of the results for the primary endpoints. Subjects' inclusion/exclusion from the PP population will be determined and documented prior to the database lock and unblinding.

8.4.3. Safety Population

The Safety Populations are defined as the following:

- The Safety Population in Period 1 is defined as all subjects who are randomized at baseline and have received at least one dose of study drug during Period 1.
- The Safety Population in Period 2 is defined as all subjects who received at least one dose of avacopan during Period 2.
- The All Avacopan Treated Population is defined as all subjects who receive at least one dose of avacopan in any treatment period.

The Safety Populations will be analyzed according to the assigned treatment group. In the event that a subject receives a treatment regimen that does not correspond to the assigned treatment, the subject will be included in the analysis group of the treatment actually received.

8.5. Efficacy Endpoints

8.5.1. Primary Endpoint

The primary endpoint is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 12.

This endpoint is considered appropriate because it was able to measure meaningful improvements in HS subjects in previous studies (Kimball et al, 2014; Zouboulis et al, 2015; Kimball et al, 2016b). This endpoint was also used successfully in two Phase 3 clinical trials with adalimumab (Kimball et al, 2016a).

8.5.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

1. Reduction of IHS4 score relative to baseline at Week 12;
2. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Day 1 in the subject's global assessment of skin pain (NRS30) in subjects with a baseline NRS of at least 3, evaluated at Week 12; weekly averages of daily pain will be calculated based on subjects' daily diary recording of the worst pain experienced in the previous 24 hours;
3. Change from Day 1 to Week 12 in the modified Sartorius score to quantify the severity change of HS;
4. Proportion of subjects with baseline Hurley Stage II who achieved an abscess and inflammatory nodule count of 0, 1, or 2 at Week 12.

8.5.3. Other Efficacy Endpoints

The following efficacy endpoints will be analyzed from Day 1 to each timepoint up to Week 44, where applicable:

1. Proportion of subjects achieving HiSCR;
2. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Day 1 in subject's global assessment of skin pain (NRS30), in subjects with a Day 1 NRS of at least 3;
3. Proportion of subjects with baseline Hurley Stage II who achieved an abscess and inflammatory nodule count of 0, 1, or 2;
4. Change from Day 1 in inflammatory nodule count, abscess count, draining fistula count, and total AN count;
5. Change from Day 1 in the Sartorius score, modified Sartorius score, IHS4 score, and HS-PGA to quantify the severity change of HS;

6. Change from Day 1 in patient-reported outcomes: SF-36 v2, EQ-5D-5L, HiSQOL, and DLQI;
7. Proportion of subjects who experienced flare, defined as an at least 25% increase in AN counts with a minimum increase of 2 AN lesions relative to Day 1;
8. Duration of flare in days (calculated from the day when flare is observed to the day prior to the observation that flare is no longer present; of note, there could be multiple periods that flares are observed, in which case, the total days from the multiple periods will be used);
9. Proportion of subjects who experience at least 25% increase in draining fistula counts with a minimum increase of 2 draining fistula counts relative to Day 1;
10. During Period 2, Proportion of subjects with a loss of response (LOR), defined as loss of at least 50% of AN count improvement achieved from Day 1 to Week 12;
11. Time to LOR during Period 2;
12. Proportion of subjects who received oral antibiotic rescue therapy;
13. Proportion of subjects who start disallowed opioid pain therapy;
14. Proportion of subjects who undergo lesion intervention due to HS;
15. Number of lesion interventions due to HS;
16. Health-economic information:
    a. WPAI:SHP: Change from Day 1 to each timepoint during Period 1 and Change from Week 12 to each timepoint during Period 2 and including the follow-up period;
    b. Hospitalizations (cumulative): Number of Hospitalizations total and due to HS, Number of days hospitalized, Number of days missed from work;
    c. Emergency or Urgent Care visits (cumulative): Number of visits total and due to HS, Number of days (or hours where applicable) missed from work;
    d. Lesion interventions for HS (cumulative): Number of days (or hours where applicable) missed from work due to HS lesion interventions.

8.6. Safety Endpoints

Safety endpoints include:

1. Subject incidence of treatment-emergent serious adverse events, adverse events, and withdrawals due to adverse events;
2. Change from Day 1 and shifts from Day 1 in all safety laboratory parameters;
3. Change from Day 1 in vital signs and significant changes in physical examination abnormalities.

8.7. Pharmacokinetic Endpoints

Avacopan (and its metabolite) plasma concentrations will be used to calculate the following PK parameters on Day 1 and trough plasma concentrations (C_{min}) over the course of the clinical trial.

C_{max} Maximum plasma concentration

T_{max} Time of maximum plasma concentration

AUC_{0-6h} Area under the plasma concentration-time curve from Time 0 to Hour 6 on Day 1

8.8. Statistical Analysis Methodology

8.8.1. General Approach

All study data will be summarized by treatment using descriptive statistics. Categorical variables will be reported as frequency and percent (e.g., gender, race). Continuous variables will be reported as number of subjects, mean, standard deviation, median, minimum, and maximum (e.g., age, weight). All summaries, statistical analyses, and individual subject data listings described below will be completed using Version 9.3 or later of the SAS Statistical Analysis System (SAS Institute, Inc. Cary, NC).

All statistical testing will be two-sided, with the Type I error rate at $\alpha = 0.05$.

Baseline is defined as the last value prior to start of dosing with study drug (typically the Day 1 pre-dose value).

Non-Responder Analysis: For non-responder analysis, the following imputation rules will be applied to categorical and continuous efficacy variables, respectively:

- Categorical Efficacy Variables: Non-Responder Imputation (NRI) will be used as the primary analysis. Last Observation Carried Forward (LOCF) will be the secondary approach for the non-responder analysis.
- Continuous Efficacy Variables: LOCF will be used as the primary analysis. The valid assessments from last visit prior to the visit the subject was considered a non-responder will be carried forward to the end of study for continuous efficacy variables. Baseline efficacy evaluations will not be carried forward.

The following are examples for subjects who will be counted as non-responder:

- Concomitant anti-TNF-α treatment or other treatments with clinically relevant impact on HS;
- Antibiotic rescue therapy;
- Non-protocol specified lesion intervention, or higher than permitted frequency or number of pre-specified lesion interventions. Protocol-specified lesion interventions will *not* be counted as Non-responder.

Concomitant therapy that would qualify a subject as non-responder will be reviewed prior to database lock. More details will be provided in the Statistical Analysis Plan (SAP).

Missing Data Analysis: For missing data analysis, the following imputation rules will be applied to categorical and continuous efficacy variables, respectively:

- Categorical Efficacy Variables: NRI will be the primary approach for categorical variables. The NRI analysis will count subjects who have missing values at a specific visit as non-responders for that visit. LOCF will be the secondary approach for the missing data analysis.

- Continuous Efficacy Variables: LOCF will be the primary approach for continuous efficacy variables of missing data. The LOCF analyses will have their valid efficacy assessments from the previous visits to impute missing data at later visits. Baseline efficacy evaluations will not be carried forward.

Lesions that received intervention (incision and drainage, or intralesional injection) will be counted as permanently present from the date of the intervention.

Details of the statistical analysis will be provided in a separate statistical analysis plan (SAP), which will be finalized prior to database lock.

8.8.2. Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint, the proportion of subjects achieving HiSCR at Week 12 will be tested using the Cochran-Mantel-Haenszel (CMH) test, stratified by Hurley Stage (Stage II vs. III), concomitant antibiotic therapy with allowed antibiotics (Yes vs. No) and anti-TNF drug use (Treatment naïve vs. Previous treatment). The hierarchical testing procedure will be used for the comparisons of the 10 mg avacopan vs. placebo and 30 mg avacopan vs. placebo to maintain the overall Type I error at 0.05. The 30 mg avacopan vs. placebo will be tested first: if the p-value is less than or equal to 0.05, then 10 mg avacopan vs. placebo will be tested at the $\alpha = 0.05$ level. If the test of avacopan 30 mg vs. placebo is not significant at the $\alpha = 0.05$ level, the 10 mg avacopan vs. placebo will be tested as an exploratory analysis. The two-sided 95% confidence intervals for the difference in proportions (avacopan minus placebo control) will be calculated using the stratified Newcombe hybrid-score method. The primary efficacy analysis will be carried out in the mITT1 Population. In addition, the primary efficacy endpoint will be analyzed in the Per-Protocol Population.

The proportion of subjects achieving HiSCR at Week 12 will be calculated as those subjects having at least a 50% reduction from baseline in abscess and inflammatory nodule count, with no increase in abscess count and no increase in draining fistula count number at Week 12 divided by the total number of subjects randomized to the particular treatment group.

8.8.3. Analysis of Secondary and Other Efficacy Endpoints in Period 1

The Secondary and Other Efficacy Endpoints for Period 1 will be tested separately for the 10 mg and 30 mg avacopan groups at Type I error at 0.05. The analyses will be carried out in the mITT1 Population. Analysis of other efficacy endpoints will be conducted from Day 1 to each timepoint.

Categorical variables of change from Day 1 to Week 12 will be analyzed using CMH test stratified for baseline Hurley Stage (Stage II vs. III), concomitant antibiotic therapy with allowed antibiotics (Yes vs. No) and anti-TNF-α drug use (Treatment naïve vs. Previous treatment) similar to the analysis of the primary efficacy endpoint.

Continuous variables will be analyzed using a mixed effects model for repeated measures. This model will include treatment group, visit, treatment-by-visit interaction, and randomization strata (Hurley Stage II or Hurley Stage III, previous anti-TNF-α drug use or anti-TNF-α drug naïve, concomitant antibiotic therapy use or not) as factors, and baseline as covariate. Subjects will be considered as repeated measure units over visits. Testing p-values, point estimates and corresponding 95% confidence intervals will be estimated for the difference between the

avacopan group and the placebo control group across 12 weeks using linear contrast from the model.

For the analysis of subject's global assessment of skin pain (NRS30) up to Week 12, subjects who received analgesics of disallowed pain therapy will be counted as non-responder for categorical variables. For continuous variables, LOCF applies. Hereby, the last pain assessment is carried forward from the start day of the analgesics or day of the intervention until 14 days after the stop of analgesic use or day of the intervention. Concomitant medication for treatment of pain will be reviewed. Disallowed pain therapy will be determined by a blinded data review prior to database lock.

The test of 10 mg vs. 30 mg avacopan groups will be conducted at each timepoint for the endpoint of the proportion of subjects achieving HiSCR and the secondary endpoints. A detailed Type I management plan for the secondary endpoint testing will be provided in SAP.

8.8.4. Analysis of Secondary and Other Efficacy Endpoints in Period 2

The efficacy data for secondary and other endpoints by timepoint in Period 2 will be summarized using the mITT2 population. Analysis of other efficacy endpoints will be conducted from Day 1 to each timepoint.

For the analysis of time to loss of response (LOR), the treatment difference between the 10 mg and 30 mg avacopan groups will be analyzed using the stratified log-rank test with baseline randomization stratification factors as the stratification variables.

8.8.5. Safety Analyses

All subjects who are randomized and received at least one dose of study drug will be included in the safety population.

All clinical safety and tolerability data will be summarized by treatment group and listed by treatment group and by subject.

All reported adverse events will be coded using MedDRA and listed by System Organ Class, Preferred Term, and verbatim term.

- Treatment-emergent adverse events will be summarized and listed by treatment group by System Organ Class and Preferred Term, by relatedness and by maximum severity.
- Treatment-emergent serious adverse events and adverse events leading to withdrawal will be summarized by treatment group.

Individual vital signs and change from baseline in vital signs will be summarized by treatment group and listed by treatment group, subject, and study visit.

Laboratory data will be listed by treatment group, subject, and study visit. Abnormal laboratory values will be flagged. Laboratory data (actual values and change from baseline) will be summarized by treatment group and study visit. Shift tables will be generated for shifts in laboratory parameters by study visit.

8.8.6. Pharmacokinetic Analysis

Individual plasma concentrations of avacopan and significant metabolites will be listed, plotted, and summarized descriptively and graphically. PK analysis may be performed in a subject subset only. The following parameters will be determined, where possible:

C_{max} Maximum plasma concentration

T_{max} Time of maximum plasma concentration

AUC_{0-3h} Area under the plasma concentration-time curve from Time 0 to Hour 3 on Day 1

C_{min} Trough level plasma concentrations at post-Day 1 visits

The relationship between PK parameters (e.g., C_{min}) and efficacy endpoints such as HiSCR may also be evaluated.

8.8.7. Subject Disposition

The number of subjects who were screened, who screen failed (by reason), who were randomized, who completed Week 12, Week 36, and Week 44 of the study, respectively, and who withdrew early from the study, along with the reasons for withdrawal, will be presented by treatment group.

8.8.8. Demographics and Baseline Characteristics

All subject baseline characteristics and demographic data, i.e., age, sex, race, ethnicity, weight, height, body mass index, anatomic location of HS, number of inflammatory nodules, abscesses, draining fistulae and hypertrophic scars, Hurley Stage of HS, HS disease duration (from time of diagnosis), subject's global assessment of skin pain NRS, Sartorius and modified Sartorius scores, IHS4 score, and HS-PGA, previous systemic treatment, previous antibiotic treatment, previous TNF inhibitor use, prior surgery for HS, SF-36 v2, EQ-5D-5L, and HiSQOL index will be summarized and listed by treatment group.

Physical examination abnormalities, medical history, previous and concomitant medications (including HS medication use) at study entry will be summarized and listed by treatment group.

8.8.9. Prior and Concomitant Medications

All medications will be coded using the World Health Organization Drug Dictionary (WHODD). All prior (within 12 months of Screening for HS medications, and within 6 months of Screening for all other medications) and concomitant medications (including HS medications) will be summarized and listed by WHODD Anatomic Therapeutic Chemistry (ATC) classification and preferred term.

8.8.10. Study Drug Exposure and Compliance

Subject drug exposure will be calculated comparing the daily drug diary, study drug dispensing and return records, as well as avacopan plasma concentrations over the course of the study. The study drug exposure (duration, total dose, and average daily dose) and compliance will be summarized for the double-blind and active treatment periods separately. Individual subject data listings will also be provided.

8.8.11. Handling of Missing Data

For binary variables, non-response imputation will be used for missing data (primary approach). Sensitivity analyses will include last observation carried forward (LOCF) and multiple imputation. For continuous variables, LOCF and observed without adjustment for missing data will be performed as sensitivity analyses. Baseline data will not be carried forward.

8.8.12. Covariates and Subgroups

The analysis of the efficacy endpoints may be adjusted by the following variables in the form of covariate analysis, stratified analysis, and/or subgroup analysis:

- Randomization stratification variables
  - Hurley Stage II vs. Hurley Stage III
  - Concomitant antibiotic therapy (Yes vs. No)
  - Anti-TNF-α treatment (Treatment naïve vs. Previous treatment)
- Sex
- BMI
- Baseline weight
- Age at diagnosis of HS
- Age at study entry
- Duration of HS
- Subject's age, race, and ethnicity
- Baseline inflammatory nodule count
- Baseline abscess count
- Baseline draining fistula count
- Baseline Sartorius and modified Sartorius scores
- Baseline AN count
- Geographic distribution

8.9. Interim Analyses

An interim analysis for futility may be conducted (for example, if enrollment is much slower than expected) by an independent statistical data center when at least 30% of the planned study participants have completed Period 1 of the study. This interim futility analysis will not affect the Type I error of the overall study. Based upon the futility analysis, it is possible that the low dose of avacopan or the entire study may be stopped. The details regarding the futility analysis boundaries will be provided in the SAP.

9. STUDY COMPLETION AND TERMINATION

The primary analysis can be performed when all subjects have completed at least the Week 12 visit. Another analysis will be performed when all subjects have completed the full study.

9.1. Study Completion

A subject has completed the study when s/he has completed the study procedures per protocol.

9.2. Study Termination

The end of study is defined as the last study visit of the last clinical trial subject.

The study will be terminated early if there is an insurmountable safety concern that cannot be addressed by protocol amendment. This will be determined in conjunction with the DMC. In this case, the Investigators, competent authorities (CAs), IRB/ECs will be notified expeditiously and appropriate measures taken to safeguard the study subjects.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Informed Consent

A properly executed, written, and appropriately explained Informed Consent Form, in compliance with the Declaration of Helsinki, ICH GCP, and US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 46, Subpart A), will be signed by each subject prior to entering the trial. Consent forms will be provided to subjects in their native language and will describe in detail the study intervention, study procedures, and risks.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be approved by the applicable IRB or EC and the participant will be asked to read and review the document. The Investigator or the Investigator's designee will explain the clinical trial to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures.

10.1.2. Study Discontinuation and Closure

Determination of unexpected, significant, or unacceptable risk to participants may warrant termination or suspension of the clinical trial. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor or its designee to Investigators and applicable regulatory agencies/competent authorities. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants and the applicable IRB/EC, and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the applicable IRBs/ECs and regulatory agencies/competent authorities.

10.1.3. Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the Sponsor and its designees. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/EC, regulatory agencies/competent authorities may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study sites will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/EC, Institutional policies, or Sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Sponsor's designated CRO. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the CRO's staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Sponsor's designated CRO.

10.1.4. Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Sponsor's designated CRO. At the end of the study, these data will be transferred to the Sponsor or to a Sponsor-delegated storage location.

Biological samples collected from study participants will be shipped from the study sites to the CRO's central laboratory for analysis. Plasma samples collected for PK analysis will be shipped

from the CRO's central laboratory to the Sponsor's designated PK laboratory for analysis. Once the assays are completed, the data verified, and all analyses completed, the samples will be destroyed.

10.1.5. Key Roles and Study Governance

10.1.5.1. Investigator Responsibilities

The Investigator and site staff will be the primary contact for the study subjects. The Investigator and its staff will communicate all relevant study-related information to the subjects and conduct all study-specific procedures including collection of blood and urine samples. The Investigator agrees that neither s/he nor any of the study staff will supply study drug to any persons other than those enrolled in the study.

Prior to trial initiation, the Investigator will provide the Sponsor with a fully executed and signed FDA Form 1572, a Financial Disclosure Form, and a curriculum vitae. Financial Disclosure Forms will also be completed for all sub-Investigators listed on the Form 1572 who will be involved directly in the treatment or evaluation of research subjects in this trial.

The study will be conducted in accordance with the Declaration of Helsinki (amended by the 59th World Medical Association General Assembly, October 2008) and GCP according to ICH guidelines. Specifically, the study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed by a properly constituted IRB/EC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the subjects will be respected; and each subject or his/her legal guardian will give his/her written Informed Consent before any protocol-specific tests or evaluations are performed.

The Investigator agrees to complete a subject identification register, which will be used for the purpose of long term follow-up, if needed. This form will be treated as confidential, and will be filed by the Investigator in a secure locked place. Otherwise, all reports and communications relating to the study will identify participants by initials and/or assigned number only.

10.1.5.2. Sponsor and Its Designees

This clinical trial will be sponsored by ChemoCentryx, Inc. ChemoCentryx will designate to its CRO several clinical trial activities including those related to study oversight, clinical, medical and safety monitoring, site communication, data management, safety laboratory measurements, statistical analysis, report writing, and site contract and investigator payment. The Sponsor will maintain oversight by having regular meetings with its designated CRO. The Sponsor will also designate measurement of plasma PK samples to a CRO that will use validated methods for measurements of avacopan and metabolites.

10.1.5.3. Institutional Review Boards/Ethics Committees

Prior to initiating the study, the Investigator will obtain written confirmation from the IRB/EC that the IRB/EC was properly constituted and met the definition of all United States Code of Federal Regulations Title 21, Section 312.3(b) and Part 56, and/or the applicable local, regional or national Regulatory requirements. A copy of the confirmation will be provided to the Sponsor. The Principal Investigator will provide the IRB/EC with all appropriate materials, including the

protocol and Informed Consent documents. The trial will not be initiated until IRB/EC approval of the protocol, the Informed Consent document, and all recruiting materials are obtained in writing by the Investigator and copies are received by the Sponsor. Appropriate reports on the progress of the study will be made to the IRB/EC and the Sponsor by the Principal Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

10.1.6. Safety Oversight and Data Monitoring Committee

The study Medical Monitor will review aggregate blinded safety data regularly over the course of the study according to the Safety Monitoring Plan. The Medical Monitor will keep the Sponsor's Medical Director apprised of all relevant safety findings over the course of the study.

In addition to continuous safety monitoring by the Medical Monitor and clinical staff, an external Data Monitoring Committee (DMC) will monitor the safety of subjects over the course of the study. The DMC will consist of external physicians and a biostatistician, with at least one member being a dermatologist knowledgeable in HS. Members of the DMC will be independent from the study conduct and free of conflict of interest. A DMC charter will be developed and the DMC will function according to the charter.

It is anticipated that the DMC will have regular meetings as specified by the DMC Charter depending on study enrollment rate. Ad hoc meetings may be scheduled if unanticipated safety events occur. After review of data at each meeting, the DMC will make recommendations about further conduct of the study.

Safety data from the study will be summarized for review by the DMC at various points over the course of the study.

No Type I error adjustment will be made based on the DMC review of the data, since results from these analyses will be kept confidential and not be shared with the study team, Investigators, or subjects.

10.1.7. Study Monitoring

The Sponsor has ultimate responsibility to take all reasonable steps to ensure proper conduct of the study with respect to subject rights and safety, adherence to the currently approved protocol/amendment, compliance with ICH GCP and applicable regulatory requirements, and data validity and integrity.

Study monitoring responsibility may be transferred to a Sponsor representative or CRO, who will be held to execute the study with high standards.

The study will be closely monitored throughout its duration, in the form of personal visits with the study investigator/site staff as well as appropriate communications by telephone, fax, mail, or email. The purpose of these contacts is to review study progress, Investigator and subject adherence to the protocol, to identify and mitigate any risk of subject safety, and to evaluate data integrity.

The following key areas will be assessed as part of study site monitoring on an ongoing basis, in addition to the details provided in the Clinical Monitoring Plan:

- Continued suitability and qualification of the site to conduct the study, including proper training of the Investigator and site staff;
- Informed consent and other regulatory documentation;
- Subject accrual and follow up;
- Continued compliance with protocol, including documentation of protocol deviations and implementation of corrective and preventive measures;
- Documentation of all adverse events and concomitant medications, and proper reporting of all serious adverse events;
- Timely data entry, accuracy, completeness and 100 % verifiability of data when compared to source documents, and
- Study drug accountability.

The Investigator and their staff are expected to cooperate and support monitors during their visits and provide access to relevant study documents and systems. A monitoring report and visit follow up communication will be generated for every visit and filed in the trial master files.

10.1.8. Quality Assurance and Quality Control

Clinical sites are responsible for quality management of the study and proper documentation. Quality control (QC) procedures to ensure data quality will be accomplished through implementation of a validated data entry system and data QC checks that will be run on the study database. As part of monitoring, any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, the monitors will verify that the clinical trial is conducted, data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., Good Laboratory Practices, Good Manufacturing Practices).

All study site documentation pertaining to this clinical study may be subject to quality assurance audits by personnel designated by ChemoCentryx, the FDA, and/or other regulatory agencies with similar responsibilities. Upon request, the auditor will have access to inspect, copy, review and audit all source documentation and eCRFs. Other documentation subject to quality assurance audits include the Investigator's IRB files, study staff training and delegation records, laboratory certifications, pharmacy processes and standard operating procedures for study management processes. In addition, the Sponsor or designee may inspect conditions of storage of study drug, and observe any aspect of the clinical study or its supporting activities both from within and outside of the Investigative site.

10.1.9. Data Handling and Record Keeping

10.1.9.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic data capture (EDC) system must be consistent with the data recorded on the source documents.

Clinical data (including disease characteristics, medical history, subject-reported outcome measures, AEs, and concomitant medications) will be entered into the CRO's database, a 21 CFR Part 11-compliant data capture system. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Central laboratory data will be captured and transferred directly from the laboratory database.

Upon completion of the study, electronic copies of the CRFs will be provided to the Investigators and should be included as part of his/her study files and retained as per FDA or local regulations.

10.1.9.2. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. The Sponsor will inform the Investigator when these documents no longer need to be retained.

10.1.10. Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study site staff. As a result of deviations, corrective actions must be developed by the site and implemented promptly.

It is the responsibility of the Investigator to use continuous vigilance to identify and report significant protocol deviations to the Clinical Research Associate (CRA) as soon as possible upon identification of the protocol deviation. All deviations must be addressed in study source documents. Protocol deviations must be sent to the IRB/EC per their policies. The Investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements.

Significant protocol deviations will be listed and summarized by deviation category in the Clinical Study Report.

The Sponsor will assess any protocol deviations and decide whether any of these should be reported to CAs as a serious breach of GCP and the protocol. Protocol waivers are not acceptable.

10.1.11. Protocol Modifications

Only the Sponsor may modify the protocol. The only exception is when the Investigator considers that a subject's safety would be compromised without immediate action. In this circumstance, immediate approval of the chairperson of the IRB/EC must be sought, and the

Investigator should inform the Sponsor's Medical Monitor and the full IRB/EC within five working days after the emergency occurred.

All other amendments that have an impact on subject risk or the study objectives, and/or that require revision of the ICF, must receive approval from the IRB/EC prior to their implementation, except when the changes involve only logistical or administrative aspects of the trial. The IRB/EC must be notified of changes that are made to study contact personnel, but IRB/EC review or approval of these changes is not required. If protocol amendments are substantial and are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or if they are otherwise significant, the Sponsor shall notify the FDA and other CAs concerned of the reasons for, and content of, these amendments according to the European Directive "Detailed guidance on the request to the CAs for authorization of a clinical trial on a medical products for human use, the notification of substantial amendments and the declaration of the end of trial (CT 1)(2010/C 82/01)" and other regulatory guidance. In case of a substantial amendment to the protocol, approval will be sought from CAs before implementation.

10.1.12. Study Registration, Use of Information and Publication

The study will be registered in clinicaltrials.gov and other country-specific registries, as required, prior to initiation.

It is understood by the Investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product and therefore may be disclosed to government agencies in various countries. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

The Sponsor recognizes the importance of communicating study data and will disclose or publish the results in a suitable form regardless of outcome. The Sponsor will publish the results of this study in scientific journals, at seminars or conferences, and/or in other manner(s) it so chooses. Results from this study shall not be made available to any third party by the investigating team without the express permission of the Sponsor.

11. BENEFIT/RISK ASSESSMENT

11.1. Non-Clinical Evaluation

Single-dose and repeat-dose toxicology, safety pharmacology, and genotoxicity studies have been conducted with avacopan. General toxicity studies of up to 26-week duration in rats and 44-week duration in cynomolgus monkeys have been conducted at avacopan doses up to 200 and 45 mg/kg/day, respectively, significantly higher than the highest human daily dose of 30 mg twice daily (b.i.d.) being tested in this clinical trial and other indications.

Based on in vivo safety pharmacology studies, which included neuropharmacology, pulmonary, and renal safety studies in rats, and a cardiovascular safety study in conscious telemetered cynomolgus monkeys, there was no evidence of toxicity of avacopan. No evidence of electrocardiographic alterations was seen in the monkey 4-week, 20-week, or 44-week studies or in in vitro cardiovascular safety studies (IC_{50} values for hERG inhibition was determined to be

>2.3 µM for avacopan and >3.0 µM for its metabolite CCX168-M1, the limit of solubility for both compounds). A safety margin for avacopan and metabolite CCX168-M1 of at least 3,500 fold relative to expected steady state human unbound maximum plasma is projected.

Genotoxicity studies, including in vitro bacterial mutagenicity (Ames test) and in vitro mammalian cell mutagenicity (mouse lymphoma) studies, in vivo bone marrow rat micronucleus and in silico mutagenicity evaluation of starting materials, intermediates and chemical impurities utilized and formed during the synthesis of avacopan were also conducted and did not identify any safety concerns or significant potential for drug-drug interactions. In an acute toxicology study, single doses of avacopan up to 100 mg/kg in rats produced no remarkable effects. No effects on IgG and IgM antibody production in rats or monkeys were noted following immunization with keyhole limpet hemocyanin antigen. Immunophenotypic analyses performed in the 44-week monkey study did not reveal any avacopan-related effects. No phototoxicity potential was observed for avacopan in the in vitro 3T3 assay.

Avacopan was well tolerated in studies up to 26 and 44 weeks in rats and cynomolgus monkeys, respectively, up to the highest doses tested (200 mg/kg/day in rats and 45 mg/kg/day in cynomolgus monkeys). These doses provide an exposure margin of ~19-fold and ~6-fold, respectively, compared to the projected avacopan steady-state exposure with the 30 mg twice daily therapeutic dose in humans. There were no significant toxicological findings of concern in these chronic studies or the preceding sub-chronic studies. Metabolite CCX168-M1 (which has been identified in humans) was present in samples collected in the rat 26-week and the monkey 44-week studies at relatively high levels indicating that this metabolite has been qualified.

No avacopan-related effects were observed upon pregnancy or embryo-fetal development in studies at doses up to 1000 mg/kg and 200 mg/kg in hamsters and rabbits, respectively. No evidence of histopathological alterations to the male or female reproductive system was seen in rats or monkeys in toxicology studies. A pre and post-natal development study (Segment III) in hamsters with avacopan given at doses up to 1,000 mg/kg/day (500 mg/kg b.i.d.) from GD 6-12 and through lactation until weaning of the offspring, resulted in no adverse findings in either the F_0 dams or the F_1 offspring, including developmental, behavioral, immunological or reproductive measures (PC0673_168). Analysis of avacopan plasma levels in the lactating dams and the plasma levels in nursing offspring showed the presence of avacopan, suggesting avacopan is likely excreted into the milk of lactating hamsters.

In summary, no safety findings in toxicology studies in rats, cynomolgus monkeys, rabbits and hamsters have been observed that would preclude dosing to humans at the 30 mg twice daily dose in this clinical trial.

11.2. Clinical Evaluation

Five Phase 1 studies have been completed at avacopan doses ranging from 1 mg up to 100 mg (CL001_168, CL004_168, CL007_168, CL008_168, and CCX1101). Avacopan was generally well tolerated in these studies.

The most frequently reported adverse events in subjects receiving avacopan in Phase 1 clinical studies were headache (14.6% vs. 14.3% for placebo), diarrhea (6.7% vs. 7.1% for placebo), dizziness (4.5% vs. 0% for placebo), upper respiratory tract infection (4.5% vs. 0% for placebo), nausea (3.4% vs. 0% for placebo), oropharyngeal pain (3.4% vs. 7.1% for placebo), and WBC

count decreased (3.4% vs. 0% for placebo). All other adverse events occurred at an incidence less than 3%.

In addition, a Phase 1 study in subjects with mild (N=8) or moderate (N=8) hepatic impairment (as defined using Child-Pugh [C-P] Classification of the Severity of Liver Disease criteria) compared to healthy matched controls (N=8) studying a single dose of 30 mg avacopan was completed. The single dose of 30 mg avacopan was well tolerated in all subjects and there was no pharmacokinetically relevant impact on avacopan exposure. As a result, no dose adjustment is necessary for subjects with mild to moderate hepatic impairment.

An ethno-bridging Phase 1 study (CCX1101) was conducted in 40 healthy, male Japanese subjects. The study was conducted to test the safety and PK of avacopan and its major metabolite CCX168-M1 in the Japanese subjects compared to 24 Caucasian healthy adult males.

In addition, two Phase 2 clinical trials (CL002_168 and CL003_168) have been conducted in 109 subjects with AAV; 73 of these were randomized to receive avacopan in these trials. A total of 60 subjects received 30 mg avacopan twice daily and 13 subjects received 10 mg avacopan twice daily for 12 weeks.

As anticipated, since all subjects received rituximab or cyclophosphamide, and most also received glucocorticoids, serious infections were the most common serious adverse event. The incidence of serious infections was similar in subjects receiving avacopan compared to the control group. Vasculitis or renal vasculitis (worsening) was also reported at a similar incidence in the two groups.

The most commonly reported treatment-emergent adverse events in subjects with AAV receiving avacopan in studies CL002_168 and CL003_168 combined were hypertension (17.8% vs. 16.7% in the control group), nausea (17.8% vs. 19.4% in the control group), vomiting (13.7% vs. 0.0% in the control group), headache (11.0% vs. 11.1% in the control group), nasopharyngitis (11.0% vs. 8.3% in the control group), peripheral edema (9.6% vs. 11.1% in the control group), arthralgia (8.2% vs. 2.8% in the control group), and diarrhea (8.2% vs. 2.8% in the control group). Grade 3 lymphopenia has been observed in more subjects receiving avacopan plus cyclophosphamide or rituximab compared to cyclophosphamide or rituximab alone. This lymphopenia occurred within the first 2 weeks of treatment, and was not progressive with continued treatment. Avacopan did not show evidence of pro-arrhythmic potential in an intensive ECG study (CL007_168).

Caution should be exercised when avacopan is given with potent CYP3A4 inhibitors such as itraconazole, since the avacopan plasma exposure may increase approximately two-fold.

Avacopan has shown evidence of efficacy in Phase 2 study CL002_168 based on BVAS, quality of life measurements, renal response, urinary albuminuria, and urinary MCP-1:creatinine results. This efficacy was demonstrated across a number of relevant immunological and clinical subgroups, i.e., subjects with MPO ANCA-positive disease vs. PR3 ANCA-positive disease, newly diagnosed vs. relapsing subjects, subjects on cyclophosphamide vs. those on rituximab.

It is of note that as avacopan is a selective C5aR blocker, it does not appear to affect the formation of C5b and the membrane attack complex (MAC) or terminal complement complex (TCC) which is needed to protect against *Neisseria* infections. Nevertheless, subjects should adhere to all local vaccination program requirements, Investigators should be vigilant in

reporting all infections occurring during clinical trials and should attempt to identify the organisms involved in all infections.

In an ongoing Phase 3 study (CL010_168) of approximately 300 subjects with AAV, subjects receive avacopan and background therapy of cyclophosphamide followed by azathioprine, or in combination with rituximab. The control group receives high dose glucocorticoids on background therapy with cyclophosphamide followed by azathioprine, or in combination with rituximab. The study remains blinded to the Sponsor, Investigators and subjects. An unblinded Data Monitoring Committee (DMC) of study CL010_168 recommended notification be sent to Investigators with the following observations: (a) urticaria with angioedema in two subjects, and (b) elevated liver transaminases in several subjects on blinded study drug (with one event of biopsy consistent-hepatocellular damage in a subject receiving active study drug in combination with immunosuppressive and other drugs), and (c) events of nausea, vomiting, and diarrhea. Informed Consent Form(s) were also updated.

Therefore, the Reference Safety Information section of the Investigator's Brochure has been updated to include the potential risk of urticaria, angioedema, and of hepatotoxicity, and to state that general gastrointestinal adverse events (e.g., nausea, diarrhea) observed in Phase 2 AAV studies have been observed in the ongoing Phase 3 CL010_168 study at approximately the same frequency and severity.

Further, as a result of the DMC review of safety data from all completed and ongoing studies of avacopan, the frequency of monitoring of hematology has been increased to monthly and rules for pausing administration of blinded study drug have been modified. These changes to the protocol were based on observations of neutropenia and neutropenic sepsis in a blinded study in a subject with C3 glomerulopathy (CL011_168) and agranulocytosis in the ongoing and blinded Phase 3 study of avacopan in subjects with AAV (ADVOCATE, CL010_168). In all reported cases, subjects were receiving multiple immunosuppressants (e.g., cyclophosphamide, rituximab, mycophenolate mofetil, others) in addition to study medication.

11.3. Summary Benefit-Risk Statement

Based on the nonclinical and clinical study results, the potential benefits of testing avacopan in subjects with HS outweigh the potential risks.

Subjects participating in clinical trials must be closely monitored for any adverse events, and laboratory, physical examination, or vital signs abnormalities. WBC and differential counts, and liver enzyme values must be monitored over the course of the studies.

As with all investigational compounds, the potential exists for unanticipated serious or life-threatening toxicities or adverse events not predicted by the animal toxicology or clinical studies conducted to date. Investigators should exercise vigilance in the monitoring of subjects involved in this clinical trial with avacopan.

For additional details, please refer to the current version of the Investigator's Brochure.

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