

Protocol Number: M1095-HS-201

**Official Title: Phase 2, Randomized, Parallel-group, Double-blind, Placebo-controlled Study of
Sonelokimab in Patients With Active Moderate to Severe Hidradenitis Suppurativa**

NCT Number: NCT05322473

Document Date: 16 August 2022

TITLE PAGE

CLINICAL STUDY PROTOCOL TITLE:

Phase 2, randomized, parallel-group, double-blind, placebo-controlled study of sonelokimab in patients with active moderate to severe hidradenitis suppurativa

Protocol Number:	M1095-HS-201 Version 2.1 (DE)
Test Product:	Sonelokimab
Indication:	Active moderate to severe hidradenitis suppurativa
Development Phase:	2
Short Title:	Evaluation of Sonelokimab for the treatment of patients with active moderate to severe HS
Sponsor:	MoonLake Immunotherapeutics AG
Legal Registered Address:	Dorfstrasse 29 6300 Zug Switzerland
Regulatory Agency Identifying Numbers(s):	
Investigational New Drug (IND) Number:	135169
EudraCT:	2021-005928-38
Approval Date:	16 August 2022

The confidential information in this document is provided to you as an investigator, potential investigator, or consultant for review by you, your staff and applicable Independent Ethics Committee and/or Institutional Review Board. It is understood that the information will not be disclosed to others without written authorization from MoonLake Immunotherapeutics AG except to the extent necessary to obtain informed consent from those persons, or their legally authorized representative, to whom the drug may be administered.

SPONSOR SIGNATURE PAGE

PROTOCOL TITLE: Phase 2, randomized, parallel-group, double-blind, placebo-controlled study of sonelokimab in patients with active moderate to severe hidradenitis suppurativa

PROTOCOL NUMBER: M1095-HS-201 Version 2.1 (DE)



Date (day/month/year)

1 GENERAL INFORMATION

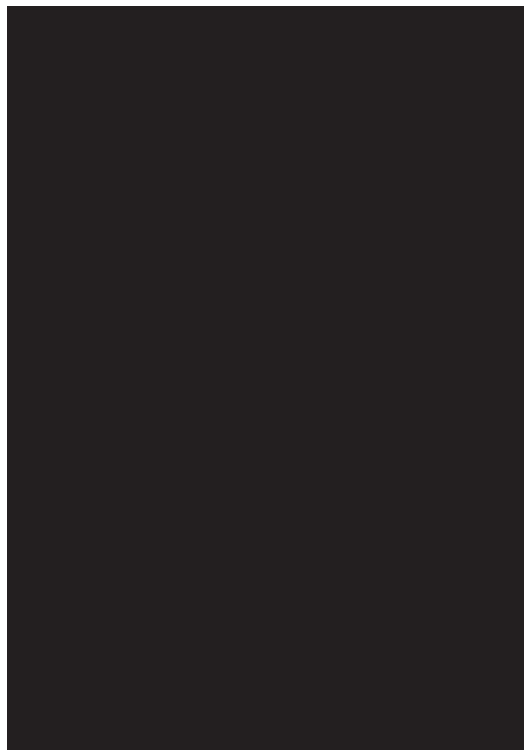
PROTOCOL TITLE: Phase 2, randomized, parallel-group, double-blind, placebo-controlled study of sonelokimab in patients with active moderate to severe hidradenitis suppurativa

Protocol Number:	M1095-HS-201
Amendment:	Version 2.1 (DE)
Approval Date:	16 August 2022
Sponsor:	MoonLake Immunotherapeutics AG Dorfstrasse 29 6300 Zug Switzerland

Clinical Research Organization:

Sponsor Signatory:

Sponsor Medical Expert:



PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Approval Date
Original protocol	17 Dec 2021
Version 2.1 (DE)	16 Aug 2022

Version 2.1 Summary of Changes	
Reason for Change	Sections Changed
Add an ultrasound sub-study. At a subset of sites, patients who consent to the additional procedures will undergo ultrasound to assess the diameter of a draining tunnel, blood flow at a target site, draining tunnel opacity, and epidermal thickness at a target site.	Synopsis, SOA, Sections 8.1, 8.3.2, Appendix IV (added)
CRP test will be replaced with an hs-CRP test.	Synopsis, SOA, LOA, Sections 7.2.3, 11.3.7, 11.8
Add additional re-test for TB (with Medical Monitor approval) if there is a potential false-positive result.	Synopsis, SOA, Sections 9.1.2, 11.1.4
Add a DSMB to monitor safety.	Synopsis, Sections 6.3, 6.3.3, 8.1, 11.3.1.4, 11.3.12 (added)
Add information regarding the risk of hypersensitivity reactions and anaphylaxis.	Section 11.5 (added), Reference List (added) Appendix III (added)
Update statistical analyses to specify Cochran-Mantel-Haenszel test instead of Mantel-Haenszel test.	Synopsis, Sections 12.3.2.1, 12.3.3.4
Revise the text regarding sample storage for immunogenicity testing.	Section 11.6
Specify time points used for IHS4 endpoints.	Synopsis, Sections 7.2.2, 7.2.3
Correct 2-unit reduction for PGA of Skin Pain in NRS30 to a 1-unit reduction.	Synopsis, Sections 7.2.2, 12.3.3.1
Update language regarding handling of electronic data and clarify accessibility of source data/documents.	Section 15.1
Update SARS-CoV-2 testing language to state that either a PCR or antigen retest is acceptable.	Synopsis, SOA, Sections 9.1.2, 11.1.7, Appendix I
Update the descriptions of the drug product and placebo.	Sections 10.1.1, 10.1.2
Clarify that non-opioid analgesics may be taken PRN for pain.	Section 10.5.2
Add reflex testing for urinalysis.	Section 11.3.7

Version 2.1 Summary of Changes	
Reason for Change	Sections Changed
Make editorial changes to improve clarity, readability, and consistency.	Throughout

Abbreviations: CRP = C-reactive protein; DSMB = Data and Safety Monitoring Board; hs-CRP = high-sensitivity C-reactive protein; IHS4 = International Hidradenitis Suppurativa Severity Score System; LOA = List of Abbreviations; NRS = Numerical Rating Scale; PCR = polymerase chain reaction; PGA = Patient's Global Assessment; PRN = as needed; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; SOA = Schedule of Assessments; TB = tuberculosis

2 STUDY SYNOPSIS

Name of Sponsor/Company: MoonLake Immunotherapeutics AG	
Name of Product: Sonelokimab	
Name of Active Ingredient: Sonelokimab	
Title of Study: Phase 2, randomized, parallel-group, double-blind, placebo-controlled study of sonelokimab in patients with active moderate to severe hidradenitis suppurativa.	
Study Center(s): It is planned that approximately 60 centers will be initiated for this study.	
Planned Study Period: March 2022 to December 2023	Development Phase: Phase 2
Disclosure Statement: This is a randomized parallel-group, placebo-controlled study with 4 arms that is participant and investigator blinded.	
Objectives: Primary Objective: 1. To evaluate the efficacy of sonelokimab at 2 different dose levels (120 mg, 240 mg) compared with placebo in the treatment of participants with active moderate to severe hidradenitis suppurativa. Secondary Objectives: 1. To evaluate the safety and tolerability of sonelokimab at 2 different dose levels (120 mg, 240 mg) compared with placebo in the treatment of participants with active moderate to severe hidradenitis suppurativa; 2. To assess the pharmacokinetics (PK) and immunogenicity of sonelokimab at 2 different dose levels (120 mg, 240 mg) in the treatment of participants with active moderate to severe hidradenitis suppurativa.	Efficacy Endpoints: Primary Endpoint: 1. Percentage of participants achieving Hidradenitis Suppurativa Clinical Response (HiSCR) 75 at Week 12, where HiSCR75 is defined as at least a 75% reduction from baseline in abscess and inflammatory nodule (AN) count, with no increase from baseline in abscess or draining fistula count. Key Secondary Endpoints: 1. Proportion of participants achieving HiSCR50 at Week 12; 2. Change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) at Week 12; 3. Proportion of participants achieving a Dermatology Life Quality Index (DLQI) total score of ≤ 5 at Week 12; 4. Proportion of participants achieving at least 30% reduction and at least 1-unit reduction from baseline in Numerical Rating Scale (NRS) 30 in Patient's Global Assessment (PGA) of Skin Pain at Week 12 among subjects with baseline NRS ≥ 3 . Other Secondary Endpoints: 1. Proportion of participants who achieve HiSCR75 at time points other than Week 12; 2. Proportion of participants who achieve HiSCR50 at time points other than Week 12; 3. Proportion of participants who achieve HiSCR90;

	4. Proportion of participants achieving at least 30% reduction and at least 1-unit reduction from baseline in PGA of Skin Pain NRS among subjects with baseline NRS ≥ 3; 5. Proportion of participants achieving at least 30% reduction and at least 1-unit reduction from baseline in PGA of Skin Pain NRS at Week 12 among subjects with baseline NRS ≥ 3, with participants using permitted analgesic therapy for ≥ 4 days in the previous week counted as non-responders; 6. Proportion of participants achieving AN count of 0, 1, or 2; 7. Proportion of participants achieving at least 50%, 75%, 90%, and 100% reduction in total AN count (AN50, AN75, AN90, and AN100); 8. Proportion of participants achieving complete elimination of abscesses at Week 12 among those participants with abscesses at baseline; 9. Proportion of participants achieving complete elimination of draining fistulas/tunnels at Week 12 among those participants with draining fistulas/tunnels at baseline; 10. Proportion of participants achieving complete elimination of inflammatory nodules at Week 12 among participants with inflammatory nodules at baseline; 11. Proportion of participants with change of ≥ 1 score points from baseline in Patient Global Impression of Severity (PGI-S); 12. Proportion of participants reporting 'minimal symptoms' or 'absent symptoms' on the PGI-S; 13. Change from baseline in IHS4 at time points other than Week 12; 14. Change from baseline in HS-Physicians Global Assessment 6 pt. score; 15. Change from baseline in the number of abscesses; 16. Change from baseline in number of draining fistulas/tunnels; 17. Change from baseline in number of inflammatory nodules; 18. Change from baseline in Hidradenitis Suppurativa Quality of Life (HiSQOL) domain scores (symptoms, psychosocial, activities, adaptations);
	20. Change from baseline in Work Productivity and Activity Impairment (WPAI) score;

	21. Change from baseline in mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score; 22. Change from baseline in EuroQol five-dimension questionnaire (EQ-5D) Visual Analog Scale (VAS) and in EQ-5D index scores by visit over time; 23. Change from baseline in high-sensitivity C-reactive protein (hs-CRP); 24. Change from baseline in Neutrophil to Lymphocyte Ratio (NLR); 25. Proportion of participants experiencing 1 or more flares (flare is defined as $\geq 25\%$ increase in AN count with an absolute increase in AN count of ≥ 2 relative to baseline); 26. Participants achieving DLQI Total Score ≤ 1; 27. Participants achieving a DLQI Total Score of ≤ 5; 28. Participants achieving a DLQI improvement (reduction) of ≥ 4 points among participants with DLQI ≥ 4 at baseline. Safety Endpoints: 1. Incidence, relatedness, severity and seriousness of AEs; 2. Withdrawal due to AEs; 3. Clinically relevant abnormalities in vital signs (body temperature, blood pressure, heart rate, and respiration rate) and body weight; 4. Standard 12-lead electrocardiogram (ECG) intervals (RR, PR, QRS, QT, and QT intervals corrected for heart rate using Bazett's and Fridericia's formulas [QTcB and QTcF, respectively]), Clinically relevant abnormalities in ECG variables; 5. Clinically relevant abnormalities in clinical laboratory variables (hematology, biochemistry, and urinalysis). PK and Immunogenicity Endpoints: 1. PK of sonelokimab (trough levels); 2. Anti-drug antibodies (ADAs).
Study Design: This is a Phase 2 multi-center randomized, parallel-group, double-blind, placebo-controlled 2-part study evaluating the efficacy, safety, PK and immunogenicity of sonelokimab in participants with active moderate to severe hidradenitis suppurativa (HS). The study includes a dalimumab treatment as an active reference arm; however, no formal comparison of sonelokimab vs. a dalimumab is planned. At the Screening Visit, each participant will provide informed consent, be assigned a unique participant number via the Interactive Response Technology (IRT), be assessed for eligibility with the inclusion and exclusion criteria	

and perform study activities as described in the Schedule of Activities in [Table 1](#). Participants will undergo screening for up to 4 weeks before randomization to establish eligibility.

In Part A, eligible participants will be randomized (2:2:2:1) to receive either sonelokimab 120 mg or sonelokimab 240 mg, or matching placebo, or adalimumab up to Week 12. Participants randomized to adalimumab will receive 160 mg on Day 1 and 80 mg every 2 weeks up until Week 10. Randomization will be stratified by Hurley Stage status (II and III) and prior biologic use (Yes/No).

The primary efficacy analysis will be performed at Week 12, comparing each of the sonelokimab treatment groups (sonelokimab 120 mg and sonelokimab 240 mg) vs. placebo.

In Part B, participants who were initially randomized to sonelokimab 120 mg or 240 mg will continue treatment for the remainder of the study. Participants initially randomized to placebo will be re-randomized (1:1) to either sonelokimab 120 mg or 240 mg and will receive this treatment for the remainder of the study. Re-randomization will also be stratified by baseline Hurley Stage status (II and III) and prior biologic use (Yes/No at screening). Participants initially randomized to the adalimumab reference arm will be reallocated to treatment with sonelokimab 240 mg for the remainder of the study.

After the End of Treatment Visit at Week 24, all participants will be followed for safety for an additional 4 weeks, i.e., through Week 28.

On an ongoing basis, safety data will be reviewed by an independent Data and Safety Monitoring Board (DSMB; Section [11.3.12](#)).

Depending on site and participant availability a subset of participants will undergo ultrasound assessments as part of an exploratory sub-study (Section [21.4](#)).

Number of Participants:

Approximately 210 participants will be assigned to randomized treatment (60 participants in each of the 2 sonelokimab study arms, 60 participants in the placebo arm, and 30 participants in the adalimumab reference arm). Enrollment of participants currently using antibiotics will be capped at 30%. The number of participants in Hurley Stage III will be capped to 40%.

Diagnosis and Main Criteria for Inclusion/Exclusion

Inclusion criteria:

To receive randomized treatment assignment, participants must satisfy the following inclusion criteria at the Screening Visit and prior to the initiation of study treatment, unless another time is specified:

1. Participant is ≥ 18 years of age;
2. Participant has been diagnosed with HS as determined by the investigator and has a history of signs and symptoms of HS dating back at least 6 months prior to the Screening Visit;
3. Participant has a total AN count (i.e., abscesses and/or inflammatory nodules) of ≥ 5 ;
4. Participant has HS lesions present in ≥ 2 distinct anatomical areas, at least one of which must contain single or multiple fistulas (i.e., be Hurley Stage II or III);
5. Participant had an inadequate response to appropriate systemic antibiotics for treatment of HS (or demonstrated intolerance to, or had a contraindication to, systemic antibiotics for treatment of their HS), in the investigator's opinion;
6. Participant must be, in the opinion of the investigator, at both the Screening Visit and study treatment initiation, a suitable candidate for treatment with adalimumab per approved local product information. If a chest X-ray or computed tomography (CT) for tuberculosis (TB) screening is required per local guidance, the X-ray or CT must have been taken within 3 months prior to the Screening Visit;
7. If the participant is female, must be of non-childbearing potential or – if of childbearing potential, participant must agree to use highly effective methods of contraception. See Appendix II (Section [21.2](#)) for the definition of non-childbearing potential, childbearing potential and highly effective methods of contraception;
8. Women of childbearing potential (as defined in Appendix II in Section [21.2](#)) must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at screening and a negative urine pregnancy test at Week 0/Day 1 prior to the first administration of study treatment;

9. If male, participant must be willing to use a condom when sexually active with a partner of childbearing potential during the study and for 12 weeks after the last dose of study drug, unless surgically sterile;
10. Participant is considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the investigator;
11. Participant is able to understand and provide signed informed consent.

Exclusion criteria:

Participants who satisfy the following exclusion criteria at the Screening Visit or prior to study treatment initiation, unless another time is specified, must be excluded from receiving randomized treatment:

1. Participants with known hypersensitivity to sonelokimab or any of its excipients;
2. Participants with known hypersensitivity to a dalimumab or any of its excipients;
3. Participant has a draining fistula count of ≥ 20 at the Screening Visit;
4. Participant has any other active skin disease or condition that may, in the opinion of the investigator, interfere with the assessment of HS;
5. Participant who currently uses or plans to use one or more prohibited treatments specified in this protocol. Prohibited treatments and washout periods are provided in Section 10.5.1;
6. For participants enrolling in the non-antibiotic strata: use of systemic antibiotics for the treatment of HS within 28 days before initiation of study treatment;

Note: For participants enrolling in the antibiotic strata: participants enter the study under concomitant treatment with systemic antibiotics (as per protocol) on a stable dose (defined as a dose or dose regimen that has not changed in the previous 28 days before baseline and is considered unlikely to change at least for the first 12 weeks during the study).

7. Participants with previous exposure or participation in a study of brodalumab (anti-IL-17RA) and/or bimekizumab (anti-IL17 A/F);
8. Participant who is unsuitable for interleukin (IL)-17A therapy according to the investigator's discretion (e.g., documented primary non-responder to previous therapy with secukinumab and/or ixekizumab);
9. Participant who is unsuitable for anti-tumor necrosis factor alpha (TNF α) therapy according to the investigator's discretion (e.g., documented primary non-responder to previous anti-TNF α therapy);
10. Prior exposure to more than 2 biologic response modifiers;
11. Participant has a diagnosis of ulcerative colitis or Crohn's disease;
12. Participant has an active infection or history of infections including any of the following:
 - a. Any infection (exception: common cold) requiring systemic treatment within 14 days before initiation of study treatment;
 - b. Serious infection, defined as requiring hospitalization or intravenous anti-infectives, within 2 months before initiation of study treatment;
 - c. History of opportunistic, recurrent, or chronic infections that, in the opinion of the investigator, might cause study participation to be detrimental to the participant;
 - d. Opportunistic infections caused by uncommon pathogens (e.g., *Pneumocystis jirovicii*, *Blastomyces*, *aspergillus*, cryptococcosis), or severe infections caused by common pathogens (e.g., cytomegalovirus, severe herpes zoster e.g. multidematomal herpes zoster, herpes zoster with organ involvement, ophthalmic herpes, or recurrent herpes zoster [recurrent is defined as 2 episodes within 2 years prior to study treatment initiation]);
 - e. *Candida* infection requiring systemic therapy for ≥ 7 days in the last 12 months prior to study treatment initiation;
 - f. Previous esophageal or systemic candidiasis;
 - g. Current active candidiasis or *candida* infection within the last 3 months prior to the Screening Visit.
13. Participant with evidence of TB infection as defined by a positive QuantiFERON[®]-TB-Gold test (or interferon-gamma release assay [IGRA] equivalent) at screening unless the following criteria apply:

- a. A full TB work-up (according to local practice/guidelines) completed within 12 weeks prior to randomization establishes conclusively that the participant has no evidence of active or latent TB infection.
 - b. Participants positive for latent TB per work-up must have completed sufficient treatment according to local routine clinical practice at least 4 weeks before randomization.
- Note 1:* If a QuantiFERON®-TB-Gold test (or IGRA equivalent) at screening is indeterminate, it can be repeated once. The results of the second test are to be used. If the second QuantiFERON®-TB-Gold test is also indeterminate, the participant should be managed as for subjects with positive QuantiFERON®-TB-Gold test (or IGRA equivalent).
- Note 2:* If there is reasonable medical doubt about a potentially false-positive QuantiFERON®-TB-Gold test (or IGRA equivalent) result, the test can be repeated once after obtaining Medical Monitor approval, and the result of the second test will prevail.
14. Participant with any current nontuberculous mycobacterial (NTM) infection or any history of pulmonary NTM infection at the Screening Visit;
15. Participant has a concurrent acute or chronic viral hepatitis B or hepatitis C infection at Screening Visit
16. Evidence of human immunodeficiency virus (HIV) infection at the Screening Visit;
17. Participant tests positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection at the Screening Visit;
- Note:* A participant with an initial positive SARS-CoV-2 result may enter the study provided they are asymptomatic and a negative test (polymerase chain reaction [PCR] or antigen) has been provided prior to study treatment initiation;
18. Participant with a concurrent malignancy or a history of malignancy during the past 5 years of the Screening Visit with the following exceptions:
 - a. ≤3 successfully excised or ablated, basal cell carcinomas of the skin;
 - b. One squamous cell carcinoma of the skin not worse than Stage T1 that has been successfully treated with no signs of recurrence or metastases for at least the past 2 years before study treatment initiation;
 - c. Actinic keratosis;
 - d. Squamous cell carcinoma in situ of the skin successfully treated >6 months before study treatment initiation;
 - e. Localized carcinoma in situ of the cervix treated and considered cured.
19. Participant has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease;
20. Participant has primary immunodeficiencies, prior splenectomy, or suppressive conditions, including participants taking immunosuppressive therapy following organ transplants;
21. Participant has had major surgery (e.g., hip replacement, aneurysm removal) within 6 months before the Screening Visit or is planning to have major surgery during the study;
22. Participant has history or concurrent clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition, that in the opinion of the investigator would compromise the safety or interfere with the participant's participation in the study, would make the participant an unsuitable candidate to receive study drug, or would put the participant at risk;
23. Participant has received live (including a attenuated) vaccination within 8 weeks before study treatment initiation or planned during the study and up to at least 12 weeks after the last dose of study drug. Examples of restricted vaccinations include, but are not limited to:
 - a. Zoster (Zostavax®);
 - b. Measles-mumps-rubella or measles-mumps-rubella-varicella;
 - c. Monovalent live attenuated influenza A (intranasal);
 - d. Oral polio;
 - e. Rotavirus;

- f. Seasonal trivalent live attenuated influenza (intranasal);
 - g. Smallpox;
 - h. Oral typhoid;
 - i. Varicella (chickenpox);
 - j. Yellow fever.
24. Participant has received Bacillus Calmette-Guérin vaccination within 1 year before study treatment initiation;
25. [REDACTED]
26. [REDACTED]
27. Participant has severe cardiovascular comorbidities including history of myocardial infarction, unstable angina pectoris, stroke or heart failure (New York Heart Association [NYHA] III or IV), or uncontrolled hypertension (characterized by 2 blood pressure measurements separated by at least 15 min with systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg);
28. Participants with clinically significant electrocardiogram (ECG) abnormalities on centrally read ECG at the Screening Visit;
29. Participant with laboratory abnormalities at the Screening Visit, including any of the following:
- a. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) $>3 \times$ upper limit of normal (ULN);
 - b. Serum direct bilirubin >1.5 ULN (in the absence of known Gilbert syndrome);
 - c. White blood cell count $<3 \times 10^9/L$;
 - d. Absolute neutrophil count (ANC) $<1.5 \times 10^9/L$;
 - e. Absolute lymphocyte count $<0.7 \times 10^9/L$;
 - f. Platelet count $<100 \times 10^9/L$;
 - g. Hemoglobin <85 g/L;
 - h. Creatinine clearance <60 mL/min (by Cockcroft Gault formula);
 - i. Any other laboratory abnormality which, in the opinion of the investigator, might compromise participant's safety, prevent the participant from completing the study or would interfere with the interpretation of the study results.
- Note:* An initial laboratory result may be re-tested one time after consultation with the Medical Monitor. The result of the second test will then be used.
30. Participant is enrolled in another interventional investigational study for a device or drug or has been so enrolled in the last 28 days prior to the Screening Visit or within 5 half-lives of the investigational study drug prior to the Screening Visit, whichever is longer;
31. Participant is pregnant or breastfeeding or plans to become pregnant while enrolled in the study and up to 12 weeks after the last dose of study drug;
32. Participant has a history of chronic alcohol or drug abuse in the past year prior to the Screening Visit;
33. Participant is an employee, or direct relative of an employee, of the sponsor, at a study site, or of a third-party organization involved in the study.

Test Product, Dose and Mode of Administration:

Sonelokimab will be presented as a prefilled syringe as sterile solution for subcutaneous (SC) injection.

Depending on the randomized treatment arm, participants in the sonelokimab treatment arms will receive either:

- Arm 1: sonelokimab 120 mg at Weeks 0, 2, 4, 6, 8, followed by injections every 4 weeks through Week 20; at Weeks 10, 14, and 18 participants will receive placebo injections to maintain the blind;
- Arm 2: sonelokimab 240 mg at Weeks 0, 2, 4, 6, 8, followed by injections every 4 weeks through Week 20; at Weeks 10, 14, and 18 participants will receive placebo injections to maintain the blind.

Reference Therapy, Dose and Mode of Administration:

Depending on the randomized treatment arm, participants in the placebo or a dalimumab arms will receive either:

- Arm 3: sonelokimab-matching placebo will be given as SC injection through Week 12, with injections at Week 0, 2, 4, 6, 8, and 10.
 - Sonelokimab-matching placebo will be presented as a prefilled syringe as sterile solution for SC injection.
 - At the beginning of Part B at Week 12, participants in the placebo group will be re-randomized to one of the following 2 groups:
 - Sonelokimab 120 mg at Weeks 12, 14, 16, 18, and 20;
 - Sonelokimab 240 mg at Weeks 12, 14, 16, 18, and 20.
- Arm 4: a dalimumab will be given as 160 mg at Week 0, followed by 80 mg once every 2 weeks; at Weeks 2, 4, 6, 8, and 10.
 - Adalimumab will be presented as a prefilled syringe as sterile solution for SC injection.
 - At the beginning of Part B at Week 12, participants in the a dalimumab reference arm will be reallocated to receive sonelokimab 240 mg treatment for the remainder of the study at Weeks 12, 14, 16, 18, and 20.

Duration of Treatment:

The planned study duration for individual participants will be up to 32 weeks, including a screening period of up to 4-weeks, 24-week treatment period, and a 4-week Safety Follow-up period.

Statistical Methods and Sample Size Calculation:

A sample size of n=60 participants in each of the sonelokimab 120 mg, sonelokimab 240 mg, and placebo groups, therefore 180 participants in total, results in a power of more than 80%, while assuming an overall 2-sided alpha of 0.05 and a difference in HiSCR75 response rate of 25% between placebo and sonelokimab 120 mg and of 35% between placebo and sonelokimab 240 mg. An additional 30 participants will be randomized in the adalimumab group. The adalimumab treatment will be used as active reference arm, however, no formal direct comparison of sonelokimab or placebo vs. a dalimumab is planned. Eligible participants will be randomized in a 2:2:2:1 ratio to sonelokimab 120 mg, sonelokimab 240 mg, placebo, or adalimumab, respectively. The number of participants in Hurley Stage III and currently using antibiotics will be capped to 40% and 30%, respectively. Due to the use of the full analysis set with non-responder imputation, no accounting for dropout is required, therefore a total of approximately 210 participants will be randomized.

Analysis Sets:

For Part A analysis, the following analysis sets are defined: The safety analysis set (SAF) will include all randomized participants who received at least one dose of study drug. The full analysis set (FAS) will include all randomized participants. The per-protocol set (PPS) will include all participants in the FAS who had no major protocol deviations during the Part A, as confirmed during a data review meeting prior to database lock.

For Part B analysis, the following populations are defined: The safety analysis set for the Part B (SAF-B) will include all randomized participants who received at least one dose of study drug during the Part B. The full analysis set for the Part B (FAS-B) set will include all randomized participants who are assigned for the Part B. Further analysis sets may be defined in the Statistical Analysis Plan (SAP).

Efficacy Analyses:

For the primary analysis of the primary endpoint, the hypotheses to be tested are that the proportion of participants who achieve an HiSCR75 response rate at Week 12 in the sonelokimab 120 mg and sonelokimab 240 mg groups

are different from placebo group. The statistical methods that will be used to test these hypotheses will be a pairwise (placebo and either sonelokimab 120 mg or sonelokimab 240 mg) stratified (Hurley Stage II and III and prior biologic use [Yes/No]) Cochran-Mantel-Haenszel test. Results will be presented in terms of odds ratios, 95% confidence intervals (CIs) and estimated p-value. To adjust for multiple testing and to control the family-wise error rate, the Bonferroni-Holm method will be applied.

For the key secondary endpoints, the hypotheses to be tested are that the mean change from baseline to Week 12 in IHS4 and the proportion of participants who achieve the following endpoints (HiSCR50; DLQI total score ≤ 5 ; achieving at least 30% reduction and at least 1-unit reduction from baseline in PGA of Skin Pain NRS30 among participants with baseline NRS ≥ 3) at Week 12 in the sonelokimab 120 mg and sonelokimab 240 mg groups are different from placebo group. The statistical methods that will be used to test these hypotheses will be the same as described for the primary endpoint for dichotomous variables and mixed model for continuous variables (change from baseline). To adjust for multiple testing and to control the family-wise error rate, a serial gatekeeping testing strategy will be used.

The primary analysis of both primary and key secondary endpoints will be performed for FAS and PPS. FAS will be considered primary, and PPS will be considered supportive. As a sensitivity analysis for both endpoints, an exact logistic regression model will be applied for FAS.

For other secondary and exploratory endpoints, no confirmatory statistical testing will be performed, but statistical tests may be used only for exploratory purposes. Serum concentration data may be used for other analyses (e.g., population PK modeling), which will be reported separately. FAS will be used for secondary and exploratory endpoints analysis, as applicable.

For the dichotomous primary and key secondary endpoints non-responder imputation method will be used. For other dichotomous endpoints, a non-responder imputation method accounting for visits missed due to coronavirus disease 2019 (COVID-19) will be done and details will be defined in the SAP. For continuous endpoints, no imputation is planned.

Immunological Analysis:

Serum immunogenicity (ADA) data for sonelokimab will be listed and summarized using descriptive statistics. Further analysis may be defined in SAP.

Pharmacokinetic Analyses:

Serum concentration data for sonelokimab will be listed and summarized using descriptive statistics. Further analysis may be defined in SAP.

Safety Analyses:

Safety analyses will be done separately for the Part A and Part B. Safety data will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints. Adverse events (AEs) will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). SAF will be used for safety analysis.

Date of the Protocol: 16 Aug 2022

3 SCHEDULE OF ASSESSMENTS

The Schedule of Assessments (SOA) is presented in [Table 1](#).

Table 1 Schedule of Assessments

Period	Screening ^a	Part A										Part B					Follow-up
Scheduled Week	-	0	2	4	6	8	10	12*	14	16	18	20	24 EOT	28			
Scheduled Day	-28 Day to -1 Day	1	15	29	43	57	71	85	99	113	127	141	169	8W after last dose ^b			
Visit Window (days)	-		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±7			
Informed consent	X																
Eligibility criteria	X	X ^c															
Demography	X																
Relevant medical history / current medical condition	X																
HS medical history and previous HS therapies	X																
Drug and alcohol history	X																
Smoking history	X																
AE/SAE evaluation ^d	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication review ^e	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HisQOL		X		X				X		X			X				
FACIT-F		X		X				X		X			X				
EQ-5-D		X		X				X		X			X				
WPAI		X						X					X				
DLQI		X		X		X		X		X		X	X		X	X	
PGI-S		X		X				X		X			X		X	X	
Complete daily in eDiary																	
PGA of Skin Pain NRS and analgesics use ^f																	

Period	Screening ^a	Part A								Part B					Follow-up
Scheduled Week	-	0	2	4	6	8	10	12*	14	16	18	20	24 EOT	28	
Scheduled Day	-28 Day to -1 Day	1	15	29	43	57	71	85	99	113	127	141	169	8 W after last dose ^b	
Visit Window (days)	-		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±7	
Lesion count (inflammatory nodules, abscesses and draining fistulas/tunnels, scars) including Hurley Stage ^g	X	X	X	X		X		X	X	X		X	X		
HS-Physician's Global Assessment	X	X		X		X		X		X		X	X		
12-lead ECG	X							X					X	X	
Height	X														
Weight	X	X						X					X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Complete physical exam	X							X					X	X	
Serum/Urine pregnancy test ^h	X	X		X		X		X		X		X	X		
FSH ⁱ	X														
TB screening ^j	X														
HIV screening	X														
Hepatitis B and hepatitis C screening	X														
SARS-CoV-2 PCR virus testing ^k	X														
Safety laboratory testing (hematology, clinical chemistry including hs-CRP, urinalysis)	X	X	X	X		X		X	X	X		X	X	X	
ESR	X	X	X	X		X		X	X	X		X	X	X	
Fasting lipid panel and glucose		X											X		
ADA sampling ^l		X	X	X		X		X		X		X	X	X	
PK sampling ^l		X	X	X		X		X		X		X	X	X	
Randomization ^m		X													
Sub-study ultrasound assessment ⁿ		X						X					X		

Period	Screening ^a	Part A										Part B				Follow-up
Scheduled Week	-	0	2	4	6	8	10	12*	14	16	18	20	24 EOT			28
Scheduled Day	-28 Day to -1 Day	1	15	29	43	57	71	85	99	113	127	141	169			8W after last dose ^b
Visit Window (days)	-		±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2			±7
Study treatment administration ^o		X	X	X	X	X	X	X	X	X	X	X				

Abbreviations: ADA = anti-drug antibody; AE = adverse event; DLQI = Dermatology Life Quality Index; [REDACTED]
ECG = electrocardiogram; EOT = End of Treatment; EQ-5D = EuroQol 5-dimension questionnaire visual analog scale; ESR = erythrocyte sedimentation rate; FACIT-F = mean Functional Assessment of Chronic Illness Therapy-Fatigue; FSH = follicle-stimulating hormone; HS = hidradenitis suppurativa; HiSQoL = Hidradenitis Suppurativa Quality of Life; HIV = human immunodeficiency virus; hs-CRP = High-sensitivity C-reactive protein; IGRA = interferon-gamma release assay; MP = investigational medicinal product; NRS = numerical rating scale; PCR = polymerase chain reaction; PGA = Patient's Global Assessment of Skin Pain; PGI-S = Patient Global Impression of Severity; [REDACTED]
[REDACTED] PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; TB = tuberculosis; W = week; WPAL = Work Productivity and Activity Impairment

*Assessments at Week 12 are final assessments of Part A. Treatment at Week 12 is the first treatment of Part B.

- The screening period is a minimum of 7 days to allow for pre-treatment patient diary completion. Screening is a maximum of 28 days, including any repeat assessments that may be required.
- Participants who discontinue treatment prematurely are required to complete the EOT Visit immediately and the Safety Follow-up Visit 8 weeks after the administration of the final dose.
- Recheck inclusion and exclusion criteria prior to randomization.
- AEs /SAEs occurring after the participants have provided informed consent will be reported until Safety Follow-up.
- While all concomitant medications are recorded on the electronic case report form (eCRF), participants will record their daily analgesics use on the electronic diary (eDiary). Patients should be instructed to start collecting this information as soon as they receive the patient diary.
- Each participant will receive a device upon which to complete the daily eDiary. From screening through to Week 24, participants will complete the eDiary daily for skin pain and analgesics use.
- Assessment of individual lesions e.g. abscesses, inflammatory nodules, number of active draining tunnels, including Hurley Stage.
- To be conducted in women of childbearing potential only (as defined in Appendix II in Section 2.1.2). Serum pregnancy test at screening to confirm study eligibility (central lab); local urine pregnancy tests at Week 0 and every 4 weeks thereafter.
- To be conducted only in female participants considered to be of non-childbearing potential due to being postmenopausal (as defined in Appendix II in Section 2.1.2), unless they are >55 years of age with amenorrhea for at least 12 months without an alternative medical cause, to verify that FSH levels are >40 IU/L (see Appendix II in Section 2.1.2). Women of childbearing potential (as defined in Appendix II in Section 2.1.2) and women >55 years of age with amenorrhea for at least 12 months without an alternative medical cause are not required to have FSH levels determined.
- Quantiferon[®]-TB-Gold test (or IGRA equivalent) will be performed. A re-test is performed if the first is indeterminate; the result of the second test will then be used. If the results of both tests are indeterminate, the participant is considered a screen failure and to be excluded. A re-test can be performed if there is reasonable medical doubt about a potentially false-positive result after obtaining Medical Monitor approval; the result of the second test will prevail. If a chest X-ray or computed tomography (CT) for TB screening is required per local guidance, the X-ray or CT must have been taken within 3 months prior to the Screening Visit.

- k. PCR test for SARS-CoV-2 infection at screening may be performed by the central laboratory, or if sample collection is not possible at site due to local procedures, a test may be obtained at a suitable laboratory as long as evidence is provided and retained as source data. Local test must be between 2 days prior or 3 days post-Screening Visit. If a participant tests positive for SARS-CoV-2 infection at screening, another PCR or antigen test may be performed within the screening window. If the repeat test is negative and the participant is asymptomatic, they may enter the study.
- l. For visit where study treatment is administered the ADA, PK, [REDACTED] samples should be collected pre-dose.
- m. Participants in Arm 3 (placebo) will be re-randomized automatically at Week 12. The investigator does not need to perform any action for re-randomization.
- n. For participants taking part in the ultrasound sub-study (Section 21.4) only.
- o. Study treatment is to be administered after all other scheduled activities have been completed, in particular, after all blood samples have been collected.

4 TABLE OF CONTENTS

1	GENERAL INFORMATION.....	3
2	STUDY SYNOPSIS	6
3	SCHEDULE OF ASSESSMENTS	15
4	TABLE OF CONTENTS	19
4.1	List of Tables.....	25
4.2	List of Figures	25
5	LIST OF ABBREVIATIONS AND DEFINITION OF TERMS	26
6	INTRODUCTION	30
6.1	Background.....	30
6.1.1	Hidradenitis Suppurativa.....	30
6.1.2	Sonelokimab.....	31
6.2	Study Rationale	32
	6.3.2 Risks of Adalimumab.....	33
	6.3.3 Overall Benefit – Risk Conclusion.....	34
7	STUDY OBJECTIVES, ENDPOINTS	35
7.1	Objectives	35
7.1.1	Primary Objectives	35
7.1.2	Secondary Objectives.....	35
7.1.3	Exploratory Objective	35
7.2	Efficacy Endpoints.....	35
7.2.1	Primary Endpoints and/or Estimands	35
7.2.2	Key Secondary Endpoints and/or Estimands	36
7.2.3	Other Secondary Endpoints and/or Estimands	37
7.2.4	Safety Endpoints.....	38
7.2.5	PK and Immunogenicity Endpoints.....	38
7.2.6	Exploratory Endpoints.....	38
8	OVERALL STUDY DESIGN AND PLAN	39
8.1	Study Design Description.....	39
8.2	Start of Study Definition.....	40
8.3	Visits.....	40
8.3.1	Screening Visit.....	40

	8.3.2	Randomization and Visits During the Treatment Period.....	41
	8.3.3	End of Treatment Visit	42
	8.3.4	Safety Follow-up Visit.....	42
	8.4	End of Study Definition	43
	8.5	Study Treatment After the End of Study	43
	8.6	Rescheduling Visits	43
	8.7	Unscheduled Visits.....	43
	8.8	Protocol Deviations	44
	8.9	Rationale for the Study Design and Selection of Dose.....	44
9		STUDY POPULATION.....	46
	9.1	Eligibility Criteria.....	46
	9.1.1	Inclusion Criteria.....	46
	9.1.2	Exclusion Criteria.....	47
	9.2	Screen Failures.....	51
	9.3	Strategies for Recruitment and Retention.....	51
	9.4	Study Treatment Discontinuation	52
	9.5	Safety Follow-up After Treatment Discontinuation.....	54
	9.6	Withdrawal of Participants.....	54
	9.7	Lost to Follow-up	55
	9.7.1	Discontinuation of Study Sites.....	55
	9.8	Discontinuation of Study.....	55
10		STUDY TREATMENT	56
	10.1	Administration of Study Treatment(s).....	56
	10.1.1	Sonelokimab.....	57
	10.1.2	Placebo	57
	10.1.3	Adalimumab.....	58
	10.2	Study Treatment Packaging and Labeling.....	59
	10.2.1	Packaging.....	59
	10.2.2	Labeling.....	59
	10.3	Study Treatment Accountability	59
	10.4	Missed Doses	60
	10.5	Prior and Concomitant Medications.....	60
	10.5.1	Prohibited Medications and Therapies.....	60
	10.5.2	Permitted Concomitant Therapy.....	62
	10.5.3	Protocol-Allowed Intralesional Interventions	63

10.6	Blinding and Randomization of Study Treatment(s).....	64
10.6.1	Part A.....	64
10.6.2	Part B.....	65
10.6.3	Maintenance of Blinding.....	65
10.7	Procedure for Breaking the Randomization Code.....	65
11	STUDY ASSESSMENTS AND PROCEDURES.....	67
11.1	Screening Assessments	67
11.1.1	Medical History.....	67
11.1.2	HS Medical History and Prior HS Medications.....	67
11.1.3	Demographics.....	67
11.1.4	QuantiFERON®-TB-Gold Testing.....	67
11.1.5	Hepatitis B and Hepatitis C	68
11.1.6	Human Immunodeficiency Virus Testing.....	68
11.1.7	SARS-CoV-2 Testing.....	69
11.1.8	Height and Weight.....	69
11.2	Efficacy Assessments.....	69
11.2.1	Physician Assessments	69
11.2.1.1	Individual Lesion Count.....	69
11.2.1.2	Hurley Stage.....	70
11.2.1.3	Hidradenitis Suppurativa Physician's Global Assessment	71
11.2.2	Derived Efficacy Endpoints.....	72
11.2.2.1	Hidradenitis Suppurativa Clinical Response	72
11.2.2.2	International Hidradenitis Suppurativa Severity Scoring System.....	72
11.2.3	Patient Reported Outcomes.....	73
11.2.3.1	Hidradenitis Suppurativa Quality of Life (HiSQOL) Score	73
11.2.3.3	FACIT-Fatigue.....	73
11.2.3.4	European Quality of Life 5 Dimensions Questionnaire-3-Level.....	74
11.2.3.5	Work Productivity and Activity Impairment Questionnaire (WPAI).....	74
11.2.3.6	Dermatology Life Quality Index.....	74
11.2.3.7	Patient's Global Assessment of Skin Pain	74
11.2.3.8	Patient Global Impression-Severity of Illness (PGI-S).....	75
11.3	Safety Assessments.....	75

11.3.1	Definitions.....	75
11.3.1.1	Adverse Events.....	75
11.3.1.2	Events Meeting the Adverse Event Definition.....	75
11.3.1.3	Events NOT Meeting the Adverse Event Definition.....	76
11.3.1.4	Serious Adverse Event.....	76
11.3.1.5	Treatment-Emergent Adverse Event.....	77
11.3.1.7	Pregnancy.....	78
11.3.1.8	Deaths.....	78
11.3.2	Time Period and Frequency for Collecting AE and SAE Information.....	78
11.3.3	Method of Detecting Adverse Events and Serious Adverse Events	79
11.3.4	Recording of Adverse Events and Serious Adverse Events.....	79
11.3.4.1	Assessment of Intensity.....	79
11.3.4.2	Assessment of Causality.....	80
11.3.4.3	Other Data to Be Recorded for Adverse Events.....	80
11.3.5	Follow-up of Adverse Events/Serious Adverse Events.....	81
11.3.6	Reporting of Serious Adverse Events.....	81
11.3.6.1	Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators.....	81
11.3.6.2	24/7 Medical Emergency Coverage for Urgent Protocol-related Medical Questions.....	82
11.3.7	Laboratory Assessments	82
11.3.8	Electrocardiogram Assessments.....	83
11.3.9	Physical Examination.....	83
11.3.10	Vital Signs.....	84
11.3.12	Data and Safety Monitoring Board.....	85
11.4	Overdose.....	85
11.5	Hypersensitivity Reactions and Anaphylaxis.....	86
11.6	Immunogenicity Assessments	86
11.7	Pharmacokinetics.....	86

12	STATISTICAL CONSIDERATIONS	88
12.1	Sample Size and Power.....	88
12.2	Populations for Analysis	88
12.2.1	Participant Disposition.....	89
12.3	Statistical Analyses.....	90
12.3.1	General Statistical Considerations.....	90
12.3.2	Primary Endpoints.....	91
12.3.2.1	Primary Analysis.....	91
12.3.2.2	Type I Error Control.....	91
12.3.2.3	Sensitivity Analysis.....	91
12.3.3	Secondary Endpoints.....	92
12.3.3.1	Key Secondary Endpoints.....	92
12.3.3.2	Type I Error Control.....	92
12.3.3.3	Sensitivity Analysis.....	93
12.3.3.4	Other Secondary Endpoints.....	93
12.3.3.5	Part B Analysis.....	94
12.3.4	Exploratory Endpoints.....	94
12.3.5	Safety Analyses.....	94
12.3.5.1	Adverse Events.....	94
12.3.5.2	Other Safety Endpoints.....	95
12.3.6	Subgroup Analyses	95
12.4	Handling of Missing Data	96
12.5	Primary Analysis Timing.....	96
13	ETHICS	97
13.1	Independent Ethics Committee/Institutional Review Board	97
13.2	Written Informed Consent.....	97
14	QUALITY CONTROL AND QUALITY ASSURANCE	98
14.1	Conduct of the Study	98
14.2	Site Monitoring.....	98
15	DATA HANDLING AND RECORD KEEPING	100
15.1	Case Report Forms/Source Data Handling.....	100
15.2	Data Protection.....	100
15.3	Dissemination of Clinical Study Data.....	101
15.4	Retention of Essential Documents.....	101

16	FINANCING AND INSURANCE.....	102
16.1	Contractual and Financial Details.....	102
16.2	Insurance, Indemnity, and Compensation.....	102
16.3	Financial Disclosure	102
18	CONFLICT OF INTEREST POLICY	104
19	SIGNATURE OF INVESTIGATOR.....	105
20	REFERENCE LIST	106
21	APPENDICES	110
21.1	Appendix I SARS-CoV-2 (COVID-19) Guidance	110
21.2	Appendix II Childbearing Potential and Contraception.....	111
21.3	Appendix III Clinical Criteria for Diagnosing Anaphylaxis	113
21.4	Appendix IV Ultrasound Sub-study.....	115

4.1 List of Tables

Table 1	Schedule of Assessments.....	15
Table 3	Prohibited Medications and Therapies and Washout Periods Prior to Initiating Study Treatment.....	61
Table 4	Hidradenitis Suppurativa Physician's Global Assessment Scale.....	72
Table 5	Definition of Causality Terms for Adverse Events.....	80
Table 6	Clinical Laboratory Tests.....	83
Table 7	Part A Populations for Analysis.....	89
Table 8	Part B Populations for Analysis	89

4.2 List of Figures

Figure 1	Study Design.....	40
Figure 2	Interpretation and Management of HBV Serologic Test Results.....	68

5 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AN	Abscess and inflammatory nodule
ANC	Absolute neutrophils
AST	Aspartate aminotransferase
BMI	Body mass index
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for AEs
DBL	Database lock
DLQI	Dermatology Life Quality Index
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOT	End of Treatment
EQ-5D	EuroQol five-dimension questionnaire
ESR	Erythrocyte sedimentation rate
EudraCT	European Union Drug Regulatory Agency Clinical Trial
FAS	Full analysis set
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase

GMP	Good Manufacturing Practices
HBV	Hepatitis B virus
HCV	Hepatitis C virus
hCG	Human chorionic gonadotropin
HiSCR	Hidradenitis Suppurativa Clinical Response
HiSQOL	Hidradenitis Suppurativa Quality of Life
HIV	Human immunodeficiency virus
HS	Hidradenitis suppurativa
hs-CRP	High-sensitivity C-reactive protein
IB	Investigator's brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGRA	Interferon-gamma release assay
IHS4	International Hidradenitis Suppurativa Severity Score System
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAK	Janus Kinase
mAB	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minute
MMRM	Mixed model repeated measures
NLR	Neutrophil to Lymphocyte Ratio
NRS	Numerical Rating Scale
NTM	Nontuberculous mycobacterial
NYHA	New York Heart Association
PASI100	Psoriasis Area and Severity Index 100
PCR	Polymerase chain reaction
PGA	Patient's Global Assessment
PGI-S	Patient Global Impression of Severity

PK	Pharmacokinetic
PPS	Per-protocol set
PRN	As needed
PRO	Patient Reported Outcomes
PT	Preferred term
PUVA	Psoralen plus ultraviolet A
PVSS	Pharmacovigilance and Safety Services
QTc	Heart rate corrected QT interval
QTcB	QTc corrected according to Bazett's formula
QTcF	QTc corrected according to the Fridericia formula
RA	Reallocation
RBC	Red blood cells
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Subcutaneous
SD	Standard deviation
SIB	Suicidal ideation and behavior
SOA	Schedule of Assessments
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TNF α	Tumor necrosis factor-alpha
Th	T helper cells
ULN	Upper limit of normal
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual Analog Scale

WBC	White blood cells
WOCBP	Women of childbearing potential
WPAI	Work Productivity and Activity Impairment

6 INTRODUCTION

6.1 Background

6.1.1 Hidradenitis Suppurativa

Hidradenitis suppurativa (HS) is a chronic, inflammatory, recurrent debilitating skin disease that usually presents in early adulthood. Predisposing risk factors include family history, with ~34% of first-degree relatives affected¹, in addition to smoking and obesity². HS manifests as painful inflammatory skin lesions in the axillary, inguinal, gluteal, and perianal regions and is characterized by inflammatory nodules and abscesses complicated by the formation of pus-discharging dermal tunnels, also known as sinus tracts or fistulas^{2,3}. Dermal tunnels are a unique morphologic feature of HS, recognized as a source of inflammation and an active mediator of disease pathogenesis⁴. Clinically, tunnels cause significant pain and morbidity for patients, and are predictors of poor prognosis and a more aggressive disease course⁴.

Over time, chronic, uncontrolled, and inadequately treated inflammation results in irreversible tissue destruction and scarring, which is not susceptible to medical therapy^{2,5}. Severe scarring is associated with further debilitating complications, including contractures, limitations in limb mobility, and lymphedema^{2,6}. Once fibrotic architectural changes occur, surgery is the only recommended therapeutic option to reduce the volume of fibrotic tissue and symptom burden; however, recurrence rates following surgery are significant^{7,8,9}. Therefore, targeting the inflammatory phase of HS and reducing inflammatory lesion burden should be a core element of disease management to prevent irreversible tissue destruction and debilitation².

The high symptom burden of HS (chronic pain, large amounts of purulent secretions, malodor, and fatigue) has a profound impact on patient quality of life and contributes to a significant deterioration in physical and mental health^{10,11}. People with HS suffer from greater pain and associated psychologic comorbidities, including depression, anxiety, disability, and impairments in quality of life, compared with those with other dermatologic conditions¹².

Management of HS requires a multifaceted approach, which may include lifestyle modifications, pain management, topical therapies (antibiotics, antiseptics, and intralesional corticosteroids), systemic therapies (antibiotics, retinoids, and biologics), and invasive surgical treatments (incision and drainage of active lesions, deroofting procedures, and radical excision)^{13,14}. The only approved biologic treatment option for patients with moderate to severe HS is the anti-tumor necrosis factor (TNF) inhibitor adalimumab (Humira®), with Hidradenitis Suppurativa Clinical Response (HiSCR) 50 response rates over placebo of approximately 16% (41.8% adalimumab [N=153] vs. 26% placebo [N=154]) and 31% (58.9% adalimumab [N=163] vs. 27.6% placebo [N=163]) reported at Week 12 in the PIONEER I and II studies, respectively¹⁵. Clinical response, defined as an at least 50% improvement in inflammatory lesion count, in only 50–60% of patients indicates

significant unmet medical need for new, more efficacious therapies with a favorable safety profile and alternative mechanisms of action¹⁶.

There is increasing scientific evidence to support interleukin (IL)-17-mediated inflammation as a key driver of the pathogenesis of HS. Upregulation of IL-17A and IL-17F mRNA in lesional tissue and elevated serum IL-17 levels in patients with HS support this hypothesis^{17,18,19}. IL-17-producing T helper cells have been shown to distinctly infiltrate lesional dermis²⁰, with an enrichment of IL-17-producing cells found in the lesional and perilesional skin of patients with HS compared with healthy controls²¹. IL-17+ CD4 T cells were shown to be enriched by more than 40-fold in HS-involved skin compared with normal skin, while the ratio was approximately 2-fold for psoriasis²². HS dermal tunnels were shown to be in part dependent upon IL-17 signaling, with elevated levels of IL-17A and IL-17F mRNA observed. In addition, tunnel diameter and drainage were significantly decreased in patients treated with the IL-17RA antagonist brodalumab⁴. Targeted inhibition of IL-17A and IL-17F-mediated inflammation has shown potential to improve the signs and symptoms of HS. In a Phase 2a study in patients with HS (N=88), a monoclonal antibody (mAB) that binds IL-17A and IL-17F (thereby also blocking IL-17A, IL-17F and IL-17A/F), bimekizumab, showed a HiSCR75 response rate over placebo of approximately 39% (50% bimekizumab [n/N=20/40] vs. 11% placebo [n/N=2/18])²³. These results outline the opportunity for targeted inhibition of IL-17A- and IL-17F-mediated inflammation to reach a greater threshold of clinical response for patients with HS

6.1.2 Sonelokimab

Sonelokimab is a tri-specific nanobody that selectively inhibits IL-17A and IL-17F. The central moiety binds to serum albumin to extend the half-life *in vivo*. Sonelokimab is expressed in the yeast *Pichia pastoris* and is composed of 378 amino acids with a predicted molecular weight of 40.1 kDa; it is therefore around a quarter of the size of conventional monoclonal antibodies (150 kDa).



In Phase 1 (M1095-PSO-101) and Phase 2 (M1095-PSO-201) studies, in patients with moderate to severe plaque-type psoriasis, sonelokimab demonstrated a rapid improvement with considerable numbers of patients achieving high levels of clinical response with no unexpected safety findings^{28,29}. In the Phase 1 (M1095-PSO-101) in patients who received sonelokimab a decrease to normal skin levels was observed in the expression of several disease related genes encoding key markers such as IL-17A, IL-17F, IL-8, CCL20 and keratin-16²⁸.

6.2 Study Rationale

The aim of the present study is to assess the efficacy, safety, pharmacokinetics and immunogenicity of 2 doses (120 mg and 240 mg) of sonelokimab in patients with moderate to severe HS.



6.3.2 Risks of Adalimumab

The active reference therapy in this clinical study is adalimumab a TNF-alpha (TNF α) blocker approved by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) and indicated for a variety of immune-related disorders in adult and pediatric patients, including reducing signs and symptoms in adult patients with HS. The most common

adverse reactions (>10%) are upper respiratory infection, headache, rash, and sinusitis. Warnings and precautions include serious infections including TB, malignancies, hypersensitivity reactions, hepatitis B reactivation, neurologic reactions, hematological reactions, heart failure, increased risk of infection when used with other TNF α blockers, and autoimmunity.

6.3.3 Overall Benefit – Risk Conclusion

Patients with HS have high symptom burden (chronic pain, large amounts of purulent secretions, malodor and fatigue) which has a profound impact on patient quality of life and contributes to a significant deterioration in physical and mental health. Although sonelokimab has not been studied in patients with HS, studies have been conducted in healthy volunteers and patients with psoriasis and has been well tolerated and safe in these populations. Preliminary clinical evidence indicates that blockade of IL-17A and IL-17F has the potential to induce high levels of clinical response in patients with HS.

The study has been designed to minimize potential risks to participants. All subjects will undergo screening procedures aimed at reducing the likelihood and impact of any such risks. In addition, regular safety monitoring during the treatment period for all subjects will ensure that any unanticipated effects of study participation are identified promptly and managed appropriately. In addition, safety data will be reviewed on an ongoing basis by an independent DSMB (Section [11.3.12](#)).

Based on the current knowledge, the benefit-risk evaluation for patients participating in this clinical study with sonelokimab is considered acceptable.

7 STUDY OBJECTIVES, ENDPOINTS

7.1 Objectives

7.1.1 Primary Objectives

To evaluate the efficacy of sonelokimab at 2 different dose levels (120 mg, 240 mg) compared with placebo in the treatment of participants with active moderate to severe HS.

7.1.2 Secondary Objectives

- To evaluate the safety and tolerability of sonelokimab at 2 different dose levels (120 mg, 240 mg) compared with placebo in the treatment of participants with active moderate to severe HS.
- To assess the pharmacokinetic (PK) and immunogenicity of sonelokimab at 2 different dose levels (120 mg, 240 mg) in the treatment of participants with active moderate to severe HS.

7.2 Efficacy Endpoints

7.2.1 Primary Endpoints and/or Estimands

The attributes of the primary estimand are as follows:

- Target population: adults diagnosed with HS as determined by the investigator and with a history of signs and symptoms of HS dating back at least 6 months prior to the Screening Visit;
- Treatment: sonelokimab at 2 different doses: sonelokimab 120 mg or sonelokimab 240 mg;
- Primary endpoint: Percentage of participants achieving HiSCR75 at Week 12, where HiSCR75 is defined as at least a 75% reduction from baseline in abscess and inflammatory nodule (AN) count, with no increase from baseline in abscess or draining fistula count;
- Intercurrent events: intercurrent events include the following:
 - Use of prohibited concomitant medication (Section 10.5): subjects will be analyzed as a treatment failure after taking prohibited medication, i.e., non-responder imputation will be performed after the first episode of prohibited medication for all future assessments (composite strategy);
 - Withdrawal from treatment due to any reason (Section 9.6): subjects will be considered non-responders to treatment if they discontinue the study prior to the Week 12 Visit due to any reason (composite strategy);

- Study drug non-adherence (missing doses) or drug administration error: subjects will be analyzed the same if the event occurs or not (treatment policy strategy).
- Population level summary: the primary estimator will be the improvement compared to placebo over the 12-week Part A based on HiSCR75.

7.2.2 Key Secondary Endpoints and/or Estimands

The attributes of the key secondary estimand are as follows:

- Target population: adults diagnosed with HS as determined by the investigator and with a history of signs and symptoms of HS dating back at least 6 months prior to the Screening Visit;
- Treatment: sonelokimab at 2 different doses: sonelokimab 120 mg or sonelokimab 240 mg;
- Key secondary endpoint: The secondary endpoints are as follows:
 1. Proportion of participants achieving HiSCR50 at Week 12;
 2. Change from baseline in International Hidradenitis Suppurativa Severity Score System (IHS4) at Week 12, where the IHS4 severity score is defined as: $(\text{number of inflammatory nodules} \times 1) + (\text{number of abscesses} \times 2) + (\text{number of draining tunnels} \times 4)$;
 3. Proportion of participants achieving a Dermatology Life Quality Index (DLQI) total score of ≤ 5 at Week 12;
 4. Proportion of participants achieving at least 30% reduction and at least 1-unit reduction from baseline in Patient's Global Assessment (PGA) of Skin Pain Numerical Rating Scale (NRS) 30 at Week 12 among subjects with baseline NRS ≥ 3 .
- Intercurrent events: intercurrent events include the following:
 - Use of prohibited concomitant medication (Section 10.5): subjects will be analyzed as a treatment failure after taking prohibited medication, i.e., non-responder imputation will be performed after the first episode of prohibited medication for all future assessments (composite strategy);
 - Withdrawal from treatment due to any reason (Section 9.6): subjects will be considered non-responders to treatment if they discontinue the study prior to the Week 12 Visit due to any reason (composite strategy);
 - Study drug non-adherence (missing doses) or drug administration error: subjects will be analyzed the same if the event occurs or not (treatment policy strategy).

- Population level summary: the primary estimator will be the improvement compared to placebo over the 12-week Part A based on the endpoint of interest.

7.2.3 Other Secondary Endpoints and/or Estimands

1. Proportion of participants who achieve HiSCR75 at time points other than Week 12;
2. Proportion of participants who achieve HiSCR50 at time points other than Week 12;
3. Proportion of participants who achieve HiSCR90;
4. Proportion of participants achieving at least 30% reduction and at least 1-unit reduction from baseline in PGA of Skin Pain NRS among subjects with baseline NRS ≥ 3 ;
5. Proportion of participants achieving at least 30% reduction and at least 1-unit reduction from baseline in PGA of Skin Pain NRS at Week 12 among subjects with baseline NRS ≥ 3 , with participants using permitted analgesic therapy for ≥ 4 days in the previous week counted as non-responders;
6. Proportion of participants achieving AN count of 0, 1, or 2;
7. Proportion of participants achieving at least 50%, 75%, 90%, and 100% reduction in total AN count (AN50, AN75, AN90, and AN100);
8. Proportion of participants achieving complete elimination of abscesses at Week 12 among those participants with abscesses at baseline;
9. Proportion of participants achieving complete elimination of draining fistulas/tunnels at Week 12 among those participants with draining fistulas/tunnels at baseline;
10. Proportion of participants achieving complete elimination of inflammatory nodules at Week 12 among participants with inflammatory nodules at baseline;
11. Proportion of participants with change of ≥ 1 score points from baseline in Patient Global Impression of Severity (PGI-S);
12. Proportion of participants reporting 'minimal symptoms' or 'absent symptoms' on the PGI-S;
13. Change from baseline in IHS4 at time points other than Week 12;
14. Change from baseline in HS-Physicians Global Assessment 6 pt. score;
15. Change from baseline in the number of abscesses;
16. Change from baseline in number of draining fistulas/tunnels;
17. Change from baseline in number of inflammatory nodules;
18. Change from baseline in Hidradenitis Suppurativa Quality of Life (HiSQOL) domain scores (symptoms, psychosocial, activities, adaptations);

- 
20. Change from baseline in Work Productivity and Activity Impairment (WPAI) score;
 21. Change from baseline in mean Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score;
 22. Change from baseline in EuroQol five-dimension questionnaire (EQ-5D) Visual Analog Scale (VAS) and in EQ-5D index scores by visit over time;
 23. Change from baseline in high-sensitivity C-reactive protein (hs-CRP);
 24. Change from baseline in Neutrophil to Lymphocyte Ratio (NLR);
 25. Proportion of participants experiencing 1 or more flares (defined as $\geq 25\%$ increase in AN count with an absolute increase in AN count of ≥ 2 relative to baseline);
 26. Participants achieving DLQI Total Score ≤ 1 ;
 27. Participants achieving a DLQI Total Score of ≤ 5 ;
 28. Participants achieving a DLQI improvement (reduction) of ≥ 4 points among participants with DLQI ≥ 4 at baseline.

7.2.4 Safety Endpoints

1. Incidence, relatedness, severity, and seriousness of AEs;
2. Withdrawal due to AEs;
3. Clinically relevant abnormalities in vital signs (body temperature, blood pressure, heart rate, and respiration rate) and body weight;
4. Standard 12-lead electrocardiogram (ECG) intervals (RR, PR, QRS, QT, and QT intervals corrected for heart rate using Bazett's and Fridericia's formulas [QTcB and QTcF, respectively]), Clinically relevant abnormalities in ECG variables;
5. Clinically relevant abnormalities in clinical laboratory variables (hematology, biochemistry, and urinalysis).

7.2.5 PK and Immunogenicity Endpoints

1. PK of sonelokimab (trough levels);
 2. ADAs.
- 

8 OVERALL STUDY DESIGN AND PLAN

8.1 Study Design Description

This is a Phase 2, randomized, parallel-group, double-blind, placebo-controlled study of sonelokimab in participants with active moderate to severe HS (Figure 1). It will be conducted in approximately 60 centers in 9 countries. The study includes a screening period of up to 28 days, a 24-week treatment period and a 4-week Safety Follow-up period. This study also has an active reference arm of adalimumab treatment; however, no formal comparison of sonelokimab vs. adalimumab is planned. The treatment period will be divided into 2 parts:

On the first day of Part A (Day 1) eligible participants will be randomized (2:2:2:1) to 1 of 4 treatment arms:

- Arm 1: sonelokimab 120 mg;
- Arm 2: sonelokimab 240 mg;
- Arm 3: placebo;
- Arm 4: adalimumab;
 - Participants in the adalimumab arm will receive 160 mg adalimumab at Day 1 and then 80 mg every 2 weeks from Week 2 until Week 10.

Randomization will be stratified by Hurley Stage status (II and III) and prior biologic use (Yes/No).

At the beginning of Part B, at Week 12, participants initially randomized to placebo will be re-randomized (1:1) to sonelokimab 120 mg or 240 mg, and they will continue with this treatment through Week 20. Re-randomization of Arm 3 will also be stratified by baseline Hurley Stage status (II and III) and prior biologic use (Yes/No).

At the beginning of Part B, at Week 12, participants in the adalimumab arm will be reallocated to receive 240 mg sonelokimab and will continue this treatment through Week 20.

The final dose of study treatment is scheduled to occur at Week 20. An End of Treatment (EOT) Visit will be performed at Week 24. A Safety Follow-up Visit will be performed 8 weeks after the administration of the final dose of study treatment.

On an ongoing basis, safety data will be reviewed by an independent DSMB (Section 11.3.12).

A subset of participants at selected sites will undergo exploratory ultrasound assessment as part of a sub-study (Section 21.4) to evaluate the effect of sonelokimab at 2 different dose levels (120 mg, 240 mg) compared with placebo on target active draining tunnels and epidermal thickness.

Figure 1 Study Design



Abbreviations: EOT = End of Treatment; q4w = once every 4 weeks; R = randomization; RA = reallocation

- a The last dose is scheduled to occur at Week 20. The EOT Visit is scheduled to occur at Week 24. The Safety Follow-up Visit is to occur 8 weeks after the last dose is administered. The total duration of the Safety Follow-up period is 4 weeks.
- a At the beginning of Part A at Day 1, all eligible participants will be randomized 2:2:2:1 to 1 of 4 arms and stratified by baseline Hurley Stage status (II and III) and prior biologic use (Yes/No).
- b At the beginning of Part B at Week 12, participants initially randomized to placebo (Arm 3) will be re-randomized 1:1 to either sonelokimab 120 mg or 240 mg and stratified by Hurley Stage status (II and III) and prior biologic use (Yes/No) at screening.
- c Participants initially randomized to adalimumab (Arm 4) will be reallocated to receive 240 mg sonelokimab and will continue this treatment through Week 20.

8.2 Start of Study Definition

The start of the study is defined as the date the first participant provides informed consent.

8.3 Visits

Participants are to adhere to the visit schedule as described in the SOA in Section 3, Table 1. Each visit date (with its window) is to be counted from Day 1.

8.3.1 Screening Visit

At the Screening Visit, each participant will first provide informed consent. A participant is considered to be enrolled in the study immediately after they provide informed consent.

The participant will then be assigned a unique participant number via the Interactive Response Technology (IRT), be assessed for eligibility with the inclusion and exclusion criteria, and perform study activities as described in the SOA in Section 3, [Table 1](#).

Screening begins immediately after the participant provides informed consent and must be completed within 28 days; i.e., all results of assessments, including laboratory results must be available to evaluate a participant's eligibility against the inclusion criteria (Section [9.1.1](#)) and exclusion criteria (Section [9.1.2](#)) within 28 days of signing informed consent. The screening period will be a minimum of 7 days to allow for pre-treatment patient diary completion.

A participant who does not fulfill the criteria for participation in this study is considered a screen failure (Section [9.2](#)) and is to be registered as such within the IRT. Screen failures are not to be re-screened. An initial laboratory result obtained at the Screening Visit may be re-tested one time prior to the randomization after consultation with the Medical Monitor. The result of the second test will then be used to assess a participant's eligibility as indicated in Section [9.1](#).

Each participant will receive a device upon which to complete the daily eDiary and the PGA of Skin Pain.

8.3.2 Randomization and Visits During the Treatment Period

After eligibility is confirmed, randomization via IRT will be performed at the Day 1 Visit. Once randomized treatment is assigned to a participant, the study activities as described in the SOA in Section 3, [Table 1](#) are to be performed. The treatment period is planned to continue for 24 weeks.

At each scheduled study visit, study procedures and activities are to be performed as listed in the SOA in Section 3, [Table 1](#).

The following patient reported outcomes (PROs) are to be completed by the participant on their own in a quiet area/room before blood draws and other visit assessments, and, if possible, before any interaction with the investigator or other members of the study team. The recommended order of completion for PROs (at relevant visits according to the SOA in Section 3, [Table 1](#)) will be as follows:

1. HiSQOL Score;
2. Functional Assessment of Chronic Illness Therapy for Fatigue (FACIT-Fatigue);
3. European Quality of Life 5 Dimensions Questionnaire-3-Level;
4. Work Productivity and Activity Impairment Questionnaire (WPAI);
5. Dermatology Life Quality Index (DLQI);
6. Patient Global Impression- Severity of Illness (PGI-S);

The PGA of Skin Pain will be measured daily using the eDiary. At each visit the investigator or designee will remind the participant to complete the daily eDiary.

Measurement of vital signs, physical examinations, evaluation of AEs, review of concomitant medications, all blood draws, and disease assessments administered by the investigator or qualified designee will also be performed.

Disease assessments performed by the investigator or a qualified designee are as follows:

1. For participants in the ultrasound sub-study, ultrasound activities are scheduled for Week 0, Week 12, and Week 24/EOT (Section 21.4). Ultrasound parameters are to be collected before drug administration.
2. Lesion count;
3. Hurley Stage;
4. HS-Physician's Global Assessment.

The administration of study treatment must be the final activity at study visits.

The order of activities at visits presented above is recommended. However, it is required that the collection of blood samples for ADA, ██████████ PK, and safety laboratory testing are performed after the participant completed the PRO assessments and before the administration of study treatment. Additionally, for participants in the ultrasound sub-study, ultrasound measurements are to be made before the clinical assessment of lesions and before drug administration.

The final dose administration is scheduled for Week 20.

8.3.3 End of Treatment Visit

An EOT Visit will be performed at Week 24 or at withdrawal. The activities to be performed at the EOT are listed in the SOA in Section 3, Table 1.

8.3.4 Safety Follow-up Visit

All participants are to attend a Safety Follow-up Visit, 8 weeks after the administration of the final dose of study treatment.

If the participant no longer wants to take part in the study (i.e., discontinue the study and/or withdraw consent), they will attend the EOT Visit as described in the SOA in Section 3, Table 1, and be discontinued from the study. Every reasonable effort will be made to have discontinued participants attend the Safety Follow-up Visit 8 weeks after the last dose of study treatment.

8.4 End of Study Definition

A participant is considered to have completed the study if they have completed all parts of the study, including the post-treatment Safety Follow-up period, which concludes with the Safety Follow-up Visit 8 weeks after the administration of the last dose of study treatment.

The end of the study is defined as the date of the last visit for the last participant in the study globally.

8.5 Study Treatment After the End of Study

No additional study treatment will be available after completion of the study or early discontinuation. After study completion, or after completion of the EOT Visit, participants are to be treated as per the local standard of care.

8.6 Rescheduling Visits

If any visit has to be rescheduled, subsequent visits will follow the original visit date schedule. Visits can take place on the scheduled day ± 2 days. If a visit is unavoidably delayed outside of this window, it may be rescheduled up to Day +7 after approval by the Medical Monitor.

If a visit cannot take place by Day +7 then the visit should be skipped and the dose from the missed visit will not be administered. The participant is to proceed to the next scheduled visit. For further information on missed doses, see Section 10.4.

The activities performed at the rescheduled visit are to be those activities scheduled for the visit that was delayed, including the administration of any study treatment, as applicable.

Doses of study treatment are to be administered at least 7 days apart. Thus, care will be taken to avoid scheduling a visit within 7 days of the previous or next scheduled dose.

Additional unscheduled visits for the purpose of re-testing of laboratory parameters or safety monitoring may be included as deemed necessary by the investigator.

8.7 Unscheduled Visits

An unscheduled visit is defined as any visit to the investigator site outside of the protocol-specified time points due to safety reasons or when a repeated measurement is required (e.g., obvious measurement errors, confirmation of out-of-range results), where the participant is seen by study personnel.

All unscheduled visits and assessments performed during the visits will be recorded in the participant's electronic case report form (eCRF). During any unscheduled visits the investigator or qualified designee will record any AEs and concomitant medications as well as performing any assessments or collecting samples deemed necessary at the discretion of the investigator.

8.8 Protocol Deviations

All deviations from planned study procedures are to be recorded. Protocol deviations will be reviewed as part of the ongoing data cleaning process.

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, are not permitted.

If there are restrictions to the clinical study as a result of the coronavirus disease 2019 (COVID-19) pandemic, it may be necessary to adjust the visit schedule, convert in-person visits to telephone contacts, and postpone study procedures until the next available study visit. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

8.9 Rationale for the Study Design and Selection of Dose

The double-blind, randomized, parallel-group, placebo-controlled design will enable evaluation of the effectiveness and safety of 2 sonelokimab doses in an adequate and well-controlled setting.

The primary and secondary endpoints reflect the most important outcome domains in HS, as prioritized by participants and healthcare professionals³⁰.

The primary endpoint will be HiSCR75. This builds on the validated HiSCR50 outcome assessment^{15,31}, raising the threshold to at least 75% reduction in total AN count with no increase in abscess or draining tunnel count relative to baseline. In recognition of the profound burden of HS from a patient's perspective, a broad range of patient reported secondary outcomes such as pain, HS-specific quality of life, fatigue, and work productivity will be assessed at scheduled timepoints throughout the study.

The primary endpoint will be evaluated at Week 12, after which point all participants will have the opportunity to receive active treatment with sonelokimab. Given the severely debilitating nature of HS, the study design will further minimize the risk to participants who are randomized to placebo by allowing inclusion of participants receiving a stable systemic antibiotic therapy and by allowing limited intralesional intervention in the case of a problematic lesion.

The study population will consist of a representative group of adult male and female participants (aged ≥ 18 years) with moderate to severe HS (a total AN count [i.e., abscesses and/or inflammatory nodules] of ≥ 5 and HS lesions present in ≥ 2 distinct anatomical areas at least one of which must contain single or multiple fistulas [i.e., be Hurley Stage II or III]). The study will be international with multiple sites in North America and Europe and aims to randomize approximately 210 participants with moderate to severe HS.

It is expected that the majority of participants entering the study will have previously received topical and systemic antibiotics during the previous course of their disease. To align with regional clinical practice habits, the study will allow a proportion of participants to remain on a stable dose of systemic antibiotics during the study. The number of study participants taking a stable dose of antibiotics will be capped at 30% of all participants enrolled. It is expected that participants who had an inadequate response to or who are intolerant to systemic antibiotics will enter the study without need for chronic use and will be included in a non-antibiotic stratum. Information on the previous use of systemic therapies will be collected at baseline.

The sonelokimab doses selected for the study (120 mg and 240 mg) are based on safety and observed response in previous clinical studies of sonelokimab in healthy volunteers and patients with psoriasis. In a Phase 1 study (M1095-PSO-101) in 41 participants with cutaneous psoriasis, a significant improvement in Psoriasis Area and Severity Index 100 (PASI100) score in all 4 cohorts of subjects who received 30 mg, 60 mg, 120 mg, or 240 mg sonelokimab, compared with the placebo group was observed. All doses were well tolerated.

In a subsequent Phase 2 study (M1095-PSO-201) in 313 participants with cutaneous psoriasis, sonelokimab 120 mg demonstrated a greater clinical response (PASI100) at Week 24 compared with sonelokimab 60 mg, with no unexpected safety findings observed.

In addition to the 120 mg dose, the second dose 240 mg every 4 weeks will be evaluated.

As outlined below, the available nonclinical observations and clinical data from other targeted antibody therapies indicate that a higher dose than that typically licensed for psoriasis may be required for participants with HS to achieve optimal efficacy:

- IL-17+CD4 T cells were shown to be enriched more than 40-fold in HS-involved skin compared with normal skin, while the ratio was approximately 2-fold for psoriasis²².
- The presence of deep dermal morphologies that are unique to HS (e.g., tunnels with a strong IL-17 inflammatory signature) may necessitate higher local exposure compared with psoriasis¹⁷.
- Previous clinical experience with adalimumab in participants with HS supports a dosing regimen involving higher exposure than PSO^{15,33}.
- Based on baseline characteristics described in previous clinical studies, enrolled participants with HS are expected to have a higher mean body mass index (BMI) compared with the psoriasis population^{15,23,34,35}, potentially necessitating higher doses to achieve adequate exposure.
- Based on these data the doses proposed for evaluation in this study are 120 mg and 240 mg 2 weekly to Week 8 and then every 4 weeks.

9 STUDY POPULATION

9.1 Eligibility Criteria

9.1.1 Inclusion Criteria

To receive randomized treatment assignment, participants must satisfy the following inclusion criteria at the Screening Visit and prior to the initiation of study treatment, unless another time is specified:

1. Participant is ≥ 18 years of age;
2. Participant has been diagnosed with HS as determined by the investigator and has a history of signs and symptoms of HS dating back at least 6 months prior to the Screening Visit;
3. Participant has a total AN count (i.e., abscesses and/or inflammatory nodules) of ≥ 5 ;
4. Participant has HS lesions present in ≥ 2 distinct anatomical areas at least one of which must contain single or multiple fistulas (i.e., be Hurley Stage II or III);
5. Participant had an inadequate response to appropriate systemic antibiotics for treatment of HS (or demonstrated intolerance to, or had a contraindication to, systemic antibiotics for treatment of their HS), in the investigator's opinion;
6. Participants must be, in the opinion of the investigator, at both the Screening Visit and study treatment initiation, a suitable candidate for treatment with adalimumab per approved local product information. If a chest X-ray or computed tomography (CT) for tuberculosis (TB) screening is required per local guidance, the X-ray or CT must have been taken within 3 months prior to the Screening Visit;
7. If the participant is female, must be of non-childbearing potential or – if of childbearing potential, participant must agree to use highly effective methods of contraception. See Appendix II (Section 21.2) for the definition of non-childbearing potential, childbearing potential and highly effective methods of contraception;
8. Women of childbearing potential (as defined in Appendix II in Section 21.2) must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at screening and a negative urine pregnancy test at Week 0/Day1 prior to the first administration of study treatment;
9. If male, participant must be willing to use a condom when sexually active with a partner of childbearing potential during the study and for 12 weeks after the last dose of study drug, unless surgically sterile;
10. Participant is considered reliable and capable of adhering to the protocol, visit schedule, or medication intake according to the judgment of the investigator;

11. Participant is able to understand and provide signed informed consent.

9.1.2 Exclusion Criteria

Participants who satisfy the following exclusion criteria at the Screening Visit or prior to study treatment initiation, unless another time is specified, must be excluded from receiving randomized treatment:

1. Participants with known hypersensitivity to sonelokimab or any of its excipients;
2. Participants with known hypersensitivity to adalimumab or any of its excipients;
3. Participant has a draining fistula count of ≥ 20 at the Screening Visit;
4. Participant has any other active skin disease or condition that may, in the opinion of the investigator, interfere with the assessment of HS;
5. Participant who currently use or plan used one or more prohibited treatments specified in this protocol. Prohibited treatments and washout periods are provided in Section 10.5.1;
6. For participants enrolling in the non-antibiotic strata: use of systemic antibiotics for the treatment of HS within 28 days before initiation of study treatment;

Note: For participants enrolling in the antibiotic strata: participants enter the study under concomitant treatment with systemic antibiotics (as per protocol) on a stable dose (defined as a dose or dose regimen that has not changed in the previous 28 days before baseline and is considered unlikely to change at least for the first 12 weeks during the study);

7. Participants with previous exposure or participation in a study of brodalumab (anti-IL-17RA) and/or bimekizumab (anti-IL17 A/F);
8. Participant who is unsuitable for interleukin (IL)-17A therapy according to the investigator's discretion (e.g., documented primary non-responder to previous therapy with secukinumab and/or ixekizumab);
9. Participant who is unsuitable for anti-TNF α therapy according to the investigator's discretion (e.g., documented primary non-responder to previous anti-TNF α therapy);
10. Prior exposure to more than 2 biologic response modifiers;
11. Participant has a diagnosis of ulcerative colitis or Crohn's disease;
12. Participant has an active infection or history of infections including any of the following:
 - a. Any infection (exception: common cold) requiring systemic treatment within 14 days before initiation of study treatment;
 - b. Serious infection, defined as requiring hospitalization or intravenous anti-infectives, within 2 months before initiation of study treatment;

- c. History of opportunistic, recurrent, or chronic infections that, in the opinion of the investigator, might cause study participation to be detrimental to the participant;
- d. Opportunistic infections caused by uncommon pathogens (e.g., *Pneumocystis jirovicii*, *Blastomyces*, *aspergillus*, cryptococcosis), or severe infections caused by common pathogens (e.g., cytomegalovirus, severe herpes zoster e.g. multidermatomal herpes zoster, herpes zoster with organ involvement, ophthalmic herpes, or recurrent herpes zoster [recurrent is defined as 2 episodes within 2 years prior to study treatment initiation]);
- e. *Candida* infection requiring systemic therapy for ≥ 7 days in the last 12 months prior to study treatment initiation;
- f. Previous esophageal or systemic candidiasis;
- g. Current active candidiasis or *candida* infection within the last 3 months prior to the Screening Visit.

13. Participant with evidence of TB infection as defined by a positive QuantiFERON®-TB-Gold test (or interferon-gamma release assay [IGRA] equivalent) at screening unless the following criteria apply:

- a. A full TB work-up (according to local practice/guidelines) completed within 12 weeks prior to randomization establishes conclusively that the participant has no evidence of active or latent TB;
- b. Participants positive for latent TB per work-up must have completed sufficient treatment according to local routine clinical practice at least 4 weeks before randomization.

Note 1: If a QuantiFERON®-TB-Gold test (or IGRA equivalent) at screening is indeterminate, it can be repeated once. The results of the second test are to be used. If the second QuantiFERON®-TB-Gold test is also indeterminate, the participant should be managed as for subjects with positive QuantiFERON®-TB-Gold test (or IGRA equivalent);

Note 2: If there is reasonable medical doubt about a potentially false-positive QuantiFERON®-TB-Gold test (or IGRA equivalent) result, the test can be repeated once after obtaining Medical Monitor approval, and the result of the second test will prevail.

14. Participant with any current nontuberculous mycobacterial (NTM) infection or any history of pulmonary NTM infection at the Screening Visit;

15. Participant has a concurrent acute or chronic viral hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at the Screening Visit;

16. Evidence of human immunodeficiency virus (HIV) infection, at the Screening Visit;

17. Participant tests positive for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection at the Screening Visit;

Note: A participant with an initial positive result may enter the study provided they are asymptomatic and a negative test (polymerase chain reaction [PCR] or antigen) has been provided prior to study treatment initiation;

18. Participant with a concurrent malignancy or a history of malignancy during the past 5 years of the Screening Visit with the following exceptions:

- a. ≤ 3 successfully excised or ablated, basal cell carcinomas of the skin;
- b. One squamous cell carcinoma of the skin not worse than Stage T1 that has been successfully treated, with no signs of recurrence or metastases for at least the past 2 years before study treatment initiation;
- c. Actinic keratosis;
- d. Squamous cell carcinoma in situ of the skin successfully treated >6 months before study treatment initiation;
- e. Localized carcinoma in situ of the cervix treated and considered cured.

19. Participant has a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease;

20. Participant has primary immunodeficiencies, prior splenectomy, or suppressive conditions, including participants taking immunosuppressive therapy following organ transplants;

21. Participant has had major surgery (e.g., hip replacement, aneurysm removal) within 6 months before the Screening Visit or is planning to have major surgery during the study;

22. Participant has history or concurrent clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition, that in the opinion of the investigator would compromise the safety or interfere with the participant's participation in the study, would make the participant an unsuitable candidate to receive study drug, or would put the participant at risk;

23. Participant has received live (including attenuated) vaccination within 8 weeks before study treatment initiation or planned during the study and up to at least 12 weeks after the last dose of study drug. Examples of restricted vaccinations include, but are not limited to:

- a. Zoster (Zostavax);
- b. Measles-mumps-rubella or measles-mumps-rubella-varicella;
- c. Monovalent live attenuated influenza A (intranasal);

- d. Oral polio;
 - e. Rotavirus;
 - f. Seasonal trivalent live attenuated influenza (intranasal);
 - g. Smallpox;
 - h. Oral typhoid;
 - i. Varicella (chicken pox);
 - j. Yellow fever.
24. Participant has received Bacillus Calmette-Guérin vaccination within 1 year before study treatment initiation;
25. [REDACTED]
26. [REDACTED]
27. Participant has severe cardiovascular comorbidities including history of myocardial infarction, unstable angina pectoris, stroke or heart failure New York Heart Association (NYHA) III or IV), or uncontrolled hypertension (characterized by 2 blood pressure measurements separated by at least 15 min with systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg);
28. Participant with clinically significant ECG abnormalities on centrally read ECG at the Screening Visit;
29. Participant with laboratory abnormalities at the Screening Visit, including any of the following:
- a. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase (ALP) >3 × upper limit of normal (ULN);
 - b. Serum direct bilirubin >1.5 ULN (in the absence of known Gilbert syndrome);
 - c. White blood cell count <3 × 10⁹/L;
 - d. Absolute neutrophil count <1.5 × 10⁹/L;
 - e. Absolute lymphocyte count <0.7 × 10⁹/L;

- f. Platelet count $<100 \times 10^9/L$;
- g. Hemoglobin $<85 \text{ g/L}$;
- h. Creatinine clearance $<60 \text{ mL/min}$ (by Cockcroft Gault formula);
- i. Any other laboratory abnormality which, in the opinion of the investigator, might compromise participant's safety, prevent the participant from completing the study or would interfere with the interpretation of the study results.

Note: An initial laboratory result may be re-tested one time after consultation with the Medical Monitor. The result of the second test will then be used.

- 30. Participant is enrolled in another interventional investigational study for a device or drug or has been so enrolled in the last 28 days prior to the Screening Visit or within 5 half-lives of the investigational study drug prior to the Screening Visit, whichever is longer;
- 31. Participant is pregnant or breastfeeding or plans to become pregnant while enrolled in the study and up to 12 weeks after the last dose of study drug;
- 32. Participant has a history of chronic alcohol or drug abuse in the past year prior to the Screening Visit;
- 33. Participant is an employee, or direct relative of an employee, of the sponsor, at a study site, or of a third-party organization involved in the study.

9.2 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. 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).

Clinical laboratories performed at the Screening Visit may be repeated once if they are outside the acceptable range indicated in the exclusion criteria values (Section 9.1). The second value will be used to assess eligibility provided it is received within 28 days of the participant signing the ICF. If the second laboratory value is not received within 28 days of the participant signing the informed consent form (ICF), the participant is considered a screen failure.

Participants who do not fulfill the criteria for participation in this study are not to be re-screened.

9.3 Strategies for Recruitment and Retention

All recruitment material will be approved by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB) prior to implementation.

Regular study monitoring will enable identification of any potential issues related to participant retention.

9.4 Study Treatment Discontinuation

Participants may voluntarily discontinue study treatment for any reason at any time. If the participant no longer wants to take part in the study, they will attend a final assessment visit and be discontinued from the study. The investigator should discontinue study treatment of a given participant if, on balance, they believe that continuation would be detrimental to the participant's well-being. Unless the participant withdraws their consent to participate in the study, they should attend the post-treatment follow-up visit for 8 weeks after their last dose of study medication.

Study treatment must be discontinued under the following circumstances and the further steps need to be discussed with the Medical Monitor:

1. Withdrawal of informed consent;
2. New diagnosis (gastroenterologist confirmed) of Crohn's disease or ulcerative colitis (these events should be captured as AESIs see Section 11.3.1.6);
3. Decision of the sponsor;
4. Anaphylactic reaction or other severe systemic reaction to study drug;
5. Diagnosis of malignancy during study;
6. Evidence of pregnancy;



8. Emergence of the following:
 - AE considered related to study treatment including:

- Clinically significant systemic hypersensitivity reaction following administration of study drug that does not respond to symptomatic treatment;
- Severe (Grade 3 or higher Common Terminology Criteria for AEs [CTCAE] version 5.0) anaphylaxis (symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension);
- Severe (Grade 3 or higher CTCAE version 5.0) serum sickness (severe arthralgia or arthritis; extensive rash, with steroids or intravenous fluids indicated);
- Note that if a participant experiences symptoms consistent with a Grade 2 serum sickness (moderate arthralgia, fever, rash, or urticaria, with antihistamine treatment indicated), and causality by the study drug cannot be ruled out, the participant should return to site for an unscheduled visit. There should be a documented assessment and physical examination concurrent with the event. Grade 2 serum sickness does not require discontinuation of study treatment; however, the Medical Monitor should be informed.
- Any other severe (Grade 3 CTCAE version 5.0) event that does not resolve with supportive care;
- Any life-threatening (Grade 4 CTCAE version 5.0) event.

9. Renal function values:

- Discontinue study medication for a participant if individual serum creatinine increases $\geq 50\%$ compared to the value at screening (and is considered clinically significant), or in the event of treatment-emergent proteinuria (albumin: creatinine ratio >300 mg/g or >30 mg/mmol; protein: creatinine ratio ≥ 500 mg/g or >50 mg/mmol), unless the event is not drug-related, or if the risk/benefit assessment supports continuing study treatment. *Note:* A renal event leading to participant discontinuation should be followed up until event resolution (serum creatinine within 10% of baseline, protein-creatinine ratio within 50% of baseline), stabilizes or becomes not clinically significant, or is assessed as being chronic.

10. Liver laboratory values:

- Confirmed alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $>8 \times$ ULN, or
- Confirmed ALT or AST $>5 \times$ ULN (for more than 2 weeks), or

- Elevated transaminases (ALT or AST) $>3 \times$ ULN and associated with total bilirubin $>2 \times$ ULN (without accompanying alkaline phosphatase elevation $>2 \times$ ULN suggestive of cholestasis) – i.e., subject met Hy's Law criteria, or
- Confirmed ALT or AST $>3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($>5\%$).

11. Active TB infection;

12. Any other protocol deviation that results in a significant risk to the participant's safety;

13. Administrative decision by the investigator, the sponsor, or its designee to stop the participant's study treatment for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and Good Clinical Practice (GCP);

14. Participant non-compliance (significant violation of protocol requirements or missing 2 consecutive visits).

If a clinically significant laboratory abnormality of Grade 3 or higher is considered causally related to study treatment, study treatment will be permanently discontinued and the event must be reported as AE. In cases in which a causal relationship to study treatment can be reasonably excluded, (i.e., an alternative cause is evident), study treatment will be postponed but it may be resumed when the laboratory abnormality is sufficiently normalized (see Section 10.4). A decision to resume study treatment will be made jointly by the investigator and Medical Monitor (Medical Monitor's approval is required).

In addition to these requirements for study treatment discontinuation, the investigator will discontinue study treatment for a given participant if, on balance, continuation would be detrimental to the participant's well-being.

9.5 Safety Follow-up After Treatment Discontinuation

The investigator must determine the primary reason for the participant's premature discontinuation of study treatment and record this information in the eCRF. The participant should be requested to attend the Safety Follow-up Visit.

9.6 Withdrawal of Participants

Participants may voluntarily withdraw consent to participate in the study for any reason at any time, or may be withdrawn at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

Withdrawal of consent occurs when a participant does not want to participate in the study anymore and does not want to attend any further visits or assessments, have further study-related contact, or allow analysis of already obtained biologic material.

If a participant withdraws consent, all study participation for that participant will cease and data to be collected at subsequent visits will be considered missing. Study treatments must be discontinued and no further assessments conducted. For a participant who has withdrawn consent, the investigator should establish if consent is also withdrawn for analysis of any samples taken and not tested or for future use of samples where this was initially granted. Any withdrawal of consent to sample analysis must be recorded in the study site records and be communicated to the study monitor. If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such withdrawal of consent.

If a participant withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information in the eCRF.

For safety reasons, Week 24/EOT Visit and the Safety Follow-up Visit 8 weeks after the administration of the last dose of study treatment, as described in the SOA in Section 3, Table 1, will be conducted if the withdrawn participant is willing to undergo the assessments.

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

9.7 Lost to Follow-up

All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant. Lost to follow-up is defined by the inability to reach the participant after a minimum of 3 documented contacts (e.g., phone calls, text messages, faxes, or emails) not performed on the same day. All attempts will be documented in the participant's medical records.

9.7.1 Discontinuation of Study Sites

Study site participation may be discontinued if the sponsor or designee, the investigator or IRB/IEC of the study site judges it necessary for medical or safety reasons consistent with applicable laws, regulations, and GCP.

9.8 Discontinuation of Study

The study will be discontinued if the sponsor or designee judges it necessary for medical, safety, or business reasons consistent with applicable laws, regulation, and GCP.

10 STUDY TREATMENT

Study treatment is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to the study participant according to the study protocol. Study treatments in this current study are: sonelokimab 120 mg, sonelokimab 240 mg, adalimumab, and placebo.

Study treatments must NOT be used for any purpose other than as described in this protocol.

Only participants enrolled in the study may receive study treatment and only authorized site staff may prepare, supply, or administer study treatments.

Any study treatment that is prepared but not administered to a participant should not be re-dispensed.

10.1 Administration of Study Treatment(s)

Sonelokimab will be presented as a prefilled syringe as sterile solution for subcutaneous (SC) injection.

Depending on the randomized treatment arm, participants in the sonelokimab treatment arms will receive either:

- Arm 1: sonelokimab 120 mg at Weeks 0, 2, 4, 6, 8, followed by injections every 4 weeks through to Week 20; at Weeks 10, 14, and 18 participants will receive placebo injections to maintain the blind.
- Arm 2: sonelokimab 240 mg at Weeks 0, 2, 4, 6, 8, followed by injections every 4 weeks through to Week 20; at Weeks 10, 14, and 18 participants will receive placebo injections to maintain the blind.
- Arm 3: sonelokimab-matching placebo will be given as SC injection through Week 12, with injections at Week 0, 2, 4, 6, 8, and 10.
 - Sonelokimab-matching placebo will be presented as a prefilled syringe as sterile solution for SC injection.
 - At the beginning of Part B at Week 12, participants in the placebo group will be re-randomized to one of the following 2 groups:
 - Sonelokimab 120 mg at Weeks 12, 14, 16, 18, and 20;
 - Sonelokimab 240 mg at Weeks 12, 14, 16, 18, and 20.
- Arm 4: adalimumab will be given as 160 mg at Week 0, followed by 80 mg once every 2 weeks; at Weeks 2, 4, 6, 8, and 10.

- Adalimumab will be presented as a prefilled syringe as sterile solution for SC injection.
- At the beginning of Part B at Week 12, participants in the adalimumab reference arm will be reallocated to receive sonelokimab 240 mg treatment for the remainder of the study at Weeks 12, 14, 16, 18, and 20.

Treatments will be administered as described below and as described in the SOA in Section 3, Table 1. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits will follow the original visit date schedule.

See Section 8.6 for a discussion of rescheduling visits and Section 10.4 for a discussion of missed doses.

10.1.1 Sonelokimab



Sonelokimab will be administered by a site-approved study treatment administrator, who is unblinded (see Section 10.6 for further details). Blinded study personnel will not be in attendance while study treatment is being prepared or administered. Used syringes will be placed immediately out of sight in a sealed sharps container.

During the Treatment Phase, participants in the sonelokimab treatment arms will receive either:

- Sonelokimab 120 mg at Weeks 0, 2, 4, 6, 8, followed by injections every 4 weeks through to Week 20; at Week 10, 14, and 18 participants will receive placebo injections to maintain the blind.
- or
- Sonelokimab 240 mg at Weeks 0, 2, 4, 6, 8, followed by injections every 4 weeks through to Week 20; at Week 10, 14, and 18 participants will receive placebo injections to maintain the blind.

10.1.2 Placebo

Placebo will be identical in appearance and packaging to sonelokimab in a fixed-dose, prefilled syringe to be administered via SC injection.

As with the administration of sonelokimab, placebo will be administered by a site-approved, study treatment administrator, who is unblinded (see Section 10.6 for further details). Blinded study

personnel will not be in attendance while study treatment is being prepared or administered. Used syringes will be placed immediately out of sight in a sealed sharps container.

During the 12-week Treatment Period in Part A placebo will be given as SC injection at Week 0, 2, 4, 6, 8, and 10.

Placebo will also be administered to participants in the sonelokimab arms at Weeks 10, 14, and 18 to maintain study blinding.



10.1.3 Adalimumab

Adalimumab will be provided in prefilled syringes (40 mg) as sterile solution for SC injection. Adalimumab syringes will be relabelled and repackaged to facilitate maintenance of the study blinding.

Adalimumab will be administered by a site-approved, study treatment administrator, who is unblinded (see Section 10.6 for further details). Blinded study personnel will not be in attendance while study treatment is being prepared or administered. Used syringes will be placed immediately out of sight in a sealed sharps container.

During the 12-week Treatment Period Part A adalimumab will be given as 160 mg SC at Week 0, followed by 80 mg once every 2 weeks, at Weeks 2, 4, 6, 8, and 10 according to the approved labeling. At the beginning of Part B at Week 12, participants in the adalimumab reference arm will

be reallocated to receive sonelokimab 240 mg treatment for the remainder of the study at Weeks 12, 14, 16, 18, and 20.

10.2 Study Treatment Packaging and Labeling

10.2.1 Packaging

Sonelokimab, placebo, and adalimumab will be provided in prefilled syringes packaged in individual tamper-sealed cartons. Study treatments will be suitably packaged in such a way as to protect the product from deterioration during transport and storage. Further information regarding storage and transport conditions are provided in the pharmacy manual.

10.2.2 Labeling

Study treatment labels will comply with applicable Good Manufacturing Practices (GMP) and GCP and the legal requirements of each country. Labels will be printed in the local language they will supply no information about the participants (other than participant number).



10.3 Study Treatment Accountability

Site personnel will document the use of study drug appropriately. Compliance for all treatment groups will be reviewed by the study monitor. Study drug syringes will be disposed of immediately after administration in sealed sharps containers and cannot be checked. Accountability will be performed on the packaging cartons utilized for administration before destruction. Records shall be maintained of the delivery of study treatment(s) to the study center(s), the inventory at the study center(s), the use of each participant and the return to the sponsor or designee.

These records shall include dates, quantities, batch numbers, expiry dates, and the unique code numbers assigned to the study medication and to the study participants.

The investigator shall be responsible for ensuring that the records adequately document that the participants were provided the study treatment allocated by the IRT and that all study medication received for the study is reconciled.

10.4 Missed Doses

Dose modifications are not permitted during the study.

A dose may be delayed if a visit has to be rescheduled (see Section 8.6). A dose that cannot be rescheduled within the permitted timeframe may be missed.

If the investigator judges that at a particular visit the dose should be withheld for safety reasons (e.g., to allow for monitoring of an emerging adverse event) they should contact the Medical Monitor to discuss. All other study assessments should be completed per protocol. A dose may be withheld/missed a maximum of once within Part A and once within Part B.

10.5 Prior and Concomitant Medications

All medications taken from time of consent need to be recorded in the eCRF.

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

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

Medications that stop prior to first dose of study treatment will be considered prior medications. Those that continue or start during the treatment period will be considered concomitant.

In addition, history of use of specific medications for the treatment of HS will be captured as part of the HS medical history (see Section 11.1.1).

10.5.1 Prohibited Medications and Therapies

Medications prohibited during the study and the requisite washout period prior to initiating study treatment for prohibited medications are presented in Table 3.

Table 3 Prohibited Medications and Therapies and Washout Periods Prior to Initiating Study Treatment

Prohibited medication during study	Washout period prior to study treatment initiation
Treatment with brodalumab and/or bimekizumab	Not allowed Prior exposure to brodalumab and/or bimekizumab is prohibited
Opioid analgesics	14 days
Topical antibiotic or corticosteroid therapy for HS	14 days
Use of injectable corticosteroids for the treatment of HS, except as outlined in the Intralesional Intervention Section.	14 days
Surgical, laser, or light intervention for an HS lesion except as outlined in Intralesional Intervention Section	28 days
Systemic corticosteroids for the treatment of HS	28 days
Prior exposure to systemic non-biologic therapies for the treatment of HS, including but not limited to a premilast, methotrexate, cyclosporine, retinoids, phototherapy (e.g., psoralen plus ultraviolet A [PUVA], ultraviolet A [UVA], ultraviolet B [UVB])	28 days
Spironolactone EXCEPT: Spironolactone only permitted if indicated for non-HS related condition e.g., polycystic ovary syndrome. Participant must be on stable dose at least 28 days prior to baseline	28 days
Any investigational treatment or participation in any interventional trial	28 days or 5 half-lives whichever is longer
Systemic antibiotics for the treatment of HS (non-antibiotic stratum)	28 days
Systemic anti-TB treatment	28 days
Live (including attenuated) vaccination ^a	within 8 weeks
Other immunomodulatory biologic therapies for the treatment of HS (e.g., anakinra, natalizumab, rituximab)	12 weeks
Janus Kinase (JAK) inhibitors	12 weeks
anti-IL-17A (secukinumab and/or ixekizumab)	12 weeks or 5 half-lives whichever is longer
anti-TNF α	12 weeks or 5 half-lives whichever is longer

Prohibited medication during study	Washout period prior to study treatment initiation
Biologic agents that block IL-12/IL-23 (e.g., ustekinumab) or IL-23p19 (e.g., risankizumab, guselkumab, tildrakizumab)	6 months or 5 half-lives whichever is longer

Abbreviations: HS = hidradenitis suppurativa; IL = interleukin; TB = tuberculosis; TNF α = tumor necrosis factor- α

a See Appendix I in Section 21.1 for instructions regarding vaccinations to COVID-19.

10.5.2 Permitted Concomitant Therapy

All medications taken from time of consent need to be recorded in the eCRF.

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

- Reason for use;
- Dates of administration including start and end dates;
- Dosage information including dose and frequency.

The Medical Monitor will be contacted if there are any questions regarding previous or concomitant therapy.

The following medications are permitted if taken as defined below. The dose of any concomitant medications is to remain stable where possible until the Safety Follow-up Visit 8 weeks (± 7 days) after the administration of the last dose of study treatment:

Antibiotics:

Participants in the antibiotic stratum should be on a stable dose and regimen of doxycycline, minocycline, or an equivalent systemic tetracycline for 28 days prior to study treatment initiation. The dose and regimen should remain stable through Week 12. Antibiotics taken as needed (PRN) are not considered as a stable dose and are prohibited.

Note: The number of participants taking a stable dose of antibiotic for treatment of HS will be capped at 30% of all participants enrolled.

Over-the-counter shampoos and soaps containing antibacterial agents:

Wound care dressings: Use of wound care dressings is allowed. Permitted options include alginates, hydrocolloids, and hydrogels.

Antiseptic wash: Use of antiseptic wash on HS wounds is allowed. Permitted options include chlorhexidine gluconate, benzoyl peroxide, benzalkonium chloride, benzethonium chloride, and zinc pyrithione.

Analgesic therapy:

Participants on non-opioid analgesics for HS-related pain or non-HS-related pain may continue the analgesic, including on an as-needed (PRN) basis, provided that the average dose is stable for 14 days prior to study treatment initiation and is anticipated to remain stable on average for at least 12 weeks of treatment.

In case a participant presents with uncontrolled pain related to HS during the study, ibuprofen, or acetaminophen (paracetamol) are permitted in the following doses:

- Ibuprofen as per local labeling, but not exceeding a dose of 800 mg orally every 6 h and 3.2 g orally every 24 h);
or
- Acetaminophen (paracetamol) as per local labeling.

All analgesic use must be recorded by the participant in the eDiary and reviewed by the investigator at the scheduled visits and documented in the eCRF.

10.5.3 Protocol-Allowed Intralesional Interventions

If a particularly painful HS lesion occurs that necessitates an acute intervention, investigators will have the option to perform protocol-allowed interventions.

Two types of interventions are allowed:

1. Injection with intralesional triamcinolone acetonide suspension (at a concentration of up to 10 mg/mL);
2. Incision and drainage of the lesion. If incision and drainage is performed, antiseptic wash should be used after the intervention.

Concomitant use of wound care dressings is allowed. Do not include wound care dressing or analgesic treatment in the number of protocol-allowed interventions. For guidance on wound care dressings and analgesics see concomitant therapies Section [10.5.2](#).

New systemic and topical therapies following incision and drainage (including antibiotics) are prohibited.

A total of 2 protocol-allowed interventions per participant are permitted through Part A (Week 0 to Week 12). An intervention can occur at a maximum on 2 different lesions at the same visit OR

on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same visit.

If a participant requires more than 2 interventions within the first 12 weeks, then the participant must be discontinued from treatment.

During Part B (Week 12 to Week 24), a total of 2 protocol-allowed interventions per participant are permitted. An intervention can occur at a maximum on 2 different lesions at the same visit OR on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same visit.

All study evaluations at each visit must occur before any intervention.

Any lesion that undergoes an intervention must be documented in the eCRF.

Any lesion that undergoes an intervention is to be counted as permanently present from date of intervention and must be documented on the eCRF.

10.6 Blinding and Randomization of Study Treatment(s)

10.6.1 Part A

Initial randomization will take place on Day 1 after confirmation that the participant continues to meet the inclusion/exclusion criteria. Participants will be randomized 2:2:2:1 to 1 of 4 treatment arms, stratified by Hurley Stage II and III and exposure to biologics (Yes/No) prior to the Screening Visit as follows:

- Arm 1: 120 mg sonelokimab;
- Arm 2: 240 mg sonelokimab;
- Arm 3: placebo matching sonelokimab;
- Arm 4: adalimumab;
 - adalimumab will be given as 160 mg at Week 0, followed by 80 mg once every 2 weeks; at Weeks 2, 4, 6, 8, and 10.

The IRT will be responsible for the allocation of unique identification numbers to individual participants. Before the study is initiated, the login information and directions for the IRT (including the process for emergency unblinding) will be provided to each site, plus a backup telephone number and call-in directions.

The blind will be maintained by the use of sonelokimab and matched placebo. The prefilled syringes used for all sonelokimab and placebo doses will be identical and outer packaging will be labeled in a blinded manner with no indication of the syringe contents (sonelokimab, placebo, or adalimumab). Participants will be asked to wear an eye-mask for all injections.

10.6.2 Part B

At the beginning of Part B at Week 12, participants initially randomized to receive placebo (Arm 3) will be re-randomized 1:1 to receive either sonelokimab 120 mg or sonelokimab 240 mg. Participants who received adalimumab (Arm 4) in Part A will be reallocated to sonelokimab 240 mg in Part B. Re-randomization of Arm 3 will also be stratified by Hurley Stage and prior biologic use as designated at the beginning of Part A. Participants who were randomized to receive sonelokimab in Part A will not be re-randomized and will continue on their originally assigned study treatment throughout Part B. Re-randomization will also be conducted via the IRT system and will not require any action from the investigator or site personnel.

In Part B, the participants and investigators will remain blinded to each participant's treatment allocation. Blinding of participants and investigators will be maintained in the same manner as in Part A.

10.6.3 Maintenance of Blinding

The primary analysis of 12-week data will occur at the completion of Part A, while the study is still ongoing. All sponsor personnel will remain blinded until Week 12. No unblinded participant-level data will be supplied to the study sites until the final database lock after the conclusion of the study.

Laboratory personnel performing the bioanalytical PK sample analysis may receive an open randomization list to enable analysis of relevant samples. In addition, a PK analyst and modeling/simulation scientist may receive an open randomization list to enable preparation of modeling/simulation activities. These individuals will not interact with site or contract research organization (CRO) personnel.

10.7 Procedure for Breaking the Randomization Code

Emergency treatment code breaks should only be undertaken when it is essential to treat the participant safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. The investigator is encouraged to contact the Medical Monitor prior to code break. Emergency code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, they must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the study treatment for the specified participant and a fax or email confirming this information.



It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the participant how to contact their backup in cases of emergency when they are unavailable.

11 STUDY ASSESSMENTS AND PROCEDURES

11.1 Screening Assessments

11.1.1 Medical History

Relevant medical history should be collected at the Screening Visit including COVID vaccinations, smoking history, and drug and alcohol history.

11.1.2 HS Medical History and Prior HS Medications

Relevant HS medical history should be collected at the Screening Visit, including family history of HS, date of first symptoms, date of diagnosis, and other relevant medical history. Patient history of use of specific HS medications and HS surgeries prior to entry to the study also will be collected.

11.1.3 Demographics

Demographic information will be collected including, but not limited to, sex, race, ethnicity, and year of birth.

11.1.4 QuantiFERON®-TB-Gold Testing

QuantiFERON®-TB-Gold testing (or IGRA equivalent) will be conducted at screening to evaluate the subjects' eligibility for the study. This blood-based assay is specific for *Mycobacterium tuberculosis* and is not influenced by previous *Bacillus Calmette-Guérin* vaccination or by exposure to other mycobacterial species. The assay measures the production of interferon-gamma and presents it relative to a negative and a positive control sample. The QuantiFERON®-TB-Gold assay test will be supplied by the central laboratory. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the study Laboratory Manual.

Participants with evidence of TB infection as defined by a positive QuantiFERON®-TB-Gold test (or IGRA equivalent) at screening are excluded unless the following criteria apply:

- A full TB work-up (according to local practice/guidelines) completed within 12 weeks prior to randomization establishes conclusively that the participant has no evidence of active or latent TB. Participants with evidence for active TB are excluded;
- Participants positive for latent TB per work-up must have completed sufficient treatment according to local routine clinical practice at least 4 weeks before randomization.

If a QuantiFERON®-TB-Gold test (or IGRA equivalent) at screening is indeterminate, it can be repeated once. The results of the second test are to be used. If the second QuantiFERON®-TB-Gold test is also indeterminate, the participant should be managed as for subjects with positive QuantiFERON®-TB-Gold test (or IGRA equivalent).

If there is reasonable medical doubt about a potentially false-positive QuantiFERON®-TB-Gold test (or IGRA equivalent) result, the test can be repeated once after obtaining Medical Monitor approval, and the result of the second test will prevail.

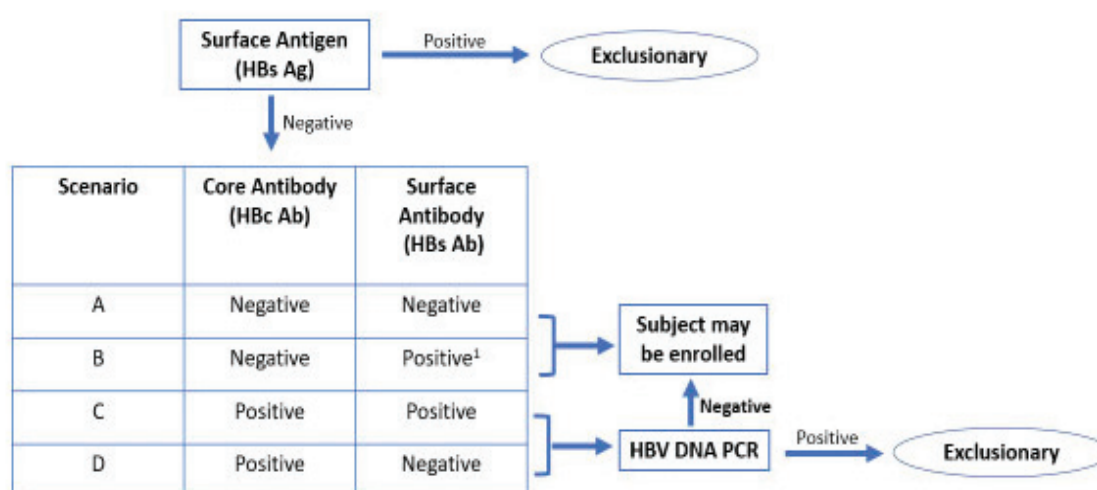
11.1.5 Hepatitis B and Hepatitis C

Participants with a known HBV or HCV infection will be excluded.

At screening, all subjects will be tested for hepatitis B and C antibodies. Participants who are HCV antibody positive (Ab+) must undergo further testing for HCV RNA by the central laboratory to be considered for enrollment. HCV RNA must be negative per the central laboratory to allow entry into the study.

Hepatitis B screening will follow the testing strategy illustrated in [Figure 2](#).

Figure 2 Interpretation and Management of HBV Serologic Test Results



Abbreviations: HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction

- 1 A positive test result for HBsAb is expected for subjects who have had a HBV vaccination. For subjects without a history of HBV vaccination (and where mandated by local requirements), a positive result for HBsAb requires HBV DNA PCR testing

11.1.6 Human Immunodeficiency Virus Testing

Subjects with a known HIV will be excluded. At screening, all subjects will be tested for HIV. Participants testing positive for HIV will be excluded from study participation.

11.1.7 SARS-CoV-2 Testing

At screening, all subjects will be tested for SARS-CoV-2 (nasopharyngeal PCR test). Participants testing positive for SARS-CoV-2 will be excluded from study participation. The screening test will be performed by the central laboratory. If sample collection for the central laboratory is not possible at sites due to local procedures, a test may be obtained at a suitable laboratory as long as evidence is provided and retained as source data. The local test must be collected between 2 days prior or 3 days post-screening visit.

If a participant tests positive for SARS-CoV-2 infection at the Screening Visit, another PCR or antigen test may be performed within the screening window. If the repeat test is negative and the participant is asymptomatic, they may enter the study.

11.1.8 Height and Weight

Height will be measured at screening. Weight will be measured at screening and at other study visits according to the SOA (Section 3, [Table 1](#)).

11.2 Efficacy Assessments

Efficacy Assessments will be conducted according to the SOA in Section 3, [Table 1](#). For assessor-rated scales, the site should make every effort for each participant to be rated by the same site personnel at each time point.

11.2.1 Physician Assessments

11.2.1.1 Individual Lesion Count

The individual lesion count will be assessed by the investigator or a qualified designee at visits as indicated in the SOA in Section 3, [Table 1](#).

The HS affected areas e.g. right and left axillary (armpit), right and left inguinal-femoral (groin), and others will be assessed by the physician for inflammatory nodules, abscesses, draining fistulas, non-draining fistulas, and other lesions.

Whenever possible, the same physician should perform the lesion count throughout the study and lesions will be counted by anatomical area. The lesion count will include any existing and newly observed lesions and will be recorded in the electronic clinical outcome assessment (eCOA) system.

Lesions:

Lesions to be assessed for each anatomical area are as follows:

1. **Inflammatory nodules:** are typically elevated, circumscribed >10 mm three-dimensional lesions, i.e., extending into the skin, that may originate in the epidermis, dermis, or subcutaneous tissue which are tender and erythematous; **non-inflammatory nodules** fulfill

the same criteria but are non- or only minimally tender and are non-erythematous. On palpation, nodules are solid lesions with no fluctuance (consider abscess).

2. **Abscesses:** are circumscribed fluctuating masses >10 mm containing a purulent fluid that may or may not exudate through an opening to the skin frequently surrounded by an erythematous area; abscesses are typically tender and painful.
3. **Draining tunnels (fistulas or sinus tracts):** are tender fluctuating longitudinal mass of variable length and depth, with communication to the skin surface draining serous or purulent fluid either spontaneously or by gentle palpation; **non-draining tunnels** may be harder to detect as they do not release fluid.
4. **Other lesions:**
 - a. Pustule; is a circumscribed, elevated lesion filled with purulent fluid, less than 1 cm in size; semi-quantitative assessment; overall lesion count: none (0), low (1), medium (2), high (3).
 - b. Papule; is a circumscribed, elevated solid lesion up to 1 cm in size; semi-quantitative assessment; overall lesion count: none (0), low (1), medium (2), high (3).
 - c. Scarring; develops frequently in participants with HS subsequent to inflammatory lesions; please semi-quantitatively capture whether scars are present in each anatomical location; physicians' assessment: absent (0), mild (1), moderate (2), severe (3).

Additional questions will be recorded per anatomical site as follows:

1. Longest distance between 2 relevant lesions (in cm) or size of lesion if single;
2. All lesions separated by normal skin (Yes/No).

The data collected from the lesion count will be used for the derivation of study efficacy variables including, but not limited to, HiSCR50/75/90, change from baseline in IHS4, and flare.

11.2.1.2 Hurley Stage

The Hurley Stage will be assessed by the investigator or a qualified designee at visits indicated in the SOA in Section 3, [Table 1](#).

The Hurley Staging system is a severity scale that assesses both current activity and past scarring, ranging from isolated abscesses in the primary stage to coalescing lesions with scarring and sinus tracts in the tertiary stage. Hurley Stage will be recorded in the eCOA.

The Hurley Stage is defined by the following criteria:

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

Hurley Stage is assigned to a given anatomic region. The overall worst Hurley Stage (i.e., the highest Hurley Stage across all anatomic regions) for a given study participant at a given visit is then the study participant-level Hurley Stage. This study participant-level Hurley Stage is important for baseline stratification and disease severity assessment.

11.2.1.3 Hidradenitis Suppurativa Physician's Global Assessment

The HS-Physician's Global Assessment (HS-PGA) will be assessed by the investigator or a qualified designee at visits indicated in the SOA in Section 3, [Table 1](#).

The HS-PGA is a validated 6-point scale that is used to measure improvement in inflammatory nodules, abscesses, and draining fistulas ([Table 4](#)). The HS-PGA scale ranges from "Clear" (no inflammatory or non-inflammatory nodules) to "Very severe" (more than 5 abscesses or draining fistulas). One global score is calculated in the eCOA following each lesion assessment. The scores will be derived on a subject-level basis (i.e., across all anatomical regions) based on the following rules in [Table 4](#).³⁶

Table 4 Hidradenitis Suppurativa Physician's Global Assessment Scale

Score	Rating	Description
0	Clear	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and 0 non-inflammatory nodule
1	Minimal	0 abscesses, 0 draining fistulas, 0 inflammatory nodules, and presence of non-inflammatory nodules
2	Mild	0 abscesses, 0 draining fistulas, and 1-4 inflammatory nodules or 1 abscess or draining fistula and 0 inflammatory nodules
3	Moderate	0 abscesses, 0 draining fistulas, and ≥ 5 inflammatory nodules or 1 abscess or draining fistula and ≥ 1 inflammatory nodules or 2 to 5 abscesses or draining fistulas and < 10 inflammatory nodules
4	Severe	2-5 abscesses or draining fistulas and ≥ 10 inflammatory nodules
5	Very Severe	> 5 abscesses or draining fistulas

11.2.2 Derived Efficacy Endpoints

11.2.2.1 Hidradenitis Suppurativa Clinical Response

HiSCR50/75/90 will be evaluated in this study. The primary component of HiSCR evaluation is the objective and uncomplicated counting of HS lesions. HiSCR is based on the principles of % reduction in total AN count with no increase in abscess or draining tunnel count relative to baseline. This builds on the validated HiSCR50 outcome assessment^{15,31}.

The HiSCR will be derived through statistical programming based on investigator documentation of the individual lesion counts, and does not require calculation on the part of the investigator.

11.2.2.2 International Hidradenitis Suppurativa Severity Scoring System

The IHS4 is a validated tool to dynamically assess HS severity³⁷. Determination of IHS4 requires counting of nodules, abscesses and draining fistulas/sinus tracts (tunnels). The IHS4 score is calculated as follows: number of nodules (multiplied by 1) plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). A total score of 3 or less signifies mild, 4 to 10 signifies moderate and 11 or higher signifies severe disease.

The IHS4 score is derived by statistical programming based on the investigator documentation of the lesion count and does not require calculation on the part of the investigator.

11.2.3 Patient Reported Outcomes

11.2.3.1 Hidradenitis Suppurativa Quality of Life (HiSQOL) Score

The HiSQOL will be self-administered by the participant at visits indicated in the SOA in Section 3, [Table 1](#).

The HiSQOL is a 17-item HS-specific health-related quality of life (HRQoL) questionnaire with a 7-day recall period. The instrument is grouped into 3 domains: symptoms, psychosocial, and functional.

11.2.3.3 FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) will be self-administered by the participant at visits indicated in the SOA in Section 3, [Table 1](#).

FACIT-Fatigue is a 13-item self-assessment of fatigue and the effect on daily activities and function over the previous 7 days. The 13 items use a 5-point Likert-type scale as follows:

- 0 = “Not at all;”
- 1 = “A little;”
- 2 = “Somewhat;”
- 3 = “Quite a bit;”
- 4 = “Very much so.”

The 13 scores are summed to create a single fatigue score and the FACIT-Fatigue assessment score range is 0 to 52.

11.2.3.4 European Quality of Life 5 Dimensions Questionnaire-3-Level

The EQ-5D will be assessed at visits indicated in the SOA in Section 3, [Table 1](#).

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

11.2.3.5 Work Productivity and Activity Impairment Questionnaire (WPAI)

The WPAI will be self-administered by the participant at visits indicated in the SOA in Section 3, [Table 1](#).

The WPAI is a 6-item questionnaire to assess the effect of health problems on ability to work and perform regular activities. Any physical or emotional problem or a symptom is considered as a health problem. The questionnaire is self-administered and includes 6 questions which need to be filled by the participant. The number of hours of actual work/missed work due health and other reasons is to be mentioned. The last 2 questions have scores of 0 (not affected) to 10 (completely prevented from work). Higher score indicates greater impact of health problems completely preventing from work.

11.2.3.6 Dermatology Life Quality Index

The DLQI questionnaire will be completed by the participant at visits indicated in the SOA in Section 3, [Table 1](#).

The DLQI is a dermatology-specific quality of life instrument designed to assess the impact of the disease on a participant's quality of life. It is a 10-item PRO questionnaire that, in addition to evaluating overall quality of life, can be used to assess 6 different aspects that may affect quality of life: symptoms and feelings, daily activities, leisure, work, or school performance, personal relationships, and treatment. The DLQI produces a numeric score that can range from 0 to 30. A higher score indicates greater health-related quality of life impairment. The measure is widely used: it has been tested across 32 different skin conditions and is available in 55 languages. The recall period is the last week, and the instrument requires 1 to 2 minutes of completion.

11.2.3.7 Patient's Global Assessment of Skin Pain

The PGA of Skin Pain NRS will be self-administered by the participant at visits indicated in the SOA in Section 3, [Table 1](#).

The PGA of Skin Pain NRS in the past 24 hours will be used to assess pain “at its worst” in the last 24 hours. Weekly averages of these daily assessments will be used in the analysis of the data. The NRS is a segmented numeric version of the VAS in which a respondent selects a whole number (0–10 integers) that best reflects the intensity of their pain ranging from 0 (no skin pain) to 10 (skin pain as bad as you can imagine). Skin Pain will be collected as specified in the assessment schedule. To assess this, the participant should concentrate on the pain that his/her HS skin lesions generate. The PGA of Skin Pain NRS will be completed by the subject using the eDiary device. The PGA of Skin Pain has minimal administrative burden.

11.2.3.8 Patient Global Impression-Severity of Illness (PGI-S)

The PGI-S will be self-administered by the participant at visits indicated in the SOA in Section 3, Table 1.

The PGI-S is a self-reported single item to evaluate all aspects of participants’ HS symptoms. Participants are asked to choose the response that best describes the severity of their HS symptoms over the past week. The question is rated on a 7-point scale ranging from 0 to 6 (0 = absent; 1 = minimal; 2 = mild; 3 = moderate; 4 = moderately severe; 5 = severe; 6 = very severe). It takes approximately 1 minute to complete the PGI-S.

11.3 Safety Assessments

The timing and frequency of safety assessments are shown in the Study SOA in Section 3, Table 1.

11.3.1 Definitions

The definition of AEs, treatment-emergent adverse events (TEAEs), AESIs, and SAEs is given below. The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, AESI, or SAE and for following up AEs throughout the study and to resolution or stabilization.

11.3.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a participant, or clinical investigation participant administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigation) product, whether or not related to the medicinal (investigational) product.

11.3.1.2 Events Meeting the Adverse Event Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after the participant has signed the consent form though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication.

11.3.1.3 Events NOT Meeting the Adverse Event Definition

- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

11.3.1.4 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that:

- Results in death. The cause of death is the AE; death is an outcome.
- Is life-threatening. The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires inpatient hospitalization or prolongs existing hospitalization. In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.
- Results in persistent or significant disability/incapacity. The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect.
- Is an important medical event. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered an SAE, when based on appropriate medical judgment, they may jeopardize the participant or the participant may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

On an ongoing basis, safety data (including SAEs) will be reviewed by an independent DSMB (Section 11.3.12). Details on the DSMB's members, roles, and procedures to ensure trial integrity will be available in the DSMB charter.

11.3.1.5 Treatment-Emergent Adverse Event

TEAEs are defined as any AE occurring or worsening on or after the first dose of study treatment.



11.3.1.7 Pregnancy

Women who become pregnant during the study must be discontinued from study medication immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even after the participant has been withdrawn from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages, ectopic pregnancy, threatened abortion, intrauterine death, and still birth should also be reported and handled as SAEs. Elective abortions without complications should not be handled as SAEs, but should be reported as a follow-up report for the pregnancy. All outcomes of pregnancy must be reported to [REDACTED] on a Pregnancy Outcomes Report Form.

Pregnancy outcomes must be collected for the female partners of any male study participants who become pregnant within 12 weeks of their partner's last dose of study treatment. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Pregnancies must be reported to [REDACTED] Pharmacovigilance and Safety Services (PVSS) within 24 hours of awareness, using the reporting details provided in Section 11.3.6.

11.3.1.8 Deaths

Any participant deaths that occur during the study should be considered SAEs and reported as per Section 11.3.6. If a death occurs, the investigator may be asked to provide a copy of any postmortem findings including histopathology.

11.3.2 Time Period and Frequency for Collecting AE and SAE Information

For the purposes of this study, any detrimental change in the participant's condition after signing the ICF and up to completion of the Safety Follow-up Visit, 8 weeks (± 7 days) after the administration of the last dose of study treatment will be considered an AE. AEs will be collected at every study visit (Section 3, Table 1). Any relevant observations made prior to the first dose of

study treatment are to be recorded on the AE eCRF but will not be considered TEAEs and will be reported separately from TEAEs.

At any time after completion of the Safety Follow-up Visit, 8 weeks (± 7 days) after the administration of the final dose of study treatment, if an investigator learns of an SAE that can be reasonably related to study treatment, they will promptly notify the sponsor.

11.3.3 Method of Detecting Adverse Events and Serious Adverse Events

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

11.3.4 Recording of Adverse Events and Serious Adverse Events

Any AE is to be recorded starting immediately after the participant provides informed consent through the end of the Safety Follow-up Period.

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

The following variables will be recorded for each AE: verbatim/AE description and date for AE start and stop, severity (refer to Section 11.3.4.1), seriousness (Section 11.3.1.4), causality rating (Section 11.3.4.2), whether or not the AE caused the participant to discontinue (Section 11.3.4.3), any other action, and the outcome. Continuous events should be recorded at the maximum severity observed.

Expedited reporting, as described in Section 11.3.6, is required for SAEs, but not required for non-serious AEs or laboratory abnormalities.

11.3.4.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and assign it to one of the following categories, and where appropriate, in accordance with the CTCAE version 5.0:

- Grade 1 (Mild): An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities.

- Grade 2 (Moderate): An event that causes sufficient discomfort and interferes with normal everyday activities.
- Grade 3 (Severe): An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- Grade 4 and Grade 5 events per CTCAE criteria are to be reported as SAEs.

An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

11.3.4.2 Assessment of Causality

The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE. The assessment will be “related,” or “not related,” as per [Table 5](#) and captured in the eCRF.

A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.

The investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. For each AE, the investigator must document in the medical notes that he/she has reviewed the AE and has provided an assessment of causality.

Table 5 Definition of Causality Terms for Adverse Events

Term	Definition
not related	Not suspected to be related to the study treatment. AE could not medically (pharmacologically/clinically) be attributed to the study treatment under study in this clinical trial protocol. A reasonable alternative explanation must be available.
related	Suspected to be related to the study treatment. AE could medically (pharmacologically/clinically) be attributed to the study treatment under study in this clinical trial protocol. In the absence of a reasonable alternative explanation a relationship to the study treatment cannot be excluded.

Abbreviations: AE = adverse event

11.3.4.3 Other Data to Be Recorded for Adverse Events

In addition to intensity and causality, the following should be recorded in the eCRF for each AE:

- Action taken with study drug due to AE;

- Other action taken;
- AE outcome.

11.3.5 Follow-up of Adverse Events/Serious Adverse Events

All ongoing AEs should be followed up for 8 weeks after the last administration of study treatment. Any ongoing study drug-related AEs, which should be followed until resolution, or stabilization. Any new SAEs occurring up to 8 weeks after the last administration of study drug should be reported to the sponsor or designee according to Section 11.3.6.

11.3.6 Reporting of Serious Adverse Events

All SAEs must be reported according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) GCP or local regulations, applying the regulation with the stricter requirements.

Within 24 hours of becoming aware of an SAE:



Initial notification via any other means than a completed SAE form does not replace the need for the investigator to provide a completed SAE report form within the designated reporting time frames.

There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always assess causality for every event before the initial transmission of the SAE data to the sponsor.

11.3.6.1 Safety Reporting to Health Authorities, Independent Ethics Committees/Institutional Review Boards and Investigators





A Suspected, Unexpected Serious Adverse Reaction (SUSAR) is a subset of SAEs. The sponsor or designee will report SUSARs to appropriate regulatory authorities, investigators, and IEC/IRBs according to local applicable laws and regulations, including European Directive 2001/20/EC, Regulation (EU) No 536/2014, and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.



On this internet page, a list of country-specific toll-free telephone numbers are provided. It should be noted that not all countries globally have access to toll-free numbers as indicated on the “24/7 Medical Help-desk” index. Countries without toll-free numbers need to dial the chargeable number as indicated above. Furthermore, there may be restrictions when dialing toll-free numbers from a mobile phone.

11.3.7 Laboratory Assessments

Unless otherwise indicated, all chemistry and hematology parameters will be analyzed using a central laboratory. The parameters will be collected as described in [Table 6](#).

Table 6 Clinical Laboratory Tests

Laboratory Testing Profile	Tests Included
Laboratory Tests Required at Screening Only	Hepatitis B serology (HBV PCR if required) including Hepatitis B surface antigen and antibody and Hepatitis B core antibody, Hepatitis C serology, HCV antibodies, confirmatory HCV PCR, HIV testing, QuantiFERON®-TB-Gold test (or equivalent IGRA), SARS-CoV-2 PCR, serum pregnancy, FSH
Blood Chemistry	Sodium, potassium, chloride, bicarbonate, total protein, blood urea nitrogen, serum creatinine, albumin, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin, calcium, GGT, creatine kinase, hs-CRP
Hematology	Hemoglobin, hematocrit, WBC with differentials (monocytes, eosinophils, basophils, neutrophils, lymphocytes) as an absolute value, RBC count, platelet count, ESR
Urinalysis	Specific gravity, pH, semi-quantitative “dipstick” evaluation of glucose, protein, bilirubin, ketones, leukocytes, blood. If the dipstick urine test is positive for protein, albumin:creatinine and protein:creatinine ratios will be determined (reflex testing). Microscopy and/or culture to be performed if clinically indicated or if urinalysis results positive (blood, protein or leukocyte esterase/WBC). Urine human chorionic gonadotropin pregnancy testing for women of childbearing potential; may be repeated more frequently than indicated if required by local practice, if a menstrual cycle is missed, or if potential pregnancy is suspected
Fasting Lipid Panel and Glucose to be performed at Day 1/Week 0 and EOT	Fasting: glucose, total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides,

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, EOT = End of Treatment; ESR = erythrocyte sedimentation rate; FSH = follicle-stimulating hormone; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; hs-CRP = high-sensitivity C-reactive protein; IGRA = interferon-gamma release assay; PCR = polymerase chain reaction; RBC = red blood cell; SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2; WBC = white blood cell

11.3.8 Electrocardiogram Assessments

Computerized 12-lead ECG recordings will be obtained at scheduled study visits after the participant has rested for at least 5 minutes in the supine position. ECG data will be submitted to a central laboratory for measurement.

11.3.9 Physical Examination

A standard complete physical examination will be performed at the weeks specified in the SOA (Section 3, Table 1). The following parameters and body systems will be examined and any abnormalities described: general appearance, skin (presence of rash), HEENT (head, ears, eyes, nose, throat), lungs (auscultation), heart (auscultation for presence of murmurs, gallops, rubs),

lower extremity exam, abdomen (palpation and auscultation), neurologic (mental status, station, gait, reflexes, motor and sensory function, coordination) and lymph nodes. Any clinically significant changes from screening should be recorded as AEs.

11.3.10 Vital Signs

Body temperature, systolic and diastolic cuff blood pressure (measured after at least 5 minutes in the supine position), heart rate (measured after at least 5 minutes in the supine position), and respiration rate will be recorded according to the SOA (Section 3, [Table 1](#)). Automatic or manual devices may be used, but the same device should be used for any given participant throughout the study. The same arm should be used for all blood pressure measurements. All devices must hold valid calibration documentation at the time of use.



11.3.12 Data and Safety Monitoring Board

An independent DSMB will be formed to review the benefit-risk profile of sonelokimab during the study and to independently safeguard the interests of study participants.

The DSMB will review selected safety and efficacy data across the study at predefined intervals. The DSMB may also be called upon ad hoc.

The DSMB will consist of at least 3 voting members and include expertise in rheumatology, dermatology, and infectious diseases. DSMB members may not participate in this trial as investigators or in any other capacity.

An experienced unblinded biostatistician will be appointed to support the DSMB process. The DSMB unblinded biostatistician will be independent from all staff involved in the evaluation of the study data reviewed by the DSMB. Unblinded data will be reviewed only in closed sessions of the DSMB that are not attended by any personnel involved in the conduct of the study or evaluation of the data

The DSMB may make recommendations to the sponsor regarding continuation, modification, or termination of the study. All recommendations of the DSMB will be made in writing, and minutes of all DSMB discussions will be kept. Minutes of closed sessions will be kept confidential until the study end.

Details on the DSMB's members, roles, and procedures to ensure trial integrity will be available in the DSMB charter.

11.4 Overdose

A drug overdose is defined as the accidental or intentional use of a drug or medicine in an amount that is higher than is normally used. Every overdose must be reported to [REDACTED] PVSS within 24 hours of awareness, using the reporting method similar to reporting SAEs as detailed in Section 11.3.6, irrespective of whether the overdose was associated with an AE/SAE.

Overdose in this study is specifically defined as any dose greater than the intended protocol dose (Section 10.1). In case of overdose, it is recommended that the participant be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment be administered immediately.

11.5 Hypersensitivity Reactions and Anaphylaxis

All protein therapeutics have the potential to be immunogenic. No anaphylactic reactions have been reported to date in patients exposed to sonelokimab and no clinically relevant ADAs have been detected.

As part of the safety monitoring strategy in this study, all sites will have immediate access to appropriate drugs and medical equipment to treat acute hypersensitivity and study personnel will be trained to recognize and treat hypersensitivity and anaphylaxis. Any potential cases of anaphylaxis will be defined and assessed using the criteria defined in the Second Symposium on the Definition and Management of Anaphylaxis in Appendix III in Section 21.3.³⁹

11.6 Immunogenicity Assessments

Antibodies to sonelokimab will be evaluated in serum samples collected from all participants according to the SOA (Section 3, Table 1). At dosing visits the samples will be collected prior to dose administration. Details on the collection and shipping of immunogenicity samples are in the Laboratory Manual. These samples will be tested by the sponsor or sponsor's designee.

The detection and characterization of antibodies to sonelokimab will be performed using a validated assay method by or under the supervision of the sponsor.

11.7 Pharmacokinetics

Blood samples will be collected for the measurement of trough serum sonelokimab levels at the visits specified in the SOA (Section 3, Table 1). At dosing visits the samples will be collected prior to dose administration. Details on the collection and shipping of PK samples is in the Laboratory Manual. Samples for PK will be analyzed using a validated assay method by the sponsor's designated laboratory.





12 STATISTICAL CONSIDERATIONS

12.1 Sample Size and Power

The sample size calculation is based on the primary efficacy endpoint (i.e., HiSCR75 response rate at Week 12) with the primary comparison of interest being: sonelokimab 120 mg vs. placebo group and sonelokimab 240 mg vs. placebo group, assuming a HiSCR75

- 40% with the lower sonelokimab dose of 120 mg;
- 50% with the higher sonelokimab dose of 240 mg; and
- 15% with placebo.

A sample size of n=60 participants in each of the sonelokimab 120 mg, sonelokimab 240 mg, and placebo groups, therefore 180 participants in total, results in a power of more than 80%, while assuming an overall 2-sided alpha of 0.05 and a difference in HiSCR75 response rate of 25% between placebo and sonelokimab 120 mg and of 35% between placebo and sonelokimab 240 mg. An additional 30 participants will be randomized in the adalimumab group. The adalimumab treatment will be used as active reference arm, however, no formal direct comparison of sonelokimab or placebo vs. adalimumab is planned.

Eligible participants will be randomized in a 2:2:2:1 ratio to sonelokimab 120 mg, sonelokimab 240 mg, placebo, or adalimumab, respectively. The number of participants in Hurley Stage III will be capped to approximately 40% and the number of participants currently using antibiotics will be capped at 30%.

Due to the use of the full analysis set (FAS) with non-responder imputation, no accounting for dropout is required, therefore a total of approximately 210 participants will be randomized.

All calculations were performed in nQuery® Software version 8.5.1.0.

12.2 Populations for Analysis

For the Part A analysis, the following populations are defined in [Table 7](#).

Table 7 Part A Populations for Analysis

Population	Description
Safety Analysis Set (SAF)	All randomized participants who received at least one dose of study drug. Participants will be analyzed based on the treatment that they actually received. The SAF will be used for all safety analyses related to the Part A.
Full Analysis Set (FAS)	All randomized participants. Participants will be analyzed in accordance to the intention-to-treat principle, i.e., based on randomized treatment, irrespective of the treatment they actually received. The FAS will be used for all efficacy analyses on efficacy endpoints related to the Part A and will serve as the primary analysis set.
Per-protocol Set (PPS)	All participants in the FAS who had no major protocol deviations during the Part A, as confirmed during a data review meeting prior to database lock. The PPS will be used for the primary and key secondary efficacy endpoints related to the Part A and will serve as a secondary analysis set.

For the Part B analysis, the following populations are defined in [Table 8](#).

Table 8 Part B Populations for Analysis

Population	Description
Safety Analysis Set for Part B (SAF-B)	All randomized participants who received at least one dose of study drug during the Part B. Participants will be analyzed based on the treatment that they actually received. The safety analysis set will be used for all safety analyses related to the Part B.
Full Analysis Set for Part B (FAS-B)	All randomized participants who are assigned for the Part B. Participants will be analyzed in accordance to the intention-to-treat principle, i.e., based on randomized treatment, irrespective of the treatment they actually received. The FAS-B will be used for all efficacy analyses on endpoints related to the Part B.

12.2.1 Participant Disposition

The number of participants screened, randomized, randomized and treated, randomized and not treated, and the number of participants in the analysis sets will be summarized for all screened participants.

The number and percentage of participants will also be summarized for the following participant disposition categories:

1. Completed study drug treatment per-protocol;
2. Discontinued study drug early and the reason for discontinuation;
3. Completed the study including post-treatment follow-up;
4. Discontinued from the study early and the reason for discontinuation.

The table will be presented by treatment arm using the FAS.

All participants' disposition data will be listed.

12.3 Statistical Analyses

The Statistical Analysis Plan (SAP) will be finalized prior to study database lock (DBL) for the primary analysis and it will include a more technical and detailed description of the statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

12.3.1 General Statistical Considerations

For continuous variables, descriptive statistics (number of observations, mean, standard deviation [SD], minimum, first quartile, median, third quartile, and maximum and 95% confidence intervals [CIs] as appropriate) will be given. Categorical variables will be presented as counts and percentages with non-missing values in each category. The count of missing observations will be provided in all descriptive tables. For all statistical analyses, p-values and 95% CIs will be given.

For Part A, descriptive statistics will be presented by sonelokimab 120 mg, sonelokimab 240 mg, placebo and adalimumab groups and by visits from Week 0 to Week 12.

For Part B, descriptive statistics will be presented by sonelokimab 120 mg, sonelokimab 240 mg, placebo-sonelokimab 120 mg, placebo-sonelokimab 240 mg and adalimumab-sonelokimab 240 mg groups by visits from Week 0 to Week 24 and repeated by visits from Week 12 to Week 24.

For both analysis sets, baseline values will be defined as the last non-missing measurement prior to first dose of study medication. For Part B analysis sets, an additional analysis will be performed from Week 12 to Week 24, where baseline values will be defined as the last assessment prior to first dose of sonelokimab treatment.

Change from baseline will be defined as the post-baseline visit value minus the baseline value.

All sensitivity analyses will be regarded as exploratory and no formal adjustment for multiplicity will be made. Details on sensitivity and planned subgroup analyses will be provided in the SAP.

All analyses will be performed using SAS® Software version 9.3 or higher.

12.3.2 Primary Endpoints

The primary endpoint is HiSCR75 response rate, defined as the proportions of participants with at least 75% improvement in the HiSCR response criteria at Week 12 compared to baseline.

12.3.2.1 Primary Analysis

For the primary analysis, the hypotheses to be tested are that the proportion of participants who achieve an HiSCR75 response rate at Week 12 in the sonelokimab 120 mg and sonelokimab 240 mg groups are different from placebo group. Only the sonelokimab 120 mg and sonelokimab 240 mg groups will be compared with placebo. A comparison of the dose groups (sonelokimab 120 mg vs. sonelokimab 240 mg) is not planned.

The statistical methods that will be used to test these hypotheses will be a pairwise (placebo and either sonelokimab 120 mg or sonelokimab 240 mg) stratified (Hurley Stage status and prior biologic use) Cochran-Mantel-Haenszel test. Results will be presented in terms of odds ratios, 95% CI, and estimated p-value.

For the primary analysis, non-responder imputation method will be used. Participants will be considered non-responders to treatment if they discontinue the study prior to the Week 12 Visit due to any reason, have a missing HS lesion count at baseline or at the Week 12 Visit due to any reason, or take prohibited protocol medication prior to the Week 12 Visit.

The primary analysis will be performed using both the FAS and PPS. The FAS will be considered primary and PPS will be considered as supportive.

12.3.2.2 Type I Error Control

To adjust for multiple testing and to control the family-wise error rate, the Bonferroni-Holm method will be applied. The smaller of the p-values p_{SLK120mg} and p_{SLK240mg} will be compared to $\alpha/2 = 0.025$, and the greater p-value to $\alpha = 0.05$, where p_{SLK120mg} is the p-value resulting from the comparison between sonelokimab 120 mg and placebo groups, and the p_{SLK240mg} is the p-value resulting from the comparison between sonelokimab 240 mg and placebo groups.

12.3.2.3 Sensitivity Analysis

As a sensitivity analysis, the primary analysis will be repeated using an exact logistic regression model including treatment, Hurley Stage status, and prior biologic use as fixed effects. Additional baseline variables may be added in case of an imbalance between treatments groups. Exact odds ratios, 95% CI, and p-values will be estimated from the model.

A non-responder imputation method will be used as described for primary analysis and the FAS will be used for the sensitivity analysis.

12.3.3 Secondary Endpoints

12.3.3.1 Key Secondary Endpoints

For the key secondary endpoints, the hypotheses to be tested are:

- The proportion of participants who achieve the following endpoints: HiSCR50; DLQI total score ≤ 5 ; and at least 30% reduction and at least 1-unit reduction from baseline in NRS30 in PGA of Skin Pain among participants with baseline NRS ≥ 3 at Week 12 in the sonelokimab 120 mg and sonelokimab 240 mg groups are different from placebo group;
- The mean change from baseline in IHS4 at Week 12 in the sonelokimab 120 mg and sonelokimab 240 mg groups are different from placebo group.

As per the primary analysis, only the sonelokimab 120 mg and sonelokimab 240 mg groups will be compared with placebo. The adalimumab arm will serve as a reference arm only. A comparison of sonelokimab 120 mg vs. sonelokimab 240 mg is not planned.

The statistical methods that will be used to test these hypotheses will be the same as described for the primary endpoint for dichotomous variables and mixed model for continuous variables (change from baseline).

A non-responder imputation method will be used as described for primary analysis of the primary endpoint.

The analysis will be performed using both the FAS and PPS. The FAS will be considered primary and PPS will be considered supportive.

12.3.3.2 Type I Error Control

To adjust for multiple testing and to control the family-wise error rate, a serial gatekeeping testing strategy will be used. The key secondary endpoints family will be analyzed as confirmatory only if both tests in the primary endpoint family have been successful, i.e., the comparisons of both sonelokimab 120 mg and sonelokimab 240 mg groups vs. placebo on the primary endpoint demonstrated a significant difference. Using this strategy, an alpha level of 0.05 will be used for the confirmatory analysis of key secondary endpoints. The family of the key secondary endpoints will be analyzed in a fixed sequence testing procedure to control for multiplicity: within the ordered key secondary endpoints as listed 1 to 4 in Section 7.2.2, sonelokimab 240 mg will be compared to placebo first, sonelokimab 120 mg to placebo second.

12.3.3.3 Sensitivity Analysis

As a sensitivity analysis an exact logistic regression model will be used as described for the primary endpoint.

A non-responder imputation method will be used as described for primary analysis and FAS will be used for this sensitivity analysis.

12.3.3.4 Other Secondary Endpoints

For the other secondary endpoints, no confirmatory statistical testing will be performed, but statistical tests may be used for exploratory proposes only. All endpoints will be assessed at time points as outlined in the Schedule of Activities unless specified otherwise.

All continuous endpoints will be summarized descriptively and analyzed using a mixed model repeated measures (MMRM) model including treatment group, visit, Hurley Stage, and prior exposure to biologic agents as fixed effects and subject as random effect (interactions between visit and treatment and between visit and baseline variables will be investigated). An unstructured covariance matrix will be used for the MMRM analysis, unless the model does not converge, in which case the covariance matrix will be decided upon model convergence status and the Akaike information criterion. The least-squares means in each group, the least-squares mean difference between groups and its 95% CIs and p-values will be estimated from the model. Treatment effect estimates will be also extracted by visit.

All dichotomous endpoints will be summarized descriptively and analyzed using Cochran-Mantel-Haenszel tests with odds ratios and its 95% CIs and p-values.

For dichotomous endpoints, a non-responder imputation method accounting for visits missed due to COVID-19 will be done and details will be defined in the SAP. For continuous endpoints, no imputation is planned.

FAS will be used for all other secondary endpoints analysis.

Immunological Analyses:

Serum immunogenicity (ADA) data for sonelokimab will be listed and summarized using descriptive statistics. Further analysis may be defined in SAP.

Pharmacokinetic Analyses:

Serum concentration data for sonelokimab will be listed and summarized using descriptive statistics. Further analysis may be defined in SAP.

12.3.3.5 Part B Analysis

For Part B analysis, no confirmatory statistical testing will be performed. All efficacy endpoints will be seen as secondary and descriptive statistics will be presented by visit from Week 0 to Week 24 and repeated by visit from Week 12 to Week 24.

For dichotomous endpoints, a non-responder imputation method will be used as described for the other secondary endpoints. For continuous endpoints, no imputation is planned.

The FAS-B will be used for all Part B analysis sets.



12.3.5 Safety Analyses

For any of the safety endpoints, no formal statistical testing will be performed.

Safety analyses will be done separately for the Part A and Part B. AEs will be assigned to either the Part A or to the Part B using the event start date and time. AEs which will start after first treatment of the Part B will be used within the Part B analysis. For Part A, 4 groups will be considered: sonelokimab 120 mg, sonelokimab 240 mg, placebo, and adalimumab groups. For Part B or for the whole treatment period, 5 groups will be considered: sonelokimab 120 mg, sonelokimab 240 mg, placebo-sonelokimab 120 mg, placebo-sonelokimab 240 mg and adalimumab-sonelokimab 240 mg groups.

All participants will be followed for safety up until the end of the Safety Follow-up Visit, i.e., for an additional 4 weeks after the EOT Visit.

SAF will be used for safety analysis.

The following safety endpoints will be assessed.

12.3.5.1 Adverse Events

A summary table will be presented with total number and number of participants with:

- TEAEs;
- SAEs;
- Related TEAEs;
- Related SAEs;
- TEAE leading to discontinuation;
- Fatal AEs.

TEAEs will be described using descriptive statistics and coded according to the Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and MedDRA preferred term (PT), by treatment arms. Drug-related TEAEs and SAEs will also be summarized by treatment arms. Incidence rates of TEAEs during Part B and for the combined Part A + Part B analysis will be adjusted for exposure duration to study treatment (i.e., exposure adjusted incidence rates [EAIR]).

AEs will also be tabulated by intensity and relationship to treatment (“not related/related”).

12.3.5.2 Other Safety Endpoints

Clinical safety laboratory (hematology, biochemistry, urinalysis); vital signs including body weight; ECGs; and physical examinations data will be presented by treatment group and overall. For each visit, the actual result and the change from baseline will be presented. Shift tables for values outside the normal ranges will be presented, as appropriate.

Otherwise, safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate. For continuous measurements (laboratory and vital signs data), change from baseline to each assessment time point will be additionally summarized by treatment group. Patient listings will be produced for all safety parameters.

12.3.6 Subgroup Analyses

Subgroup analyses for the primary endpoint and key secondary endpoints may be considered for baseline variables.

- Age;
- Sex (male, female);
- Disease duration;
- Geographic region;
- Weight;
- Prior exposure to non-biologic systemic agents (Yes/No);
- Prior exposure to biologic agents (Yes/No);
- Concomitant antibiotic use (Yes/No);
- Baseline hs-CRP;
- Treatment-emergent ADA status;
- Hurley Stage status.

All summaries will be based on imputed data as appropriate and will include descriptive statistics.

12.4 Handling of Missing Data

Missing data in this study may result from participants discontinuing from the study prematurely or missing intermediate visits or selected assessments while remaining on study. Every reasonable effort will be made to obtain the protocol-required data for all study assessments that are scheduled for all participants who have been enrolled.

For the dichotomous primary and key secondary endpoints, non-responder imputation method will be used. For other dichotomous endpoints a non-responder imputation method accounting for visits missed due to COVID-19 will be done and details will be defined in the SAP. For continuous endpoints, no imputation is planned.

For continuous efficacy endpoints, missing observations will not be formally imputed. MMRM analysis will use all available data, including participants with partial data (i.e., with missing data) in order to arrive at an estimate of the mean treatment effect. MMRM is based on the assumption of missing at random (MAR), i.e., dropout would behave similarly to other participants in the same treatment group, and possibly with similar covariate values, had they not dropped out.

Unless otherwise indicated, in other cases the observed data will be used and no imputation will be performed.

12.5 Primary Analysis Timing

The primary analysis and unblinding of the data collected during Part A will be performed when all data up to and including Week 12 has been collected.

The study will be continued regardless of the results of the primary analysis.

13 ETHICS

13.1 Independent Ethics Committee/Institutional Review Board

Prior to the start of the study, the investigator is responsible for ensuring that the protocol and consent form have been reviewed and approved by a relevant IEC/IRB. The IEC/IRB shall be appropriately constituted and perform its functions in accordance with FDA, ICH GCP, and local requirements as applicable.

The IEC/IRB shall approve all protocol amendments (except for logistical or administrative changes), written informed consent documents and document updates, participant recruitment procedures (e.g., advertisements), written information to be provided to the participants, IB, available safety information, information about payment, and compensation available to participants, the investigator's curriculum vitae and/or other evidence of qualifications and any other documents requested by the IEC/IRB and Regulatory Authority (Competent Authority) as applicable.

13.2 Written Informed Consent

The nature and purpose of the study shall be fully explained to each participant. They must be informed that participation is voluntary.

Written informed consent must be obtained from each participant prior to any study procedures being performed. The process of obtaining informed consent must be documented in the participant's source documents. The authorized person obtaining the informed consent must also sign the ICF, and a copy of the ICF must be provided to the participant.

The consent documents to be used for the study shall include all the elements of informed consent as outlined in accordance with FDA, ICH GCP, and local requirements as applicable and be reviewed and approved by the appropriate IEC/IRB prior to use.

14 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Conduct of the Study

The sponsor or designee shall implement and maintain quality control and Quality Assurance procedures with written standard operating procedures (SOPs) to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2013), FDA (CFR, Sections 312.50 and 312.56), EU (536/2014) with ICH GCP (CPMP 135/95).

The investigator will be responsible for the following:

1. Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
2. Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

The investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IEC/IRB, except when necessary to eliminate immediate hazards to the participant or when the change(s) involve(s) only logistical or administrative aspects of the study. Any deviations may result in the participant having to be withdrawn from the study and render that participant non-evaluable.

The identification and reporting of serious breaches of ICH GCP or the protocol to the Regulatory Authorities and Ethics Committees will be conducted according to local SOPs and regulations.

14.2 Site Monitoring

The monitoring strategy for the study foresees a risk-based monitoring approach, in line with the relevant FDA and EMA recommendations, and will be described in detail by the study-specific risk-based Monitoring Plan.

Site monitoring includes both source data review and source data verification. Site monitors perform source data review of critical procedures to ensure that the safety and rights of participants are being protected and that the study is being conducted in accordance with the currently approved protocol, any other study agreements, ICH GCP, and all applicable regulatory requirements. Site monitors perform source data verification of critical data to confirm transcription of data entered into the eCRF and eCOA by authorized site personnel are accurate, complete, and verifiable from source documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations/quality such as Risk Management, Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The investigator, as part of his/her responsibilities, is expected to co-operate with [REDACTED] in ensuring that the study adheres to GCP requirements. The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF and eCOA. The investigator may not recruit participants into the study until such time that a visit has been made by a sponsor/[REDACTED] monitor to conduct a detailed review of the protocol, source documents, and eCRF.

The investigator shall grant direct access of original source documents and study records to the sponsor or designee Site Monitor in order to conduct source data review, to ensure that the participants' well-being is maintained, data are being recorded in an adequate manner according to ALCOAC principles (i.e., that they are attributable, legible, contemporaneous, original, accurate, and complete), that protocol and GCP adherence is satisfactory, and to verify accurate transcription of data to the eCRF.

15 DATA HANDLING AND RECORD KEEPING

15.1 Case Report Forms/Source Data Handling

Case report forms/external electronic data, such as the results from the eCOA (including electronic patient reported outcome) assessment tools, and central laboratory results will be entered/loaded into a validated electronic database.

All required study data must be entered in the eCRF created for the study. Some assessments will be captured by an eCOA system, which is synonymous with the eCRF. These data collection tools are validated electronic data capture (EDC) systems that contain a system generated audit trail. Data required according to this protocol are recorded by investigational site personnel via data entry into the internet based EDC software system. The investigator shall ensure that all data from participant visits are promptly entered into the eCRFs and eCOA in accordance with the specific instructions given. The investigator must sign each eCRF to verify the integrity of the data recorded. All internal [REDACTED] and external investigational site personnel seeking access to the eCRF are supported by a Service Desk (if applicable). At the end of the study all data captured electronically will be provided to the investigator on CD ROM for archiving at the investigational site.

The investigator must maintain source documents, such as laboratory reports, X-rays, ECGs, consultation reports, and complete medical history and physical examination reports. All information in the eCRF must be traceable to the source documents in the participant's file.

The investigator/institution shall provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

15.2 Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor or designee will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant. The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

15.3 Dissemination of Clinical Study Data

By signing this protocol, the investigator reaffirms to the sponsor or designee that he will maintain in confidence all information furnished to him or resulting from this study. The investigator will only divulge such information as may be necessary to the IRB, the members of the staff, and the subjects who are involved in this study.

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites as necessary.

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with the clinical study report according to the applicable regulatory requirements. The sponsor will ensure that the clinical study report meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

15.4 Retention of Essential Documents

The investigator/institution should maintain the study documents as specified in the ICH guidelines on GCP and as required by the applicable regulatory requirements. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

16 FINANCING AND INSURANCE

16.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the sponsor will sign a clinical study agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

16.2 Insurance, Indemnity, and Compensation

The sponsor will maintain an appropriate clinical study insurance policy.

16.3 Financial Disclosure

The Investigator will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.



18 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the study.

19 SIGNATURE OF INVESTIGATOR

I agree to conduct the study outlined above in accordance with the terms and conditions of the protocol, ICH guidelines on GCP and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature:

Date (day/month/year)

Name:

Title:

20 REFERENCE LIST

1. Fitzsimmons JS, Guilbert PR. A family study of hidradenitis suppurativa. *J Med Genet.* 1985;22(5):367-373.
2. Sabat R, Jemec GBE, Matusiak L, Kimball AB, Prens E, Wolk K. Hidradenitis suppurativa. *Nat Rev Dis Primers.* 2020;6(1):18.
3. Wolk K, Join-Lambert O, Sabat R. Aetiology and pathogenesis of hidradenitis suppurativa. *Br J Dermatol.* 2020;183(6):999-1010.
4. Navrazhina K, Frew JW, Gilleaudeau P, Sullivan-Whalen M, Garcet S, Krueger JG. Epithelialized tunnels are a source of inflammation in hidradenitis suppurativa. *J Allergy Clin Immunol.* 2021;147(6):2213-2224.
5. Freysz M, Jemec GB, Lipsker D. A systematic review of terms used to describe hidradenitis suppurativa. *Br J Dermatol.* 2015;173(5):1298-1300.
6. Margesson LJ, Danby FW. Hidradenitis suppurativa. *Best Pract Res Clin Obstet Gynaecol.* 2014;28(7):1013-1027.
7. Alikhan A, Sayed C, Alavi A, Alhusayen R, Brassard A, Burkhart C, et al. North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management. *J Am Acad Dermatol.* (2019);81(1):91-101.
8. Mehdizadeh A, Hazen PG, Bechara FG, Zwingerman N, Moazenzadeh M, Bashash M, et al. Recurrence of hidradenitis suppurativa after surgical management: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2015;73(5 Suppl 1):S70-77.
9. Scala E, Cacciapuoti S, Garzorz-Stark N, Megna M, Marasca C, Seiringer P, et al. Hidradenitis suppurativa: where we are and where we are going. *Cells.* 2021;10(8):2094.
10. Garg A, Neuren E, Cha D, Kirby JS, Ingram JR, Jemec GBE, et al. Evaluating patients' unmet needs in hidradenitis suppurativa: results from the Global Survey of Impact and Healthcare Needs (VOICE) Project. *J Am Acad Dermatol.* 2020;82(2):366-376.
11. Matusiak Ł. Profound consequences of hidradenitis suppurativa: a review. *Br J Dermatol.* 2020;183(6):e171-e177.
12. Patel ZS, Hoffman LK, Buse DC, Grinberg AS, Afifi L, Cohen SR, et al. Pain, psychological comorbidities, disability, and impaired quality of life in hidradenitis suppurativa. *Curr Pain Headache Rep.* 2017;21(12):1-8.
13. Hendricks AJ, Hsiao JL, Lowes MA, Shi VY. A comparison of international management guidelines for hidradenitis suppurativa. *Dermatology.* 2021;237(1):81-96.

14. Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *J Eur Acad Dermatol Venereol*. 2015;29(4):619-644.
15. Kimball AB, Sobell JM, Zouboulis CC, Gu Y, Williams DA, Sundaram M, et al. HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. *J Eur Acad Dermatol Venereol*. 2016;30(6):989-994.
16. Zouboulis CC, Frew JW, Giamarellos-Bourboulis EJ, Jemec GB, Del Marmol V, Marzano AV, et al. Target molecules for future hidradenitis suppurativa treatment. *Exp Dermatol*. 2021;30(1):8-17.
17. Navrazhina K, Frew JW, Krueger JG. Interleukin 17C is elevated in lesional tissue of hidradenitis suppurativa. *Br J Dermatol*. 2020;182(4):1045-1047.
18. Rumberger BE, Boarder EL, Owens SL, Howell MD. Transcriptomic analysis of hidradenitis suppurativa skin suggests roles for multiple inflammatory pathways in disease pathogenesis. *Inflamm Res*. 2020;69(10):967-73.
19. Matusiak Ł, Szczęch J, Bieniek A, Nowicka-Suszeko D, Szepietowski JC. Increased interleukin (IL)-17 serum levels in patients with hidradenitis suppurativa: implications for treatment with anti-IL-17 agents. *J Am Acad Dermatol*. 2017;76(4):670-5.
20. Schlapbach C, Hänni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. *J Am Acad Dermatol*. 2011;65(4):790-8.
21. Lima AL, Karl I, Giner T, Poppe H, Schmidt M, Presser D, et al. Keratinocytes and neutrophils are important sources of proinflammatory molecules in hidradenitis suppurativa. *Br J Dermatol*. 2016;174(3):514-21.
22. Moran B, Sweeney CM, Hughes R, Malara A, Kirthi S, Tobin AM, et al. Hidradenitis suppurativa is characterized by dysregulation of the Th17: Treg cell axis, which is corrected by anti-TNF therapy. *J Invest Dermatol*. 2017;137(11):2389-2395.
23. Glatt S, Jemec GB, Forman S, Sayed C, Schmieder G, Weisman J, et al. Efficacy and safety of bimekizumab in moderate to severe hidradenitis suppurativa: a phase 2, double-blind, placebo-controlled randomized clinical trial. *JAMA Dermatol*. 2021;157(11):1279-1288.
24. Sun S, Ding Z, Yang X, Zhao X, Zhao M, Gao L, et al. Nanobody: a small antibody with big implications for tumor therapeutic strategy. *Int J Nanomedicine*. 2021;16:2337.
25. Li Z, Krippendorff B, Sharma S, Walz AC, Lave T, Shah DK. Influence of molecular size on tissue distribution of antibody fragments. *MAbs*. 2016;8:1113-119.

26. Coppieters K, Dreier T, Silence K, Haard HD, Lauwereys M, Casteels P, et al. Formatted anti-tumor necrosis factor α VHH proteins derived from camelids show superior potency and targeting to inflamed joints in a murine model of collagen-induced arthritis. *Arthritis Rheum.* 2006;54(6):1856-1866.
27. Jovčevska I, Muyldermans S. The therapeutic potential of nanobodies. *BioDrugs.* 2020;34(1):11-26.
28. Svecova D, Lubell MW, Casset-Semanaz F, Mackenzie H, Grenningloh R, Krueger JG. A randomized, double-blind, placebo-controlled phase 1 study of multiple ascending doses of subcutaneous M1095, an anti-interleukin 17A/F nanobody, in moderate to severe psoriasis. *J Am Acad Dermatol.* 2019;81(1):196-203.
29. Papp KA, Weinberg MA, Morris A, Reich K. IL17A/F nanobody sonelokimab in patients with plaque psoriasis: a multicentre, randomized, placebo-controlled, phase 2b study. *Lancet.* 2021;397(10284):1564-75.
30. Thorlacius L, Ingram JR, Villumsen B, Esmann S, Kirby JS, Gottlieb AB, et al. A core domain set for hidradenitis suppurativa trial outcomes: an international Delphi process. *Br J Dermatol.* 2018;179(3):642-650.
31. Kimball AB, Jemec GBE, Yang M, Kageleiry A, Signorovitch JE, Okun MM, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. *Br J Dermatol.* 2014;171(6):1434-1442.
32. Kimball AB, Okun MM, Williams DA, Gottlieb AB, Papp KA, Zouboulis CC, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. *N Engl J Med.* 2016;375(5):422-34.
33. Humira®. (Adalimumab) Summary of Product Characteristics. In. Berkshire, UK: AbbVie Ltd. (2021) Accessed at: Humira 40 mg/0.4 ml Pre-filled Syringe and Pre-filled Pen (Great Britain) - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)
34. Reich K, Gooderham M, Thaci D, Crowley JJ, Ryan C, Krueger JG, et al. Risankizumab compared with adalimumab in patients with moderate to severe plaque psoriasis (IMMvent): a randomized, double-blind, active-comparator-controlled phase 3 trial. *Lancet.* 2019;394(10198):576-586.
35. Reich K, Papp KA, Blauvelt A, Langley RG, Armstrong A, Warren RB, et al. Bimekizumab versus ustekinumab for the treatment of moderate to severe plaque psoriasis (BE VIVID): efficacy and safety from a 52-week, multicentre, double-blind, active comparator and placebo-controlled phase 3 trial. *Lancet.* 2021;397(10273):487-498.

36. Kimball AB, Kerdel F, Adams D, Mrowietz U, Gelfand JM, Gniadecki R, et al. Adalimumab for the treatment of moderate to severe hidradenitis suppurativa. *Ann Intern Med.* 2012;157:846-855.
37. Zouboulis CC, Tzellos T, Kyrgidis A, Jemec GBE, Bechara FG, Giamarellos-Bourboulis EJ, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. *Br J Dermatol.* 2017;177(5):1401-1409.

- 
39. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* 2006;117(2):391-7.
 40. Schett G, Sticherling M, Neurath M. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol.* 2020;20(5):271-272.

21 APPENDICES

21.1 Appendix I SARS-CoV-2 (COVID-19) Guidance

Inhibitors of the IL-17 pathway and TNF α inhibitors have not been associated with an increased susceptibility to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection⁴⁰.

Investigators and designees are to comply with local guidelines and regulations regarding monitoring participants for COVID-19 infections, management of participants who test positive for SARS-CoV-2, and minimizing the spread of COVID-19.

Vaccination status of participants will be recorded at screening. This includes the number and type of vaccines given.

Participants requiring vaccinations during the study period should receive them. If possible the baseline assessments (Week 0) should not be within 2 weeks of administration of SARS-CoV-2 vaccination. Vaccinations given during the study will ideally be planned to be administered in the middle of a dose interval. All vaccinations should be captured as concomitant medications.

Participants should be monitored for possible signs of COVID-19. In case a newly diagnosed SARS-CoV-2 infection, local regulations and guidelines including times of quarantine will be adhered to. Participants may therefore miss a scheduled visit (Section 8.6). Participants may resume the study if asymptomatic and following a negative test (PCR or antigen), if the provisions in Section 8.6 are observed.

21.2 Appendix II Childbearing Potential and Contraception

Women of Childbearing Potential

Women of childbearing potential are defined as:

- Having experienced menarche; and
- Are not postmenopausal (as defined below); and
- Are not permanently surgically sterilized (as defined below); and
- Are not otherwise incapable of pregnancy.

Women of Non-Childbearing Potential

Women of non-childbearing potential are defined as at least 1 of the following:

- Postmenopausal, defined as either:
 - >55 years of age with amenorrhea for at least 12 months without an alternative medical cause; or
 - ≤55 years of age with amenorrhea for at least 12 months without an alternative medical cause and a serum follicle stimulating hormone (FSH) level >40 IU/L.
- Permanently surgically sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy);
- Otherwise incapable of pregnancy.

Highly Effective Contraception

Women of childbearing potential must be practicing a highly effective (failure rate of <1% per year when used consistently and correctly) method of birth control, prior to receiving study treatment, during the study, and for at least 12 weeks after receiving the last dose of study treatment, consistent with local regulations regarding the use of birth control methods for participants participating in clinical studies. Highly effective methods include:

- Established use of oral, patch, injected, or implanted hormonal methods of contraception;
- Placement of an intrauterine device or intrauterine system;
- Barrier methods including a male condom plus spermicidal foam/gel/film/cream/suppository (if available in their locale) or an occlusive cap (diaphragm or cervical/vault caps) plus spermicidal foam/gel/film/cream/suppository (if available in their locale);
- Male partner sterilization (the vasectomized partner should be the sole partner for that participant);
- True abstinence (when this is in line with the preferred and usual lifestyle of the participant).

Note: If a female participant's childbearing potential changes after start of the study (e.g., a woman who is not heterosexually active becomes active), she must begin practicing a highly effective method of contraception, as described above.

Male Contraception

Male participants must use a condom when sexually active with a partner of childbearing potential during the study and for 12 weeks after the last dose of study drug, unless permanently surgically sterile.

21.3 Appendix III Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any one of the following 3 criteria from the Second Symposium on the Definition and Management of Anaphylaxis [Sampson H.A. et al., 2006] are fulfilled:	
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus, or flushing, swollen lips-tongue-uvula);	
AND AT LEAST ONE OF THE FOLLOWING:	
a.	Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia);
b.	Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):	
a.	Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula);
b.	Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia);
c.	Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence);
d.	Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):	
a.	Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP. ^a
b.	Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

BP= blood pressure; PEF= peak expiratory flow

a Low systolic BP for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg+[2 × age]) from 1 to 10 years, and less than 90 mmHg from 11 to 17 years.

Source: Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and

Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol 2006;117(2):391-7.

21.4 Appendix IV Ultrasound Sub-study

Introduction

Imaging of HS lesions using ultrasound can provide anatomic information that is clinically unavailable and is often used in the diagnosis and management of the disease¹.

Recently, the analytical and clinical validity of specific sonographic measurements as tools for monitoring disease activity have been evaluated². Sonographic epidermal thickness and dermal tunnel diameter showed high correlation with histological measurements. Power Doppler ultrasound also showed significant correlation with pain scores, AN count, IHS4 score, and number of draining tunnels, suggesting these measurements represent valid biomarkers in HS.

Sensitivity to change and correlation with clinical outcomes in response to pharmacological therapy have also been assessed. A sonographic biomarker study was conducted in a cohort of HS patients using the IL-17 inhibitor brodalumab³. Treatment resulted in significant reductions in epidermal thickness, tunnel diameter, and semi-quantitative power Doppler intensity at lesional sites compared to baseline. Significant differences in epidermal thickness and dermal tunnel diameter were observed in individuals who achieved high levels of HiSCR response compared to non-responders. Power Doppler intensity was also significantly different between HiSCR responders and non-responders at all levels tested (HiSCR50-HiSCR100). Although limited by small numbers, these results suggest that changes during treatment can be detected using sonographic measurements and correlate reasonably with clinical observations.

Sub-study Rationale

Based on the observations that sonographic imaging may be a valid biomarker to provide objective assessment of treatment effect in HS, this sub-study is planned to explore the effect of sonelokimab on epidermal thickness, tunnel diameter, and power Doppler intensity in a subgroup of patients participating in Study M1095-HS-201. An additional measure of lumen opacity will be included as an exploratory assessment of tunnel activity.

Sub-study Objectives and Endpoints

All objectives of this sub-study are exploratory. Depending on the number of participants that are accrued with sufficient ultrasound data, the following will be assessed:

- The effect of sonelokimab on the diameter of a target active draining tunnel at Weeks 12 and 24 compared to baseline;
- The effect of sonelokimab on power Doppler ultrasound in the area of a target active draining tunnel at Weeks 12 and 24 compared to baseline;
- The effect of sonelokimab on epidermal thickness at the target anatomical site as measured by the ultrasound entry signal at Weeks 12 and 24 compared to baseline; and

- The effect of sonelokimab on the lumen opacity of a target active draining tunnel at Weeks 12 and 24 compared to baseline.

Overall Sub-study Design

This will be a sub-study performed in a subgroup of patients participating in Study M1095-HS-201, a randomized, parallel-group, double-blind, placebo-controlled study of sonelokimab in patients with active moderate to severe HS.

Participants at selected sites who are otherwise eligible for the main study and who have a suitable target anatomical site containing a clinically active (draining) tunnel in an accessible location for ultrasound will be asked to provide separate consent to participate in this sub-study. The selected anatomical site will also ideally contain inflammatory lesions such as nodules or abscesses.

The same selected anatomical site is to be used for imaging at each time point (Week 0, Week 12, and Week 24/EOT; see the SOA in Section 3, [Table 1](#) of the main study and the study assessments and procedures, below). The location and characteristics of the anatomical site will be recorded.

After eligibility is confirmed, but before the first dose is administered in the main study, baseline ultrasound parameters will be collected. Participants who remain in the study at Week 12 will have a second ultrasound performed at the Week 12 Visit prior to the administration of the Week 12 dose. Participants who remain in the main study at Week 24 will have a third ultrasound performed at the Week 24/EOT visit.

Analysis of sub-study data will be performed at Week 12 in parallel with the primary analysis of the main study. Additional analyses, including Week 24 data, will be performed at the end of the study.

Sub-study Population

At selected sites participating in the sub-study, suitable patients who provide consent to participate in the main study will be invited to also participate in the sub-study. If possible, at least 25 patients will be recruited. The number of participants proposed to be included is expected to allow sufficient participants to complete the sub-study so as to enable trends in changes in ultrasound parameters to be observed. Recruitment will continue until accrual of patients to the main study is complete.

Enrollment Criteria

Inclusion Criteria

To be eligible for the sub-study, participants must fulfill the following criteria:

1. Participant who fulfills all of the inclusion criteria and none of the exclusion criteria for Study M109-HS-201 (see Section [9.1](#) of the main study);

2. Participant who has a suitable target anatomical site containing a clinically active (draining) tunnel in an accessible location for ultrasound. The selected anatomical site will also ideally contain inflammatory lesions such as nodules or abscesses;
3. Participant who provides signed informed consent to participate in this ultrasound sub-study in addition to providing signed informed consent for participation in the main study.

Exclusion Criteria

There are no specific exclusion criteria for the sub-study. Participants must meet none of the exclusion criteria for the main study.

Sub-study Treatment

Sonelokimab 120 mg or 240 mg, placebo, and adalimumab will be administered in accordance with the main protocol. There will be no stratification of the treatment groups based on sub-study participation.

Sub-study Assessments and Procedures

At each visit during the sub-study, measurements will be made of maximal epidermal thickness at the target site and the maximum transverse dimension (in mm) at the widest part of the target tunnel. Three separate images of the target anatomical site will be captured at each session, and one measurement of each parameter from each image performed and recorded. The mean of the 3 measurements will be used in the data analysis.

Opacity within the lumen of the tunnel (representing accumulated matter) will be measured as present or absent (Yes/No).

Maximal Power Doppler intensity (as a representation of hyperemia) will be assessed in the region of the tunnel using a semi-quantitative scoring method from 1 to 3, with “1” indicating minimal focal or no intensity, “2” indicating focal high intensity or diffuse low intensity, and “3” indicating diffuse high intensity.

At each applicable study visit, including baseline (Week 0/Day 1), ultrasound measurements will always be performed before any clinical assessments of HS lesions are performed. All measurement will be made by site personnel experienced in the use of ultrasound. Whenever possible, the same operator will perform all measurements for an individual participant.

Data will be captured in a case report form (either electronic or paper) and will be entered into a database. In addition, all images will be saved in a suitable format (e.g., JPEG file) and stored at the site. Images may later be transferred to the sponsor or collaborating research institutions for further analysis.

Detailed procedures for the capture, measurement, and storage of ultrasound parameters will be defined in an Ultrasound Sub-study Operational Manual.

Data Analysis

All analyses of sub-study data will be exploratory. In addition to the 4 treatment arms (see also Section 8.1, Figure 1 in the main study), a combined sonelokimab dose group will be presented. Descriptive statistics will be presented for each visit and for the change from baseline for the 4 endpoints:

- Epidermal thickness at the target lesion (mm);
- Maximum transverse dimension of the target tunnel (mm);
- Power Doppler intensity score;
- Proportion of subjects with a luminal opacity score of “No” among participants with a score of “Yes” at baseline.

The mean difference from placebo and associated 95% CI will be presented for each active treatment group, as well as the combined sonelokimab group for the change from baseline for each of the endpoints at Week 12. These comparisons may be omitted if there are too few participants in each group.

Additional exploratory analyses may be defined to explore the correlation of these endpoints with the endpoints for the main study.

References

1. Martorell A, Alfageme Roldán F, Vilarrasa Rull E, Ruiz-Villaverde R, Romani De Gabriel J, García Martínez F, et al. Ultrasound as a diagnostic and management tool in hidradenitis suppurativa patients: a multicentre study. *J Eur Acad Dermatol Venereol*. 2019;33(11):2137-2142.
2. Grand D, Frew JW, Navrazhina K, Krueger JG. Doppler ultrasound-based noninvasive biomarkers in hidradenitis suppurativa: evaluation of analytical and clinical validity. *Br J Dermatol*. 2021;184(4):688-696.
3. Frew JW, Grand D, Navrazhina K, Garcet S, Krueger JG. Assessing the responsiveness of sonographic biomarkers to brodalumab therapy in hidradenitis suppurativa. *J Eur Acad Dermatol Venereol*. 2021;35(12):e884-e887.