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Protocol for Study M20-040

Evaluation of Upadacitinib in Adult Subjects with Hidradenitis Suppurativa

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FULL TITLE: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adult Subjects with Moderate to Severe Hidradenitis Suppurativa

Incorporating Versions 1.0 and 2.0

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adult Subjects with Moderate to Severe Hidradenitis Suppurativa	
Background and Rationale:	Hidradenitis suppurativa (HS) is an inflammatory, debilitating skin disease with a characteristic clinical presentation of recurrent or chronic painful or suppurating lesions that most commonly present in the axilla, inguinal, and anogenital regions. Available treatment options for patients with HS include medical treatments such as topical non-antibiotics (e.g., exfoliants and peels), topical antibiotics (e.g., clindamycin), systemic antibiotics (e.g., clindamycin, tetracycline, rifampicin), anti-inflammatory therapies (e.g., corticosteroids, dapsone, ciclosporin A), hormones (e.g., antiandrogens and estrogens), retinoids (e.g., isotretinoin, acitretin), biologics (e.g., adalimumab, infliximab), analgesics (e.g., NSAIDs, opioids), and surgical treatments (e.g., deroofing, excision, laser). However, with the exception of adalimumab, most of those treatments have not been adequately studied in patients with HS or do not appear to be very effective through the course of the disease. Currently, adalimumab is the only approved therapy for moderate to severe HS, and despite the clinical benefit adalimumab offers to many HS patients, only about 50% of treated patients demonstrate achievement of Hidradenitis Suppurativa Clinical Response (HiSCR) and additional treatment options are needed for those who fail to achieve adequate efficacy. Upadacitinib (Rinvoq®) is an oral, selective and reversible JAK inhibitor that recently has received approval for the treatment of rheumatoid arthritis (RA) in the United States (US), European Union (EU), Japan, and several other countries and is also being developed for the treatment of other immune-mediated inflammatory diseases, including dermatologic conditions such as atopic dermatitis (AD). Positive results from a Phase 2b dosing ranging study with upadacitinib in adult patients with moderate to severe AD enabled advancement into Phase 3 AD registration trials that are currently ongoing with 2 doses of upadacitinib, 15 mg and 30 mg. Increased expression of various proinflammatory cytokines (i.e., interleukin [IL]-6, IL-7, and IL-15, interferon gamma [IFNγ]) has been described in affected HS skin; many of these cytokines signal through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway, which provides a strong rationale for evaluating upadacitinib in HS patients. Given the unmet medical need in HS and the strong scientific rationale, the current study with upadacitinib is designed for clinical validation of JAK inhibition in HS.
Objective(s) and Endpoint(s):	The primary objective of this study is to assess the efficacy and safety of upadacitinib 30 mg versus placebo for the treatment of signs and symptoms of moderate to severe HS in adult subjects. The primary endpoint is the achievement of HiSCR at Week 12. HiSCR

	is defined as at least a 50% reduction in the total abscess and inflammatory nodule count (AN count) with no increase in abscess count and no increase in draining fistula count relative to Baseline. The secondary endpoint is the achievement of at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment (PGA) of Skin Pain (numeric rating scale [NRS30]) – at worst at Week 12 among subjects with baseline NRS ≥ 3.
Investigator(s):	Multi-center
Study Site(s):	28 sites in 3 countries (United States, Canada, and Japan)
Study Population and Number of Subjects to be Enrolled:	Approximately 60 subjects with moderate to severe HS
Investigational Plan:	This is a Phase 2, multicenter, randomized, double-blinded, parallel-group, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in adult subjects with moderate to severe HS. The duration of the study will be up to 57 weeks and will include an approximately 35-day screening period followed by a 48-week treatment period and a 30-day follow up visit after the last dose of study drug. Subjects who meet eligibility criteria will be randomized in a 2:1 ratio to 1 of the 2 arms as shown below: • Upadacitinib 30 mg once daily (QD) (N = 40): Daily oral doses of upadacitinib 30 mg from the Baseline visit up to the Week 12 visit (Period 1). Subjects will remain on blinded upadacitinib 30 mg through Period 2. • Placebo (N = 20): Placebo for upadacitinib from the Baseline visit up to the Week 12 visit (Period 1). At Week 12, subjects will be switched to blinded upadacitinib 15 mg QD through Period 2.
Key Eligibility Criteria:	Eligible subjects will be adult females and males who are at least 18 years of age at Screening with moderate to severe HS (defined as a total AN count of ≥ 5 at Baseline, presence of HS lesions in at least 2 distinct anatomic areas, and draining fistula count of ≤ 20 at Baseline). Subjects should have a diagnosis of HS for at least 1 year prior to baseline. Subjects must also have an inadequate response (lack of efficacy after a course of therapy) or an intolerance to oral antibiotics for treatment of HS.
Study Drug and Duration of Treatment:	Upadacitinib 30 mg QD film-coated tablets for oral administration, 48 weeks in duration. Upadacitinib 15 mg QD film-coated tablets for oral administration, 36 weeks in duration. Placebo for upadacitinib QD film-coated tablets for oral administration, 12 weeks in duration.
Date of Protocol Synopsis:	25 October 2020

2 INTRODUCTION

2.1 Background and Rationale

This study will compare upadacitinib versus placebo for the treatment of adult subjects with moderate to severe hidradenitis suppurativa (HS).

HS is an inflammatory, debilitating skin disease with a characteristic clinical presentation of recurrent or chronic painful or suppurating lesions that most commonly present in the axilla, inguinal, and anogenital regions.[1,2] The estimated prevalence of HS varies between < 1% and 4%.[3-7] It is a difficult to diagnose condition, and therefore, there is a significant delay (7.2 years on average) in establishing the diagnosis of HS after its initial presentation.[8]

HS lesions (i.e., nodules, abscesses, and sinuses) are painful, typically located in the intertriginous areas, and can be malodorous with purulent discharge. This constellation of signs and symptoms results in substantial disability and social stigma of the patients and a profound impact on the quality of life.[9] Depression, anxiety, and an increased suicide risk may be seen in patients with HS, as well as a negative impact on a patient's sexual health.[10-14] Patients may have several comorbidities, such as obesity, metabolic syndrome, diabetes, arthritis, Crohn's disease, and polycystic ovary disease.[2,15] Patients with HS have an increased risk of adverse cardiovascular outcomes and all-cause mortality, and their risk of CV-associated death was shown to be higher than in psoriasis patients.[16]

Available treatment options for patients with HS include medical treatments such as topical non-antibiotics (e.g., exfoliants and peels), topical antibiotics (e.g., clindamycin), systemic antibiotics (e.g., clindamycin, tetracycline, rifampicin), anti-inflammatory therapies (e.g., corticosteroids, dapsone, ciclosporin A), hormones (e.g., antiandrogens and estrogens), retinoids (e.g., isotretinoin, acitretin), biologics (e.g., adalimumab, infliximab), analgesics (e.g., nonsteroidal anti-inflammatory drugs [NSAIDs], opioids), and surgical treatments (e.g., deroofing, excision, laser).[17] However, with the exception of adalimumab, most of those treatments have not been adequately studied in patients with HS or do not appear to be very effective through the course of the disease. The only approved treatment option for patients with moderate to severe HS is adalimumab (Humira®), a tumor necrosis factor (TNF)-α inhibitor.[18] The results from Phase 3 studies with adalimumab, PIONEER I and II, showed approximately 42% and 59% of subjects achieved Hidradenitis Suppurative Clinical Response (HiSCR) at Week 12, respectively, versus 26% and 28% in placebo.[19] HiSCR is defined as a reduction of at least 50% of total abscess and inflammatory nodule (AN) count, without an increase in abscesses or draining fistula count relative to Baseline.[19] Additional treatment options are needed for those patients who fail to achieve adequate efficacy.

The Janus kinases (JAKs) are a family of intracellular tyrosine kinases that function as dimers in the signaling process of many cytokine receptors.[20] The JAK family is composed of 4 members: JAK1, 2, 3, and tyrosine kinase 2 (Tyk2). These cytoplasmic tyrosine kinases act in tandem to activate the signal transducer and activator of transcription (STAT) that transduce cytokine-mediated signals, and are associated with multiple membrane cytokine receptors such as common gamma-chain receptors and the glycoprotein 130 trans-membrane proteins.[20] The JAKs play a critical role in both innate and adaptive immunity, making them attractive targets for the treatment of inflammatory diseases.[21-24]

The exact pathogenesis of HS has not been fully defined and cytokine studies in HS have had variable methodologies and results.[25] However, cytokines and receptors that signal via the JAK1 pathway are elevated in HS, such as interleukin (IL)-2, IL-7, Type 1 interferons (IFNs), IFNγ, the IL-10 family, as well as IL-6.[26,27] This suggests that JAK1 inhibition may be an effective target in the treatment of HS.

Upadacitinib (Rinvoq®) is an oral, selective and reversible JAK inhibitor that recently has received approval for the treatment of rheumatoid arthritis (RA) in the United States (US), European Union (EU), Japan, and several other countries[28,29] and is also being developed for the treatment of other immune-mediated inflammatory diseases, including dermatologic conditions such as atopic dermatitis (AD). Positive results from a Phase 2b dosing ranging study with upadacitinib in adult patients with moderate to severe AD enabled advancement into Phase 3 AD registration trials that are currently ongoing with 2 doses of upadacitinib, 15 mg and 30 mg.

Clinical Hypothesis

Proinflammatory cytokines identified in the lesional skin of HS patients signal via the JAK/STAT pathway. Inhibition of the JAK/STAT pathway with upadacitinib may decrease the high inflammatory burden in HS patients and improve clinical outcomes. Upadacitinib should provide superior efficacy compared to placebo with an acceptable safety profile in subjects with HS.

2.2 Benefits and Risks to Subjects

Increased expression of various proinflammatory cytokines (i.e., IL-6, IL-7, and IL-15, IFNγ) has been described in affected HS skin; many of these cytokines signal through the JAK-STAT pathway. This provides a strong rationale for evaluating upadacitinib in HS, a disease with a high unmet need due to very limited approved treatment options. The efficacy of various JAK inhibitors, including upadacitinib has shown promising results in various immune-mediated diseases including AD. Common adverse events (AEs) reported to be associated with the class of JAK inhibitors, including upadacitinib, are infections, herpes zoster reactivation, and hematologic AEs. Based on class labeling, serious infection, malignancy, and thrombosis were highlighted as a black box warning in the US package inserts.[28] Potential differences in the safety profile of upadacitinib in dermatologic versus non-dermatologic conditions will be closely monitored during the course of the clinical study and a robust safety monitoring plan, including a Data Monitoring Committee (DMC), Cardiovascular Adjudication committee and Gastrointestinal Perforation Adjudication committee, is in place to ensure patient safety.

The results of genetic toxicology testing indicate that upadacitinib is not genotoxic; however, upadacitinib may be teratogenic, which necessitates avoidance of pregnancy in females of childbearing potential. Based on an embryo fetal development study in rats, there is judged to be no risk associated with administration of upadacitinib to male partners of females of childbearing potential.

A detailed discussion of the pre-clinical and clinical toxicology, metabolism, pharmacology, and safety experience with upadacitinib can be found in the current Investigator's Brochure.

Taken together, the efficacy and safety data from upadacitinib studies to date show a favorable benefit:risk profile for upadacitinib and support the continued investigation of upadacitinib in patients with various autoimmune/inflammatory conditions including HS. Upadacitinib as a new oral therapeutic drug could expand treatment options for patients with HS.

In view of the COVID-19 pandemic, the benefit:risk profile of various immunomodulatory therapies on COVID-19 is being evaluated. At this time, the effects of upadacitinib on the course of COVID-19 are not well defined.

3 OBJECTIVES AND ENDPOINTS

Objective and Hypothesis

The objective of this study is to assess the efficacy and safety of upadacitinib 30 mg versus placebo for the treatment of signs and symptoms of moderate to severe HS in adult subjects.

The hypothesis is that upadacitinib 30 mg group should achieve a higher clinical response rate compared with the placebo group after 12 weeks of treatment.

3.1 Primary Endpoint

The primary endpoint is the achievement of HiSCR at Week 12. HiSCR is defined as at least a 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to Baseline.

3.2 Secondary Endpoint

The secondary endpoint is the achievement of at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment (PGA) of Skin Pain (numeric rating scale [NRS30]) – at worst at Week 12 among subjects with baseline NRS ≥ 3.

3.3 Additional Endpoints

The primary and secondary endpoints will also be analyzed at all visits other than Week 12. In addition, the following endpoints will be analyzed at visits as noted in the Study Activities Table (Appendix D).

- Increase in AN count of at least a 25% with a minimum increase of 2 relative to Baseline;
- Change from Baseline in Dermatology Life Quality Index (DLQI);
- Change from baseline in Hidradenitis Suppurativa Symptom Assessment (HSSA);
- Change from baseline in HS-related swelling, assessed based on the HSSA;
- Change from baseline in HS-related odor, assessed based on the HSSA;
- Change from baseline in HS-related worst drainage, assessed based on the HSSA;
- Change from baseline in Hidradenitis Suppurativa Impact Assessment (HSIA).

3.4 Safety Endpoints

Safety will be assessed by AE monitoring, physical examination, vital signs, electrocardiogram (ECG), imaging, and clinical laboratory testing during the study. Laboratory assessments will include hematologic parameters, chemistry, liver function tests, and lipid parameters.

3.5 Pharmacokinetic Endpoints

Pharmacokinetic (PK) samples will be collected from subjects at the visits indicated in Appendix D. Using the data available from these subjects, a nonlinear mixed-effects modeling approach will be used to estimate the population central values and the empirical Bayesian estimates of the individual values of upadacitinib oral clearance (CL/F) and volume of distribution (V/F). Additional parameters may be estimated if useful in the interpretation of the data. Data from this study may be combined with data from other studies for the population PK analyses.

3.6 Biomarker Research Objectives

Optional blood samples (whole blood, serum, plasma, peripheral blood mononuclear cells [PBMC]) will be collected as described in the Activity Schedule (Appendix D) to evaluate known and or novel disease related or drug related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, cellular populations, and/or metabolites. The objective of research is to analyze samples for biomarkers that will help to understand HS, related conditions, response to treatment with upadacitinib or similar compounds. Research may also include changes in epigenetics, gene expression, and proteomics that may associate with HS, related conditions, or the subject's response to treatment. This research is exploratory in nature and the results may not be included with the clinical study report.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 2, multicenter, randomized, double-blinded, parallel-group, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in adult subjects with moderate to severe HS.

The duration of the study will be up to 57 weeks and will include an approximately 35-day screening period followed by a 48-week double-blinded treatment period and a 30-day follow up visit after the last dose of study drug.

Subjects who meet eligibility criteria will be randomized in a 2:1 ratio to 1 of the 2 arms as shown below:

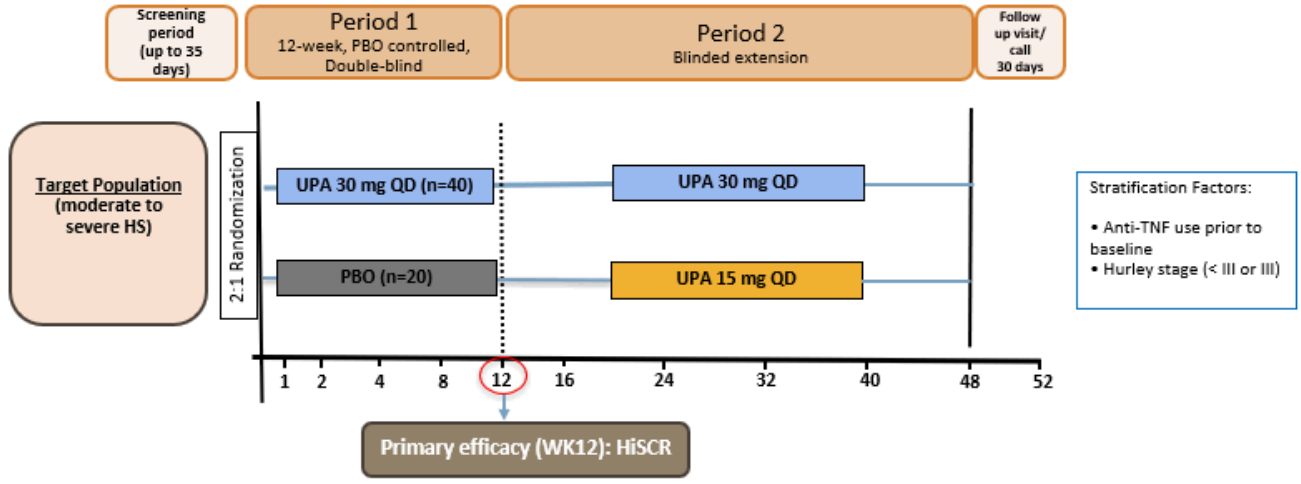
- Upadacitinib 30 mg once daily (QD) (N = 40): Daily oral doses of upadacitinib 30 mg from the Baseline visit through Period 1 and Period 2.
- Placebo (N = 20): Placebo for upadacitinib from the Baseline visit up to the Week 12 visit (Period 1). At Week 12, subjects will be switched to blinded upadacitinib 15 mg QD through Period 2.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are included in the Operations Manual (Appendix F).

See Section 5 for information regarding eligibility criteria.

The primary efficacy analysis will be conducted when all ongoing subjects have completed their Week 12 visit.

Figure 1. Study Schematic



HiSCR = ≥50% reduction from baseline in the total AN count, with no increase in abscess or draining fistula counts

PBO = placebo; UPA = upadacitinib

4.2 Discussion of Study Design

Choice of Control Group

Placebo control will be used in this study. Comparative studies utilizing a double blind, placebo-controlled design provides an unbiased assessment of the efficacy and safety profile of upadacitinib.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity or quality of life in subjects with HS. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Adult subjects with moderate to severe HS (defined as a total AN count of ≥ 5 at Baseline, presence of HS lesions in at least 2 distinct anatomic areas and draining fistula count of ≤ 20 at Baseline) are eligible for this study. Subjects are to have a diagnosis of HS for at least 1 year prior to Baseline. The criteria

relating to safety have been selected to allow subjects to be safely enrolled and treated with upadacitinib based on the current knowledge of this drug. The study population selected reflects a population typical of new treatment intervention studies in moderate to severe HS.

Selection of Doses in the Study

This study will evaluate upadacitinib 30 mg QD. The selection of this dose was informed by the safety and efficacy of the upadacitinib dosing in different indications including RA, AD, psoriatic arthritis, and Crohn's disease. Due to a high inflammatory burden in the HS population, in general, higher dosing may be required to achieve optimal clinical response compared to other autoimmune disease indications such as RA. Hence, upadacitinib 30 mg QD has been selected to establish proof-of-concept for upadacitinib in the treatment of HS in this Phase 2 study. The adalimumab PIONEER I and II studies demonstrated that 40 mg every week resulted in better efficacy than 40 mg every other week (initial prescribed dose for most indications such as RA, plaque psoriasis, etc.).[19] The results from Phase 2 dose-ranging studies with upadacitinib in AD and Crohn's disease showed upadacitinib 30 mg QD resulted in greater efficacy compared to upadacitinib 15 mg QD, which is the approved dose for RA.[30]

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographics

- 2. Adult **male or female**, at least 18 years old and functionally able to read and understand study questionnaires.
- 3. Are willing and able to comply with procedures required in this protocol.
- 4. Subject is not an employee or a family member of the sponsor and/or study site.

Disease Criteria

- 5. Diagnosis of HS for at least 1 year prior to Baseline, as determined by the investigator (i.e., through medical history and interview of subject).
- 6. Subject must have a total AN count of ≥ 5 at Baseline.
- 7. HS lesions must be present in at least 2 distinct anatomic areas.
- 8. Draining fistula count of ≤ 20 at Baseline.

- 9. Inadequate response (lack of efficacy after a course of therapy) or an intolerance to oral antibiotics for treatment of HS.

Laboratory Assessments

- 10. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) ≤ 2 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) ≤ 2 × ULN;
  - Estimated glomerular filtration rate by simplified 4-variable Modification of Diet in Renal Disease formula ≥ 30 mL/min/1.73 m^2;
  - Total white blood cell (WBC) count ≥ 2,500/µL;
  - Absolute neutrophil count (ANC) ≥ 1,200/µL;
  - Platelet count ≥ 100,000/µL;
  - Absolute lymphocyte count (ALC) ≥ 750/µL;
  - Hemoglobin ≥ 9 g/dL.

Subject History

- 11. No history of active skin disease (other than HS) that could interfere with the assessment of HS, including skin infections (bacterial, fungal, or viral) requiring systemic treatment within 4 weeks of the Baseline visit.
- 12. Subject is judged to be in good health as determined by the Principal Investigator, based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead ECG performed during Screening.
- 13. Subject must not have a history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.
- 14. Subject must have no current or past history of any of the following infections:
  - Two or more episodes of herpes zoster, or one or more episodes of disseminated herpes zoster;
  - One or more episodes of disseminated herpes simplex (including eczema herpeticum);
  - Human immunodeficiency virus (HIV) infection defined as confirmed positive anti-HIV antibody (HIV Ab) test;
  - Active tuberculosis (TB) or meet TB exclusionary parameters (specific requirements for TB testing are provided in the operations manual [Appendix F]);
  - Positive result of beta-D-glucan (screening for pneumocystis jirovecii infection) or two consecutive indeterminate results of beta-D-glucan during the Screening Period (for subjects in Japan only)

- Active infection(s) requiring treatment with intravenous anti-infectives within 30 days, or oral/intramuscular anti-infectives within 14 days prior to the Baseline Visit;
- Chronic recurring infection and/or active viral infection that, based on the investigator's clinical assessment, makes the subject an unsuitable candidate for the study;
- Confirmed COVID-19: the Baseline visit must be at least 14 days from onset of signs/symptoms or positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test; symptomatic subjects must have recovered, defined as resolution of fever without use of antipyretics and improvement of symptoms;
- Suspected COVID-19: subjects with signs/symptoms suggestive of COVID-19, known exposure, or high risk behavior should undergo molecular (e.g., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection or must be asymptomatic for 14 days from a potential exposure;
- Subjects must not have evidence of:
  - Hepatitis B virus (HBV): hepatitis B surface antigen positive (+) test or detected sensitivity on the HBV deoxyribonucleic acid (DNA) PCR qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+) (and for Hepatitis B surface antibody positive [+] subjects where mandated by local requirements);
  - Hepatitis C virus (HCV): HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody.

15. Subject must not have any of the following medical diseases or disorders:
    - Recent (within past 6 months) cerebrovascular accident, myocardial infarction, coronary stenting;
    - History of an organ transplant which requires continued immunosuppression;
    - History of gastrointestinal perforation (other than due to appendicitis or mechanical injury), diverticulitis, or significantly increased risk for gastrointestinal perforation per investigator judgment;
    - Conditions that could interfere with drug absorption including but not limited to short bowel syndrome or gastric bypass surgery; subjects with a history of gastric banding/segmentation are not excluded;
    - History of malignancy except for successfully treated nonmelanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
16. There must be no reason the investigator believes that the subject is an unsuitable candidate to participate in the study, receive study drug, or would be placed at risk by participating in the study.

Contraception

- 17. For all females of child-bearing potential: must not have a positive serum pregnancy test at the Screening Visit and must have a negative urine pregnancy test at Baseline prior to the first dose of study drug (local practices may require serum pregnancy testing at Baseline). Subjects with a borderline serum pregnancy test at Screening must have absence of clinical suspicion of pregnancy or other pathological causes of borderline results and a serum pregnancy test ≥ 3 days later to document continued lack of a positive result (unless prohibited by local requirements).
- 18. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control that is effective from Study Day 1 through at least 30 days after the last dose of study drug (local practices may require 2 methods of birth control). Female subjects of non-childbearing potential do not need to use birth control.
- 19. Females must not be pregnant, breastfeeding, or considering becoming pregnant during the study and for approximately 30 days after the last dose of study drug.

Prior and Concomitant Medications

- 20. Subject must not have been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or 5 half-lives (whichever is longer) prior to the first dose of study drug or is currently enrolled in another interventional clinical study.
- 21. Subject must have no systemic use of known strong cytochrome P450 3A (CYP3A) inhibitors from Screening through the end of study drug administration or strong CYP3A inducers 30 days prior to study drug administration through the end of study drug administration (refer to Table 1 for examples of commonly used strong CYP3A inhibitors and inducers). Subjects may not use herbal therapies or other traditional medicines with unknown effects on CYP3A from Screening through the end of study drug administration.
- 22. Subject must not have received a live vaccine within 28 days (or longer if required locally) prior to the first dose of study drug, or have expected need of live vaccination during study participation including at least 30 days (or longer if required locally) after the last dose of study drug.
- 23. Subject must not have a history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 24. Subjects who have had prior exposure to immunomodulatory biologic therapies for any indication, including but not limited to anti-TNF therapy and anti-IL-1 (e.g., anakinra, canakinumab) therapy must have discontinued the biologic therapies prior to the first dose of study drug. Subjects who need to discontinue other biologic therapies prior to the Baseline Visit to comply with this inclusion criterion must follow the washout periods specified below. If not specified below, biologic therapies must be discontinued at least 5 times the mean terminal elimination half-life of a drug or 3 months prior to Baseline, whichever is longer:
  - ≥ 4 weeks for etanercept;
  - ≥ 8 weeks for adalimumab, infliximab, certolizumab, golimumab, abatacept, tocilizumab, and ixekizumab;

- ≥ 16 weeks for secukinumab;
- ≥ 12 weeks for ustekinumab.

  No minimum washout prior to Baseline is required for a biologic therapy if an undetectable drug level measured by a commercially available assay is documented.

- 25. Subject must not have had prior exposure for 14 days or more or any prior intolerance to a JAK inhibitor for any indication. The washout period for JAK inhibitors prior to the first dose of study drug is ≥ 30 days or 5 times the half-life, whichever is longer.
- 26. No previous treatment with any cell-depleting therapies including but not limited to anti-CD20 (e.g., rituximab) within 12 months prior to Baseline or until B cell count returns to normal level or pre-treatment level.
- 27. Subjects must not have received prescription topical therapies (including topical antibiotics) that can also be used to treat HS within 14 days prior to the Baseline visit.
- 28. Subjects must not have received systemic non-biologic therapies that can also be used to treat HS within 4 weeks prior to the Baseline visit.
- 29. Subjects must not have received any systemic (including oral) antibiotic treatment for HS or any other chronic inflammatory disorder within 4 weeks prior to the Baseline visit.
- 30. Subjects must be willing to and are required to use a daily antiseptic wash on their HS lesions starting at least 14 days prior to Baseline. Allowable antiseptic washes are limited to one of the following: chlorhexidine gluconate, benzoyl peroxide, benzalkonium chloride, benzethonium chloride, or dilute bleach in bath water.
- 31. Subjects who are on non-opioid analgesics for HS or non-HS related pain, must be on a stable dose and dosing regimen for at least 14 days preceding the Baseline visit and are expected to remain on a stable dose and dosing regimen at least until the Week 16 visit. Otherwise, subjects must not have received oral analgesics including but not limited to opioids, antiepileptics (e.g., gabapentin), tricyclics (e.g., nortriptyline), or selective serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine) within 14 days prior to the Baseline visit.

  Note: For HS-related pain, analgesic therapy is limited to ibuprofen (as per local labeling, but not exceeding a dose of 800 mg orally every 6 hours and 3.2 g orally every 24 hours) AND/OR acetaminophen (paracetamol) as per local labeling.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

- Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle stimulating hormone (FSH) level > 40 IU/L.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug and for at least 30 days after the last dose of study drug. Females must commit to one of the following methods of highly effective birth control:
    - Combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure) (For Japan: only bilateral tubal ligation).
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Vasectomized sexual partner (the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence (unless not acceptable per local practices), defined as: refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
  - If required per local practices, females of childbearing potential must commit to using 2 methods of contraception (either 2 highly effective methods or 1 highly effective method combined with 1 effective method). Effective methods of birth control are the following:
    - Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1.
    - Male or female condom with or without spermicide.
    - Cap, diaphragm, or sponge with spermicide.
    - A combination of male condom with a cap, diaphragm, or sponge with spermicide (double barrier method).

Contraception recommendations related to use of concomitant therapies prescribed per standard of care should be based on the local label.

5.3 Prohibited Medications and Therapy

Background Therapies

The following therapies are prohibited until after Week 16 assessments unless otherwise specified:

1. Throughout the study, any other systemic therapy that can also be used to treat HS, including but not limited to intramuscular or intravenous corticosteroids, oral corticosteroids equivalent to > 10 mg/day of prednisone, methotrexate (> 25 mg/week), cyclosporine, mycophenolate mofetil, azathioprine, intramuscular gamma-globulin.
2. Apremilast, hormonal therapy (except for contraception), metformin (except for continuous treatment of preexisting diabetes), zinc gluconate, colchicine, retinoids, acitretin/etretinate, and fumaric acid esters, methotrexate, and oral corticosteroids are prohibited until after Week 16 assessments.
3. New topical therapies used to treat HS (other than protocol-allowed antiseptic) or changes in the concentration/frequency of current topical therapies used to treat HS (including but not limited to exfoliants, e.g., resorcinol).
4. Deroofing or skin-tissue-saving excision with electrosurgical peeling (STEEP), laser therapy, intense pulse light, local/wide/radical excision, incision and/or draining of lesions, or intralesional corticosteroid injections.
5. Concomitant use of antibiotics (topical or systemic) is not permitted for the treatment of HS or other chronic inflammatory disorders.
6. Use of any treatments for HS-related pain, other than ibuprofen or acetaminophen (paracetamol), including but not limited to opioids, antiepileptics (e.g., gabapentin), tricyclics (e.g., nortriptyline), or selective serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine). For non-HS-related pain, all other non-opioid analgesics are allowed at the recommended or prescribed dose per local label. Use of opioid analgesics for HS-related or non-HS related pain is prohibited until after Week 16 assessments.
    - Subjects who are on a documented stable dose and dosing regimen of non-opioid analgesic treatment for at least 14 days prior to the Baseline visit are not permitted to adjust their regimen at least until after the Week 16 assessment. Note: For HS-related pain, analgesic therapy is limited to ibuprofen (as per local labeling, but not exceeding a dose of 800 mg orally every 6 hours and 3.2 g orally every 24 hours) AND/OR acetaminophen (paracetamol) as per local labeling.
7. Over-the-counter topical antiseptic washes (other than those allowed as per the concomitant therapy section), creams, ointments, gels, and liquids containing antibacterial agents to treat HS, other than those allowed as per concomitant therapy section.
8. Phototherapy treatment (ultraviolet B or ultraviolet A phototherapy, including psoralen and ultraviolet A), tanning booth, or extended sun exposure.
9. Medicinal and recreational cannabis.

Biologic Therapies

Subjects must have discontinued biologic therapies at least 3 months or 5 half-lives (whichever is longer) prior to Baseline or with specified washout periods as detailed in Section 5.1. No minimum washout prior to Baseline is required for a biologic therapy if an undetectable drug level measured by a commercially available assay is documented.

Therapies including but not limited to the following biologic therapies are prohibited medications during the study (throughout Period 1 and Period 2):

- Abatacept
- Adalimumab
- Anakinra
- Belimumab
- Certolizumab
- Dupilumab
- Etanercept
- Golimumab
- Infliximab
- Ixekizumab
- Natalizumab
- Rituximab
- Secukinumab
- Tocilizumab
- Ustekinumab
- Vedolizumab
- Guselkumab
- Risankizumab

Strong CYP3A Inhibitors or Inducers

Systemic use of known strong CYP3A inhibitors (includes over-the-counter or prescription medicines, vitamins and/or herbal supplements) is not permitted from Screening through the end of study drug administration and use of strong CYP3A inducers is not permitted from 30 days prior to study drug administration through the end of study drug administration. Table 1 includes examples of commonly used strong CYP3A inhibitors and inducers. In addition, herbal therapies and other traditional medicines with unknown effects on CYP3A are not permitted from Screening through the end of study drug administration.

Table 1. Examples of Commonly Used Strong CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors	Strong CYP3A Inducers
Boceprevir Cobicistat Clarithromycin Conivaptan Grapefruit (fruit or juice) Indinavir Itraconazole Ketoconazole Lopinavir/Ritonavir Mibefradi Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Telaprevir Telithromycin Troleandomycin Voriconazole	Avasimibe Carbamazepine Phenytoin Rifampin (rifampicin) Rifapentine St. John's Wort

Investigational Drugs or Therapies

Subjects who have been treated with any investigational drug within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug are excluded from participation in this study. Investigational drugs are also prohibited during the study.

Vaccines

If the subject and investigator choose to receive/administer live vaccines, these vaccinations must be completed (per local label) at least 28 days (or longer if required locally) before first dose of study drug. Live vaccinations are prohibited during study participation including at least 30 days (or longer if required locally) after the last dose of study drug.

If the live herpes zoster vaccine is to be administered and there is no known history of primary varicella (chicken pox), preexisting immunity to varicella should be confirmed with antibody testing at or prior to Screening and prior to administration of the herpes zoster vaccine. If screening varicella antibody testing is negative, the live herpes zoster vaccine should not be administered.

Examples of live vaccines include, but are not limited to, the following:

- Monovalent live influenza A (H1N1) (intranasal);
- Seasonal trivalent live influenza (intranasal);
- Zostavax (herpes zoster, live attenuated);
- Rotavirus;

- Varicella (chicken pox);
- Measles-mumps-rubella or measles-mumps-rubella-varicella;
- Oral polio vaccine;
- Smallpox;
- Yellow fever;
- Bacille Calmette-Guérin;
- Typhoid (oral).

Administration of inactivated (non-live) vaccines is permitted prior to or during the study according to local practice guidelines. Examples of common vaccines that are inactivated, toxoid or biosynthetic include, but are not limited to, injectable influenza vaccine, pneumococcal, Shingrix (zoster vaccine, recombinant, adjuvanted), and pertussis (Tdap) vaccines.

Other Medications Prohibited During the Study

JAK inhibitors (e.g., upadacitinib [Rinvoq®], tofacitinib [Xeljanz®], ruxolitinib [Jakafi®], baricitinib [Olumiant®], peficitinib [Smyraf®], abrocitinib [PF-04965842], and filgotinib).

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of screening, and/or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate electronic case report form (eCRF). Also, medications taken for HS since date of diagnosis (based on subject recollection and available medical records) should be entered into the appropriate eCRF inclusive of the dates of first and last dose, maximum dosage taken, route of administration.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie Therapeutic Area Medical Director (TA MD)/AbbVie emergency contact. Information regarding potential drug interactions with upadacitinib can be located in the upadacitinib Investigator's Brochure.

Allowed Therapies

Antibiotics

Concomitant use of antibiotics is allowed for the treatment of acute infections during the study. Use of topical or systemic antibiotics to treat HS or other chronic inflammatory disorders is prohibited up to Week 16. After Week 16, concomitant use of any antibiotics for any indication, including HS, is permitted.

Dosing and/or frequency need to be reported in the eCRF documentation; "as needed" (PRN) use is not permitted.

Antiseptic Wash

Subjects are required to use a daily antiseptic wash on their HS lesions for the duration of the study.

Allowable antiseptic washes are limited to: chlorhexidine gluconate, benzoyl peroxide, benzalkonium chloride, benzethonium chloride, or dilute bleach in bathwater.

Wound Care

Use of wound care dressings on HS wounds is allowed. Recommended options include alginates, hydrocolloids, and hydrogels.

Lesion Intervention

Deroofing or STEEP, laser therapy, intense pulse light, local/wide/radical excision, incision and/or draining of lesions, and intralesional injections are allowed after Week 16 assessments. Refer to Section 6.2 for study drug interruption guidelines for elective and emergency surgeries.

Analgesic therapy

If a subject experiences pain (HS- related or non-HS-related) after Baseline, they may initiate analgesic treatment. For HS-related pain, analgesic therapy is limited to the following until after the Week 16 assessments:

- ibuprofen as per local labeling, but not exceeding a dose of 800 mg orally every 6 hours and 3.2 grams orally every 24 hours, AND/OR
- acetaminophen (paracetamol) as per local labeling

For non-HS-related pain, all other non-opioid analgesics are allowed at the recommended or prescribed dose.

Use of opioid analgesics for HS-related or non-HS related pain is prohibited until after Week 16 assessments.

Subjects will complete a daily diary of their analgesic use. Subjects will be required to record their analgesic use daily through Week 16. Any changes in dosing and/or frequency need to be reported in the daily dairy; documentation of only PRN use is not permitted.

Subjects who are on a documented stable dose and dosing regimen of non-opioid analgesic treatment for at least 14 days prior to the Baseline visit may not adjust their regimen until after Week 16 assessments.

5.5 Withdrawal of Subjects and Discontinuation of Study

AbbVie may terminate this study prematurely, either in its entirety or at any site. The study will be discontinued or terminated in case of an unacceptable risk, any relevant toxicity, or a negative change in the risk/benefit assessment. This might include the occurrence of AEs with a character, severity or frequency that is new in comparison to the existing risk profile. In addition, data deriving from other clinical trials or toxicological studies which negatively influence the risk/benefit assessment might cause

discontinuation or termination of the study. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator. Advance notice is not required by either party if the study is stopped due to safety concerns.

Subjects can request to be discontinued from participating in the study at any time for any reason. Subjects who discontinue the study prematurely after randomization will not be replaced. The investigator may discontinue any subject's participation at any time for any reason. The AbbVie TA MD may mandate individual subject discontinuation from study drug in case of safety concern.

Subjects must have study drug discontinued immediately if any of the following occur:

- The subject requests withdrawal from the study.
- The investigator believes it is in the best interest of the subject.
- Abnormal laboratory results or AEs that either meet the criteria for discontinuation of study drug as stated in Section 6.2 or rule out safe continuation of the study drug, as determined by the Investigator or the AbbVie TA MD.
- Serious infections (e.g., sepsis) which cannot be adequately controlled by anti-infective treatment or would put the subject at risk with continuation of the study drug.
- Confirmed diagnosis of deep vein thrombosis, pulmonary embolus, or non-cardiac, non-neurologic arterial thrombosis.
- Malignancy, except for localized NMSC or carcinoma in-situ of the cervix.
- Subject develops a gastrointestinal perforation (other than due to appendicitis or mechanical injury).
- The subject becomes pregnant or plans to become pregnant while on study drug.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Eligibility criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- Subject is significantly non-compliant with study procedures, which would put the subject at risk for continued participation in the trial

Additional requirements related to abnormal laboratory values and selected AEs of special interest are located in Section 6.2 (Toxicity Management).

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

Discontinuation of Study Drug and Continuation of Study Participation

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits as outlined in the Activity Schedule (Appendix D), unless subjects have decided to discontinue study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early. Following discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up visit (or phone call if a visit is not possible) after the last dose of study drug may be completed to determine the status of any ongoing AEs/serious adverse events (SAEs) or the occurrence of any new AEs/SAEs.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed that samples are withdrawn from research, samples will not be analyzed, no new biomarker analysis data will be collected, and the samples will be destroyed. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study and/or optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Study drug will be taken orally QD, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day, with or without food. Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit; study site personnel will document compliance.

Subjects will continue their disease-related concomitant medications therapy as allowed per protocol. AbbVie will not supply any disease-related concomitant medication therapy taken during the course of the study.

AbbVie will supply upadacitinib and matching upadacitinib placebo.

All study drug must be stored at controlled room temperature (15° to 25°C/59° to 77°F). Study drug will be packaged in quantities sufficient to accommodate study design.

Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drug will only be used for the conduct of the study.

The individual study drug information is presented in Table 2.

Table 2. Description of Study Drug

Investigational Product	Mode of Administration	Dosage Form	Strength	Blinded or Open Label	Frequency	Manufacturer
Upadacitinib	Oral	Film-coated tablets	15 mg or 30 mg	Blinded	QD	AbbVie
Placebo for upadacitinib	Oral	Film-coated tablets	Not applicable	Blinded	QD	AbbVie

In cases of state of emergency or pandemic situations, study drug shipment can be made from the study site to the subject if allowed by local regulations. Refer to the Operations Manual for details on direct-to-patient (DTP) shipment of study drug.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening Visit. For subjects who rescreen, the screening number assigned by the IRT at the initial Screening Visit should be used. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Subjects will be randomized in a 2:1 ratio to 1 of 2 treatment groups:

- Upadacitinib 30 mg QD (N = 40)
- Placebo (N = 20)

Randomization will be stratified by anti-TNF use prior to baseline and Hurley stage (< III or III).

Subjects in the placebo group will be switched to upadacitinib 15 mg QD at Week 12.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment through Week 12. Sites and subjects will remain blinded for the duration of the study. In order to maintain the blind, the upadacitinib tablets and placebo tablets provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of medical emergency.

In the event of a medical situation that requires unblinding of the study drug assignment, the investigator is requested to contact the AbbVie TA MD prior to breaking the blind. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie TA MD, the investigator can directly access the IRT system to break the blind without AbbVie notification or agreement. Unblinding is available in the IRT system via the Unblind Subject transaction, which is available only to the investigator. If the IRT system is unavailable, unblinding may occur by contacting the technical support of the IRT vendor via either phone (preferred) or email (support@endpointclinical.com). For country-specific phone numbers, please see the following website: http://www.endpointclinical.com/helpdesk/.

In the event that the blind is broken before notification to the AbbVie TA MD, we request that the AbbVie TA MD be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be conveyed to AbbVie and recorded on appropriate eCRF.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

In Japan, the investigator will record all protocol deviations in the appropriate medical records at the site.

5.10 Data Monitoring Committee

An external DMC composed of clinicians and statisticians independent of AbbVie and with relevant expertise in their field will review unblinded data from the ongoing study. The DMC is responsible for safeguarding the interests of trial subjects, assessing the safety as well as for monitoring the integrity and interpretability of the trial. The DMC will provide recommendations to the sponsor regarding ongoing trial conduct, or modifications to the trial as described in a separate DMC charter.

In order to maintain sponsor blinding, an external Statistical Data Analysis Center is responsible for performing the analyses described in the DMC charter as well as additional analyses requested by the DMC and facilitating interpretation and answering questions that arise before, during or after DMC review.

The DMC will regularly review unblinded safety data from the ongoing study according to the schedule provided in the DMC Charter, including AEs, laboratory values and vitals sign values.

A separate DMC charter will be prepared outside of the protocol and will further describe the roles and responsibilities of the DMC members, frequency and scope of the data reviews, and expectations for blinded communications.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject 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 (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has

been pre planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as an SAE within 24 hours of the site being made aware of the serious AE (refer to Section 4.3 of the Operations Manual [Appendix F] for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions reporting for the Investigational Medicinal Product in accordance with global and local requirements.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study:

- Serious infections
- Opportunistic infections
- Herpes zoster
- Active TB
- Malignancy (all types)
- Adjudicated gastrointestinal perforations
- Anemia
- Neutropenia
- Lymphopenia
- Renal dysfunction
- Hepatic disorder
- Adjudicated cardiovascular events (e.g., major adverse cardiovascular event [MACE])
- Adjudicated embolic and thrombotic events (non-cardiac, non-central nervous system)

Adverse Event Severity and Relationship to Study Drug

The Investigators will rate the severity of each AE according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 which can be accessed at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications.

If no grading criteria are provided for the reported event, then the event should be graded as follows:

Mild (Grade 1)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL; instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
Severe (Grade 3 - 5)	
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Cardiovascular Adjudication Committee

An independent, external committee of physician experts in cardiovascular adjudication will be utilized to assess potential cardiovascular, embolic, and thrombotic AEs in a blinded manner as defined by the Cardiovascular Adjudication Committee charter.

Gastrointestinal Perforation Adjudication

Two independent, internal adjudicators along with a third potential tie-breaker adjudicator who are gastroenterologists or who have other highly relevant clinical experience will be utilized to assess potential AEs of acute spontaneous gastroinestinal perforation in a blinded manner as defined by the Gastrointestinal Perforation Adjudication Charter.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

Female subjects should avoid pregnancy throughout the course of the study, starting with the Screening.

Visit through 30 days after the last study drug administration. Results of a positive pregnancy test or confirmation of a pregnancy will be assessed starting with the Screening Visit through the final study visit.

Subjects who become pregnant during the study must be discontinued from study drug treatment (Protocol Section 5.5).

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Toxicity Management

The toxicity management of the AEs including AEs of special interest consists of safety monitoring (review of AEs on an ongoing basis, and periodic/ad hoc review of safety issues by an independent Data Monitoring Committee), and, if applicable, interruption of study drug dosing with appropriate clinical management and/or discontinuation of the subjects from study drug. The management of specific AEs and laboratory parameters is described below.

For subjects who discontinue study drug but continue study participation and are on standard of care therapies, these toxicity management requirements do not apply (including alerts from the central laboratory) and any intolerability to standard of care therapies should be managed by the prescribing physician.

Serious Infections: Study drug should be interrupted if a subject develops a serious infection. Study drug may be restarted once the infection has been successfully treated. Subjects who develop active TB must be permanently discontinued from study drug.

Herpes zoster: If a subject develops herpes zoster, consider temporarily interrupting study drug until the episode resolves.

Gastrointestinal Perforation: If a diagnosis of gastrointestinal perforation is confirmed (other than due to appendicitis or mechanical injury), the subject must be permanently discontinued from study drug.

Malignancy: Subjects who develop malignancy other than NMSC or carcinoma in situ of the cervix must be permanently discontinued from study drug. Information including histopathological results should be queried for confirmation of the diagnosis. Periodic skin examination is recommended for subjects who are at increased risk for skin cancer.

Muscle-related symptoms: If a subject experiences symptoms suggestive of myositis or rhabdomyolysis consider checking CPK and aldolase, with clinical management and/or study drug interruption as deemed appropriate by the treating physician.

COVID-19: Interrupt study drug in subjects with a confirmed diagnosis of COVID-19. Consider interrupting study drug in subjects with signs and/or symptoms and suspicion of COVID-19. The COVID-19 eCRF must be completed.

Thrombosis Events: Subjects who develop symptoms of thrombosis should be promptly evaluated and treated appropriately. If the diagnosis of deep vein thrombosis, pulmonary embolus or non-cardiac, non-neurologic arterial thrombosis is confirmed, the subject must be discontinued from study drug.

Management of Select Laboratory Abnormalities: For any given laboratory abnormality, the investigator should assess the subject, apply the standard of care for medical evaluation and treatment following any local guidelines. Specific toxicity management guidelines for abnormal laboratory values are described in Table 3, and may require a supplemental eCRF to be completed. For subjects with ongoing laboratory abnormalities which require data entry into an eCRF, an additional eCRF related to subsequent laboratory abnormalities is only required if the subject has relevant changes in history (e.g., new onset signs or symptoms) or laboratory values which have returned to normal reference range or its Baseline value followed by subsequent laboratory abnormalities meeting toxicity guidelines (considered a new event). All abnormal laboratory tests that are considered clinically significant by the investigator will be followed to a satisfactory resolution. If a repeat test is required per Table 3, the repeat testing is to occur as soon as possible.

Table 3. Specific Toxicity Management Guidelines for Abnormal Laboratory Values

Laboratory Parameter	Toxicity Management Guideline
Hemoglobin	• If hemoglobin < 8 g/dL, interrupt study drug dosing and confirm by repeat testing with a new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline without an alternative etiology, interrupt study drug dosing and confirm by repeat testing with new sample. • If hemoglobin decreases ≥ 3.0 g/dL from Baseline and an alternative etiology is known or the hemoglobin value remains in the normal reference range, the subject may remain on study drug at the Investigator's discretion. • If confirmed, continue to withhold study drug until hemoglobin value returns to normal reference range or its Baseline value.
ANC	• If confirmed < 1000/µL by repeat testing with new sample, interrupt study drug dosing until ANC value returns to normal reference range or its Baseline value. • Interrupt study drug if confirmed < 500/µL by repeat testing with new sample. If value returns to normal reference range or its Baseline value, restarting study drug is allowed if there is an alternative etiology identified; documentation should include reason that rechallenge is expected to be safe for the subject. Study drug should be discontinued if no alternative etiology can be found.

Laboratory Parameter	Toxicity Management Guideline
ALC	• If confirmed < 500/µL by repeat testing with new sample, interrupt study drug dosing until ALC returns to normal reference range or its Baseline value.
Total WBC count	• If confirmed < 2000/µL by repeat testing with new sample, interrupt study drug dosing until WBC count returns to normal reference range or its Baseline value.

AST or ALT	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample and either a total bilirubin > 2 × ULN or an international normalized ratio > 1.5.
	  • A separate blood sample for international normalized ratio (INR) testing will be needed to measure INR at the time of repeat testing for ALT or AST. A repeat test of INR is not needed for determination if above toxicity management criteria are met.
	• Interrupt study drug if confirmed ALT or AST > 3 × ULN by repeat testing with new sample along with new appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5% increase from Baseline).
	• Interrupt study drug if confirmed ALT or AST > 5 × ULN by repeat testing with new sample for more than 2 weeks.
	• If ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD.
	Subjects with HBc Ab+ (irrespective of hepatitis B surface antibody status) and negative HBV DNA PCR testing at Screening who develop the following laboratory findings should have HBV DNA PCR testing performed within 1 week (based on initial elevated value):
	• ALT > 5 × ULN OR
	• ALT or AST > 3 × ULN if an alternative cause is not readily identified.
	  • A separate blood sample for HBV DNA PCR testing will be needed at the time of repeat testing for ALT or AST.
	A positive result for HBV DNA PCR testing will require immediate interruption of study drug (unless not acceptable by local practices) and a hepatologist consultation should occur within 1 week for recommendation regarding subsequent treatment.
	Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the eCRF. If ALT or AST values return to the normal reference range or its Baseline value, study drug may be restarted. If restarting study drug, documentation should include reason that rechallenge is expected to be safe. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.
	For any confirmed ALT or AST elevations > 3 ULN, complete the appropriate supplemental hepatic eCRF(s).

Laboratory Parameter	Toxicity Management Guideline
Serum Creatinine	• If serum creatinine is > 1.5 × the Baseline value and > ULN, repeat the test for serum creatinine (with subject in an euvolemic state) to confirm the results. If the results of the repeat testing still meet this criterion, then interrupt study drug and restart study drug once serum creatinine returns to ≤ 1.5 × Baseline value and ≤ ULN. For the above serum creatinine elevation scenarios, complete the supplemental renal eCRF.

Elective and Emergency Surgeries

For elective and emergency surgeries the following rules will apply:

- If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery. After emergency surgery, allow reintroduction of study drug once the physician has examined the surgical site and determined that study drug may be safely restarted.
- Elective surgery, and interruption of study drug for such a surgery, will not be allowed until after the Week 16 visit has been completed. If the subject undergoes elective surgery, the study drug should be interrupted at least 1 week prior to the planned surgery. Allow reintroduction of study drug once the physician has examined the surgical site and determined that study drug may be safely restarted.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The Primary Analysis will be conducted after all ongoing subjects have completed Week 12, data pertaining to Period 1 has been cleaned, and a database lock has occurred for the purpose of efficacy and safety analysis in Period 1. The efficacy analysis performed based on this database lock is the only and final analysis for Period 1. Study sites and subjects will remain blinded for the duration of the study.

7.2 Definition for Analysis Populations

The Intent to Treat (ITT) Population includes all randomized subjects. Subjects will be included in the analysis based on treatment as randomized. The ITT Population will be used for all efficacy analyses.

The following populations will be used for the safety analysis:

- The Safety Population in Period 1 (Safety_1) is defined as all subjects who are randomized and received at least one dose of study drug in Period 1.
- The All Upadacitinib Treated (ALL_UPA) Population is defined as subjects who received at least one dose of upadacitinib in the study. This population will be used to provide a comprehensive summary of safety.

For safety analyses, subjects will be analyzed based on the treatment actually received.

7.3 Statistical Analyses for Efficacy

Primary Efficacy Analysis

Analysis of the primary endpoint will be conducted in the ITT Population based on treatment as randomized. Comparison of the primary endpoint will be made between upadacitinib 30 mg QD and historical placebo rate using a one sample Chi-square test. For the primary analysis, Non-Responder Imputation while incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) will be used to handle missing data. A supplementary analysis will be performed to compare upadacitinib 30 mg QD versus in-trial placebo group combined with unblinded placebo data from existing trials.

Secondary Efficacy Analysis

The secondary endpoint will be analyzed using the same method as for the primary endpoint. In addition, analgesic use will be handled as follows:

- Prohibited analgesic (including opioids): A subject will be counted as a non-responder from the day that the subject initiates prohibited analgesic to 5 days after the end of such analgesic use.
- Protocol-allowed analgesic use:
  - A subject who enters the study without concomitant analgesic will be counted as a non-responder from the day that the subject initiates a protocol-allowed analgesic to 2 days after the end of such analgesic use.
  - A subject who entered the study on a stable dose of a protocol-allowed concomitant analgesic will be counted as a non-responder from the first day of an analgesic dose increase to 2 days after the end of the dose increase.

Additional Efficacy Analyses

Details on additional efficacy analyses are provided in the SAP.

Subgroup Analysis for Efficacy

To evaluate the consistency of the efficacy over demographic and other baseline characteristics, summaries will be provided for the following subgroups for the primary efficacy endpoint.

- Age group (< 40 years, ≥ 40 – < 65 years, ≥ 65 years)

- Sex (male, female)
- Race (white, non-white)
- Smoking (current, ex or never)
- Body mass index (normal: < 25, overweight: ≥ 25 – < 30, obese: ≥ 30)
- Duration of HS (by median)
- Prior exposure to TNF antagonists (yes, no)
- Baseline Hurley stage (II, III)

7.4 Statistical Analyses for Safety

All safety analyses will be performed on the safety populations. Subjects will be analyzed based on the treatment actually received. The number and percentage of subjects experiencing AEs will be tabulated using Medical Dictionary for Regulatory Activities system organ class and preferred term, as well as by severity and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient years) of SAEs, deaths, and AEs leading to discontinuation will be provided as well. For selected lab parameters, a listing of all subjects with any laboratory value above Grade 3 of Common Toxicity Criteria will be provided. Mean change in laboratory and vital signs variables will be summarized. Additional details for the safety analysis will be provided in the SAP.

7.5 Interim Analysis

No formal interim analysis of efficacy is planned for this study. Routine safety reviews will be performed by an external DMC (see details given in Section 5.10).

7.6 Overall Type I Error Control

Not applicable for this study.

7.7 Sample Size Determination

The primary endpoint is the achievement of HiSCR at Week 12. The primary analysis compares the proportion of subjects achieving HiSCR response to that of historical placebo (25% HiSCR response). Assuming the Week 12 HiSCR response is 57% for the upadacitinib 30 mg arm, 40 subjects on upadacitinib will provide more than 95% power with a one-sample Chi-square test and one-sided alpha = 0.05 significance level.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In cases of state of emergency or pandemic situations leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to the Operations Manual for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie of any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the

currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

In cases of state emergency or pandemic situations, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever is later.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AD	Atopic dermatitis
ADL	Activities of daily living
AE	Adverse event
ALC	Absolute lymphocyte count
ALT	Alanine transaminase
AN	Abscess and inflammatory nodule
ANC	Absolute neutrophil count
AST	Aspartate transaminase
CL/F	Oral clearance
COVID-19	Coronavirus disease - 2019
CXR	Chest x-ray
CYP3A	Cytochrome P450 3A
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DTP	Direct-to-patient
ECG	Electrocardiogram
eCRF	electronic case report form
EU	European Union
FSH	Follicle stimulating hormone
HBc Ab	Hepatitis B core antibody
HBV	Hepatitis B virus
HCV	Hepatitis V virus
HDL-C	High-density lipoprotein cholesterol
HiSCR	Hidradenitis Suppurative Clinical Response
HIV	Human immunodeficiency virus
HIV Ab	HIV antibody
hsCRP	High sensitivity C-reactive protein
HS	Hidradenitis suppurativa
HSSA	Hidradenitis Suppurativa Symptom Assessment

HSIA	Hidradenitis Suppurativa Impact Assessment
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IRB	Institutional Review Board
IRT	interactive response technology
ITT	Intent-to-treat
JAK	Janus kinase
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
NMSC	Nonmelanoma skin cancer
NRI	non-responder imputation
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PGA	Patient's Global Assessment
PK	Pharmacokinetic
PPD	Purified protein derivative
PRN	As needed
PRO	Patient reported outcome
QD	Once daily
RA	Rheumatoid arthritis
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
STAT	Signal transducer and activator of transcription
STEEP	Skin-tissue-saving excision with electrosurgical peeling
TA MD	Therapeutic Area Medical Director
TB	Tuberculosis

TNF	Tumor necrosis factor
Tyk2	Tyrosine kinase 2
ULN	Upper limit of normal
US	United States
V/F	Volume of distribution
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-040: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adult Subjects with Moderate to Severe Hidradenitis Suppurativa

Protocol Date: 25 October 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Study Project Manager II	Clinical Program Development
[redacted]	Senior Medical Writer	Medical Writing
[redacted]	Executive Medical Director	Immunology Development
[redacted]	Therapeutic Area Medical Director	Immunology Development
[redacted]	Senior Scientific Director	Immunology Development
[redacted]	Senior Manager	Statistics
[redacted]	Senior Director and Therapeutic Area Head (Immunology)	Statistics
[redacted]	Director and Therapeutic Area Lead (Dermatology)	Statistics
[redacted]	Director	Clinical Pharmacology and Pharmacometrics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across all visits. The individual activities are described in detail in the Operations Manual (Appendix F). Allowed modifications due to COVID-19 are detailed within the Operations Manual.

Study Activities Table

Activity	Screening	Baseline	Week 2[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 24[a]	Week 32[a]	Week 40[a]	Week 48[a]/ Premature Discontinuation	30-Day Follow Up Visit/Call
	Day –35 to Day –1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 112	Day 168	Day 224	Day 280	Day 336	
Visit Window	± 3 Days						± 7 Days					
INTERVIEWS & QUESTIONNAIRES												
Informed consent	✓											
Eligibility criteria	✓	✓										
Medical/surgical history	✓	✓										
Hidradenitis suppurativa history	✓	✓										
Alcohol and nicotine use	✓											
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Analgesic use (for HS-related pain) – daily from at least 7 consecutive days prior to Baseline and up to Week 16	✓	✓	✓	✓	✓	✓	✓					
Patient Reported Outcomes (PROs): PGA Skin Pain– daily from at least 7 consecutive days prior to Baseline and up to Week 16; afterwards for 7 consecutive days leading up to each visit	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

Activity	Screening	Baseline	Week 2[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 24[a]	Week 32[a]	Week 40[a]	Week 48[a]/ Premature Discontinuation	30-Day Follow Up Visit/Call
	Day –35 to Day –1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 112	Day 168	Day 224	Day 280	Day 336	
PROs: HSSA – 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits	✓	✓	✓	✓	✓	✓	✓	✓			✓	
PROs: HSIA		✓		✓		✓	✓					
PROs: DLQI		✓				✓	✓					
Dispense handheld ePRO device and the paper diary (for Analgesic Use for HS-related pain)	✓											
Collect handheld ePRO device											✓	
TB risk assessment questionnaire	✓											
Review and document pregnancy avoidance recommendations with females of childbearing potential	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
LOCAL LABS & EXAMS												
Chest x-ray	✓											
12-lead ECG	✓											
Height (screening only) and weight	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓				✓					✓	
Investigator assessments (abscess, inflammatory nodule, and draining fistula/tunnel count)		✓	✓	✓	✓	✓	✓	✓	✓	✓		
Hurley Stage		✓				✓			✓			
Urine pregnancy test (at Baseline and thereafter at monthly intervals)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Beta-D-glucan (Japan only)	✓											

Activity	Screening	Baseline	Week 2[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 24[a]	Week 32[a]	Week 40[a]	Week 48[a]/ Premature Discontinuation	30-Day Follow Up Visit/Call
	Day –35 to Day –1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 112	Day 168	Day 224	Day 280	Day 336	
CENTRAL LABS												
HBV/HCV screening, HIV Ab (Note: HBV testing is done every 12 weeks where required)	✓											
Serum pregnancy test, FSH (as applicable)	✓											
QuantiFERON-TB Gold Plus test (and/or local PPD skin test)	✓											
High sensitivity C-reactive protein (hsCRP)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical chemistry and hematology	✓	✓	✓	✓	✓	✓	✓[b]	✓	✓	✓	✓	
Urinalysis	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (fasting)		✓				✓		✓			✓	
Blood samples for PK assay		✓	✓		✓	✓	✓	✓				
Optional biomarker samples: Whole blood RNA		✓		✓		✓		✓			✓	
Optional biomarker sample: Whole blood DNA		✓				✓		✓				
Optional biomarker sample: Plasma/serum proteomic		✓		✓		✓		✓			✓	
Optional biomarker sample: Whole blood immunoglobulin G (IgG)		✓		✓		✓		✓			✓	
Optional biomarker sample: B cell subsets		✓		✓		✓		✓			✓	

Activity	Screening	Baseline	Week 2[a]	Week 4[a]	Week 8[a]	Week 12[a]	Week 16[a]	Week 24[a]	Week 32[a]	Week 40[a]	Week 48[a]/ Premature Discontinuation	30-Day Follow Up Visit/Call
	Day –35 to Day –1	Day 1	Day 15	Day 29	Day 57	Day 85	Day 112	Day 168	Day 224	Day 280	Day 336	
Optional biomarker sample: PBMC		✓				✓		✓				
TREATMENT												
Randomization/drug assignment		✓										
Re-Randomization/drug assignment						✓						
Dispense study drug & subject dosing diary		✓	✓	✓	✓	✓	✓	✓	✓	✓		

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. Additional clinical hematology tests are recommended at Week 20 (unscheduled visit) for subjects who have absolute neutrophil counts < 1,200/µL or hemoglobin < 9 g/dL at Week 16.

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	09 March 2020

The purpose of this version is to update safety information, correct minor clerical errors for consistency throughout the protocol, and incorporate necessary protocol modifications due to the COVID-19 pandemic as follows:

Modifications to the Protocol and Operations Manual due to State-of Emergency or Pandemic Situations

One of the purposes of this version is to provide flexibility during state-of emergency or pandemic situations so subjects may safely enroll and continue study participation as follows:

- Included information in Section 2.2 on the re-evaluation of the benefit and risk to subjects participating in the study. The benefit:risk profile of various immunomodulatory therapies is being evaluated.

  Rationale: *To clarify the benefit:risk balance to participating subjects in this study in light of the COVID-19 pandemic.*

- In Section 5.1, updated eligibility criterion #14 with details regarding subject eligibility with regards to COVID-19 infection.

  Rationale: *Modified eligibility criteria to exclude subjects with suspected or confirmed active COVID-19 infection to maintain subject safety.*

- Modify the following sections to account for state-emergency or pandemic situations:
  - Update Section 5.7 and Operations Manual Section 3.18 to permit direct-to-patient (DTP) shipment of study drug in the event the subject cannot pick up study drug onsite.
  - Update Section 8.2 with a reference to the Operations Manual to permit modifications to the study protocol as necessary due to state-of emergency or pandemic situations and note investigators should also notify AbbVie if any urgent safety measures are taken.
  - Update Section 9 to note that remote monitoring may be employed as needed.
  - Update Appendix D to add reference to Operations Manual for allowed modifications.

  Rationale: *To provide flexibility during state-of emergency or pandemic situations to ensure the safety of subjects, maintain protocol compliance, and minimize risk to the integrity of the study while trying to best manage continued care of study subjects.*

- Update Section 6.2 with toxicity management guidelines related to COVID-19.

  Rationale*: To clarify guidelines for interruption of study drug in event of confirmed diagnosis of COVID-19.*

- The following modifications were made in the Operations Manual to account for state-of emergency or pandemic situations:
  - Update Section 2 and Section 2.1 with specifics regarding activities that may be affected by state-of emergency or pandemic situations, including a table in Section 2.1 specifying alternate locations at which certain activities may be performed.
  - Update Section 3.3 to clarify subject information and informed consent in case of state-of emergency or pandemic situations.
  - Update Section 3.7 to clarify that all PROs (except at Baseline and Week 12 visits) may be conducted via phone or video conference in the case of state-of emergency or pandemic situations. Details instructions regarding PROs conducted over the phone or video conference are also provided.
  - Update Section 3.19 with instructions on performing laboratory work in the case of a state-of emergency or pandemic situation.
  - Update Section 4.1 to add COVID-19 as an event necessitating a supplemental eCRF.

  Rationale: *To provide flexibility for subject activities while ensuring subject safety during state-of emergency or pandemic situations.*

Protocol

- Added a reference in Section 2.1 and Section 12 and deleted 3 references to support text regarding cytokines and receptors that signal via the JAK1 pathway and are elevated in HS.

  Rationale: *To update text with the most recent data available.*

- In Section 3.3, updated primary and secondary endpoints will be analyzed 'at' instead of 'for' all visits other than Week 12.

  Rationale: *Corrected typographical error.*

- In Section 3.3, updated additional endpoints to be analyzed at visits noted in the Study Activities Table.

  Rationale: *To clarify additional endpoints are not measured/analyzed at all visits.*

- In Section 5.1, eligibility criterion #5, added clarification of HS diagnosis by the investigator.

  Rationale: *To clarify diagnosis of HS is determined by the investigator through medical history and subject interview.*

- In Section 5.1, eligibility criterion #27, clarified that subjects must not have received prescription topical therapies (including topical antibiotics) that can also be used to treat HS within 14 days prior to the Baseline visit.

  Rationale: *To clarify potential prescribed treatments for HS.*

- In Section 5.1, eligibility criterion #29, clarified that subjects must not have received any systemic (including oral) antibiotic treatment for HS or any other chronic inflammatory disorder within 4 weeks prior to the Baseline visit.

Rationale: *To clarify the eligibility of subjects with prior systemic antibiotic treatment for chronic inflammatory disorder other than HS.*

- In Section 5.1, eligibility criterion #31, added clarification that subjects who are on non-opioid analgesics for HS or non-HS related pain, are expected to remain on a stable dose and dosing regimen at least until the Week 16 visit.

  Rationale: *To clarify the dose and dose regimen for subjects on non-opioid analgesics for HS or non-HS related pain.*

- In Section 5.3, added that the use of methotrexate at >25 mg/week is prohibited.

  Rationale: *To clarify the maximum dose of methotrexate as a background therapy during the study.*

- In Section 5.3, clarified that the use of methotrexate and oral corticosteroids (regardless of dose) is prohibited until after Week 16 assessments.

  Rationale: *To prohibit the use of any methotrexate or oral corticosteroids until after Week 16 assessments.*

- In Section 5.3, restricted the use of new topical therapies used to treat HS (other than protocol-allowed antiseptic) or changes in the concentration/frequency of current topical therapies used to treat HS.

  Rationale: *To clarify the restriction regarding new topical therapies and changes in the concentration/frequency of current topical therapies.*

- In Section 5.3, clarified that the use of concomitant antibiotics is not permitted for the treatment of chronic inflammatory disorders.

  Rationale: *To clarify the use of antibiotics to treat other chronic inflammatory disorders besides HS.*

- In Section 5.5, updated that subjects must have study discontinued immediately if abnormal laboratory results or AEs that either meet the criteria for discontinuation of study drug as stated in Protocol Section 6.2 or rule out safe continuation of the study drug, and serious infections which cannot be adequately controlled by anti-infective treatment or would put the subject at risk with continuation of study drug.

  Rationale: *To clarify the circumstances warranting study drug discontinuation.*

- In Section 5.9, corrected that if a protocol deviation occurs (or is identified), the investigator is responsible for notifying listed committee, regulatory authorities, and sponsors.

  Rationale: *Corrected typographical error.*

- In Section 6.2, removed wording '(for Study 1 and Study 2)' from Table 3 (Specific Toxicity Management Guidelines for Abnormal Laboratory Values) title.

  Rationale: *Updated for clarity.*

- In Section 6.2, updated toxicity management guidelines from Table 3 to clarify that if ALT or AST > 8 × ULN, interrupt study drug immediately, confirm by repeat testing with a new sample, and contact the TA MD.

Rationale: *To update toxicity management guidelines according to revised upadacitinib safety standard language.*

- In Section 7.3, added clarification that for the primary analysis, Non-Responder Imputation while incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C) will be used to handle missing data.

  Rationale: *Updated primary efficacy analysis to handle missing data due to COVID-19 infection or logistical reasons.*

- In Section 7.3, updated that 'supplementary' analysis instead of 'sensitivity' analysis will be performed for the primary endpoint.

  Rationale: *Updated analysis description based on the finalization of the ICF-E9R1 guidelines.*

- In Section 7.4, deleted the following text: 'Pre-treatment AEs will be summarized separately."

  Rationale: *Removed unnecessary detail.*

- In Section 7.7, corrected sample size determination to be analyzed by a one-sample Chi-square test instead of a one-sample t-test.

  Rationale: *Corrected typographical error.*

- In Appendix C, updated the protocol signatories.

  Rationale: *to align protocol text with relevant standard operating procedures and update due to personnel changes for this study.*

- In Appendix D, updated the Activity Schedule table as follows:
  - Added visit windows.
  - Added that assessments for analgesic use (for HS-related pain), PGA Skin Pain, and HSSA will be collected at the Screening visit.
  - Added clarification that analgesic use (for HS-related pain) will be collected daily from at least 7 consecutive days prior to Baseline and up to Week 16, and that PGA Skin Pain will be collected daily from at least 7 consecutive days prior to Baseline and up to Week 16 and afterwards for 7 consecutive days leading up to each visit.
  - Added clarification that the HSSA assessment will be collected 7 consecutive days prior to the Baseline visit and the visits at Weeks 2, 4, 8, 12, 16, 24, and 48/PD.
  - Added "paper diary (for Analgesic Use for HS-related Pain" as an additional method of PRO assessment collection.
  - Added footnote 'a' to clarify the timing of study activities if subjects are out of the visit window.

  Rationale: *To clarify study conduct and activities at different visits and for consistency with Section 2 of the Operations Manual.*

Operations Manual

- Appendix F – Operations Manual was updated to include details on how to perform specific activities/procedures that may be impacted by changes in global/local regulations due to the pandemic.

  Rationale: *To reflect necessary changes in study activities and procedures due to the COVID-19 pandemic.*

- In Appendix F – Operations Manual, Section 2.1 was updated in the following ways:
  - Added text describing the visit windows for study visits.
  - Added text to specify that all visits with the exception of Screening, Baseline, and Week 12 may be conducted remotely or in the subject's home residence.
  - Added text and footnotes to clarify that laboratory draws (except for blood samples for PK assay) should be obtained as soon as feasible and preferably within the protocol-defined visit window for the scheduled visit. Blood samples for PK assay that cannot be performed on-site for a specific will be considered missing.
  - Added text to specify paper diary (for Analgesic Use for HS-related Pain) as an additional method of PRO assessment collection.
  - Added PGA Skin Pain, Analgesic Use, and HSSA as PRO assessments at the Screening visit. Updated the footnotes that Analgesic use (for HS-related pain) will be collected daily from at least 7 consecutive days prior to Baseline and up to Week 16, PGA Skin Pain will be collected daily from at least 7 consecutive days prior to Baseline and up to Week 16 and afterwards for 7 consecutive days leading up to each visit Baseline, and HSSA will be collected 7 consecutive days prior to the Baseline visit and the visits at Weeks 2, 4, 8, 12, 16, 24, and 48/PD.
  - Reordered some footnotes that were not in alphabetical order.
  - Corrected footnote 'f' to 'HBs Ab+ and HBcAb-' for Weeks 12, 24, and 48 study visit tables.
  - Added a footnote to clarity the timing of study activities if subjects are out of the visit window.
  - Added the footnote that if urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.
  - Removed footnote 'e' for pre-dose sample collection at the Week 48 visit table since there is no dosing at Week 48.

  Rationale: *For clarify regarding study conduct and consistency with Appendix D of the protocol.*

- In Section 3.12, removed wording 'annually if required by country regulatory authorities.'

  Rationale: *To clarify there is no annual requirement for the 12-lead ECG assessment.*

- In Section 3.19, the figure for the interpretation and management of HBV serologic test results was updated to reflect the correct placement of footnotes, and a related figure footnote was update to include the HBV DNA PCR test may be tested at unscheduled visits.

  Rationale: *To update hepatitis screening guidelines for interpretation and management of HBV serologic test results according to revised upadacitinib safety standard language.*

- In Section 3.20, removed wording 'except for annual TB testing.'

  Rationale: *To add clarification that annual TB testing is not required.*

In addition to these modifications, minor typographical edits and corrections were throughout the protocol and operations manual for consistency, and other revisions were made for clarity and readability (e.g., addition of abbreviations, rearrangement of text).

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M20-040

Evaluation of Upadacitinib in Adult Subjects with Hidradenitis Suppurativa

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	Upadacitinib

FULL TITLE: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate Upadacitinib in Adult Subjects with Moderate to Severe Hidradenitis Suppurativa

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted] MD AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064, USA **EMERGENCY 24 hour Number:** [redacted]	Office: [redacted] Mobile: Fax: Email:
Safety Concerns	Immunology Safety Team Bldg. AP51-3 1 North Waukegan Road North Chicago, IL 60064, USA	Phone: +1 (847) 938-8737 Email: GPRD_SafetyManagement_Immunology@abbvie.com
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Protocol Deviations and Product complaints	[redacted] AbbVie Deutschland Knollstrasse 67061 Ludwigshafen Germany	Phone: [redacted] Fax: Email:
Certified Clinical Lab	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214, USA	Phone: 1 (866) 762-6209 (Toll free) +1 (317) 271-1200 (Local calls) Fax: +1 (317) 616-2362 For country specific toll free numbers please refer to Covance Lab Manual.
Pharmacokinetic Laboratory	AbbVie Inc. Sample Receiving Dept. R46W, Bldg. AP13A, Rm. 2310 1 North Waukegan Rd. North Chicago, IL 60064, USA	Phone: +1 (847) 937-0889 Fax: +1 (847) 938-9898
Exploratory Sample Laboratory	BioStorage Technologies, Inc. BioStorage Receiving Department 2910 Fortune Circle West, Suite E Indianapolis, IN 46241, USA	Phone: +1 (317) 452-4287 Fax: +1 (317)-241-5202
Genomic Sample Laboratory	Pharmacogenetics and Pharmacogenomics Dept. R4AE, Bldg. AP32, Room 1 - 224 AbbVie 1 North Waukegan Rd. North Chicago, IL 60064, USA	Phone: +1 (847) 938-8525

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to cases of state of emergency or pandemic situations. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent sections. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted on-site due to travel restrictions or other state of emergency or pandemic-related reasons, follow the updates below on how to proceed. Supplemental study case report forms should be completed in the event of missed/virtual visits, or study drug interruptions or discontinuations related to coronavirus disease 2019 (COVID-19).

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Treatment Period Activity Schedule.

Subjects will be allowed a visit window of ± 3 days for all study visits (with the exception of the Baseline Visit, as the screening window is a maximum of 35 days) up to the Week 16 visit. Visits after the Week 16 visit will have a visit window of ± 7 days.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

During a state of emergency or pandemic situation, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- If permitted by local regulations, the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC), and the subject, some study visits and/or activities may be performed by phone/virtually. These are indicated by a hashtag (#) in the appropriate visit table(s) below.
- Some study visits and/or activities may be performed by a local clinic/hospital/laboratory. These are indicated by a plus sign (+) in the appropriate visit table(s) below. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Study visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications should be followed:
  - The Screening, Baseline, and Week 12 visits should be performed on-site only.
  - If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity. Laboratory draws for safety assessments should be obtained as soon as feasible and preferably within the protocol-defined visit window for the scheduled visit. Blood samples for PK assay that cannot be performed on-site for a specific visit will be considered missed.

SCREENING:

INTERVIEW	• Subject information and informed consent[a] • Eligibility criteria • Medical/surgical history • Hidradenitis suppurativa (HS) history • Alcohol and nicotine use	• Prior/concomitant therapy • Adverse event (AE) assessment[b] • Tuberculosis (TB) risk assessment questionnaire[c] • Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• Dispense handheld electronic patient reported outcome (ePRO) device and the paper diary (for Analgesic Use for HS-related pain) for initiation of daily data collection	• Patient's Global Assessment (PGA) Skin Pain[d] • Analgesic Use[d] • Hidradenitis Suppurativa Symptom Assessment (HSSA)[d]
EXAM	• Electrocardiogram (ECG)[e] • Height, weight • Vital signs	• Physical examination • Chest X-ray (CXR)[f]
LOCAL LAB	• Purified protein derivative (PPD) skin test[g]	• Beta-D-glucan (Japan only)
CENTRAL LAB	• Hematology • Blood chemistry • Urinalysis • QuantiFERON-TB Gold Plus test[g] • Hepatitis B virus (HBV)/hepatitis C virus (HCV) screening	• Anti-human immunodeficiency (HIV) testing[h] • Follicle stimulating hormone (FSH)[i] • Serum pregnancy test[j]

NOTES:

All screening procedures must be performed on-site.

a. Obtain informed consent prior to performing any study-related procedures.

b. Collect serious adverse events (SAEs) and protocol-related nonserious AEs that occur after a subject signs the informed consent, prior to the first dose of study dug (refer to Section 4.1 for additional details).

c. Complete entire form (Part I and Part II).

d. PGA Skin Pain and Analgesic use (for HS-related pain) will be collected daily from at least 7 consecutive days prior to Baseline. HSSA will be collected for 7 consecutive days prior to Baseline.

e. Screening ECG not required if subject had normal ECG within 90 days of Screening (refer to Section 3.12 for additional details).

f. Screening CXR not required if subject had normal CXR (posterior-anterior and lateral views) within 90 days of Screening (refer to Section 3.13 for additional details).

g. The QuantiFERON-TB Gold Plus test (or equivalent) should be performed on all subjects. The PPD skin test should be utilized when the QuantiFERON-TB Gold Plus test (or equivalent) is not possible or if both tests are required per local guidelines.

h. Anti-HIV Ab performed at Screening, unless prohibited by local regulations (refer to Section 3.19 for additional details).

i. FSH tested at Screening if female subject is ≤ 55 years of age AND has had no menses ≥ 12 months AND has no history of permanent surgical sterilization (refer to Section 3.19 for additional details).

j. For all females of childbearing potential (refer to Section 3.19 for additional details).

BASELINE VISIT[a] (DAY 1):

INTERVIEW	• Eligibility criteria • Medical/surgical history • HS history • Prior/concomitant therapy	• AE assessment • Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b] • Analgesic Use[c] • HSSA[d]	• Hidradenitis Suppurativa Impact Assessment (HSIA) • Dermatology Life Quality Index (DLQI)
EXAM	• Weight • Vital signs • Physical examination	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count) • Hurley stage
LOCAL LAB	• Urine pregnancy test[e]	
CENTRAL LAB	• Hematology • Blood chemistry • Urinalysis • High-sensitivity C-reactive protein (hsCRP) • Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (fasting)	• Blood samples for pharmacokinetic (PK) assay • Optional blood samples for biomarkers:[f] whole blood ribonucleic acid (RNA), whole blood deoxyribonucleic acid (DNA), plasma/serum proteomic, immunoglobulin G (IgG) and B cell subsets, and peripheral blood mononuclear cells (PBMC)
TREATMENT	• Randomization • Dispense study drug and dosing diary	

NOTES:

All Day 1 procedures must be performed on-site.

a. Baseline Visit procedures will serve as reference for all subsequent visits with the exception of ECG (obtained at Screening only and used as the baseline reference).

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. Analgesic use for HS-related pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16.
d. HSSA is collected for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.
e. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).
f. Samples should be collected pre-dose.

WEEK 2[a]:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b] • Analgesic Use[c]	• HSSA[d]
EXAM	• Weight • Vital signs	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count)
LOCAL LAB	#,+ Urine pregnancy test[e,f]	
CENTRAL LAB	+ Hematology + Blood chemistry	• hsCRP • Blood samples for PK assay[g]
TREATMENT	• Dispense study drug and dosing diary	

NOTES:
a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.
b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.
c. Analgesic use for HS-related pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16.
d. HSSA is collected for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.
e. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).
f. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.
g. Blood samples for PK assay that cannot be performed on-site for a specific visit due to COVID-19 will be considered missed.

WEEK 4[a]:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b] • Analgesic Use[c]	• HSSA[d] # HSIA
EXAM	• Weight • Vital signs	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count)
LOCAL LAB	#,+ Urine pregnancy test[e,f]	
CENTRAL LAB	+ Hematology + Blood chemistry + Urinalysis • hsCRP	• Optional blood samples for biomarkers:[g] whole blood RNA, plasma/serum proteomic, IgG and B cell subsets
TREATMENT	• Dispense study drug and dosing diary	

NOTES:

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. Analgesic use for HS-related pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16.

d. HSSA is collected for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.

e. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

f. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

g. Samples should be collected pre-dose.

WEEK 8[a]:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b] • Analgesic Use[c]	• HSSA[d]
EXAM	• Weight • Vital signs	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count)
LOCAL LAB	#,+ Urine pregnancy test[e,f]	
CENTRAL LAB	+ Hematology + Blood chemistry + Urinalysis	• hsCRP • Blood samples for PK assay[g]
TREATMENT	• Dispense study drug and dosing diary	

NOTES:

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. Analgesic use for HS-related pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16.

d. HSSA is collected for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.

e. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

f. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

g. Blood samples for PK assay that cannot be performed on-site for a specific visit due to COVID-19 will be considered missed.

WEEK 12[a]:

INTERVIEW	• AE assessment • Concomitant therapy	• Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b] • Analgesic Use[c] • HSSA[d]	• HSIA • DLQI
EXAM	• Weight • Vital signs • Physical examination	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count) • Hurley stage
LOCAL LAB	#,+ Urine pregnancy test[e]	
CENTRAL LAB	• Hematology • Blood chemistry • Urinalysis • HBV testing, where required[f] • hsCRP • Total cholesterol, HDL-C, LDL-C, and triglycerides (fasting)	• Blood samples for PK assay • Optional blood samples for biomarkers:[g] whole blood RNA, whole blood DNA, plasma/serum proteomic, IgG and B cell subsets, and PBMC
TREATMENT	• Study drug reassignment • Dispense study drug and dosing diary	

NOTES:

All Week 12 procedures must be performed on-site.

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. Analgesic use for HS-related pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16.

d. HSSA is collected for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.

e. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

f. Where mandated by local requirements, subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–.

g. Samples should be collected pre-dose.

WEEK 16[a]:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b] • Analgesic Use[c] • HSSA[d]	# HSIA # DLQI
EXAM	• Weight • Vital signs	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count)
LOCAL LAB	#,+ Urine pregnancy test[e,f]	
CENTRAL LAB	+ Hematology[g] + Blood chemistry + Urinalysis	• hsCRP • Blood samples for PK assay[h]
TREATMENT	• Dispense study drug and dosing diary	

NOTES:

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. Analgesic use for HS-related pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16.

d. HSSA data collection for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.

e. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

f. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

g. Additional clinical hematology tests are recommended at Week 20 (unscheduled visit) for subjects who have absolute neutrophil counts < 1,200 µL or hemoglobin < 9 g/dL at Week 16.

h. Blood samples for PK assay that cannot be performed on-site for a specific visit due to COVID-19 will be considered missed.

WEEK 24[a]:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b]	• HSSA[c]
EXAM	• Weight • Vital signs	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count)
LOCAL LAB	#,+ Urine pregnancy test[d,e]	
CENTRAL LAB	+ Hematology + Blood chemistry + Urinalysis + HBV testing, where required[f] • hsCRP + Total cholesterol, HDL-C, LDL-C, and triglycerides (fasting)	• Blood samples for PK assay[g] • Optional blood samples for biomarkers:[h] whole blood RNA, whole blood DNA, plasma/serum proteomic, IgG and B cell subsets, and PBMC
TREATMENT	• Dispense study drug and dosing diary	

NOTES:

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. HSSA data collection for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.

d. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

e. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

f. Where mandated by local requirements, subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–.

g. Blood samples for PK assay that cannot be performed on-site for a specific visit due to COVID-19 will be considered missed.

h. Samples should be collected pre-dose.

WEEK 32[a]:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b]	
EXAM	• Weight • Vital signs	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count) • Hurley Stage
LOCAL LAB	#,+ Urine pregnancy test[c,d]	
CENTRAL LAB	+ Hematology + Blood chemistry + Urinalysis	• hsCRP
TREATMENT	• Dispense study drug and dosing diary	

NOTES:

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

d. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

WEEK 40[a]:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b]	
EXAM	• Weight • Vital signs	• Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula/tunnel count)
LOCAL LAB	#,+ Urine pregnancy test[c,d]	
CENTRAL LAB	+ Hematology + Blood chemistry + Urinalysis	• hsCRP
TREATMENT	• Dispense study drug and dosing diary	

NOTES:

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

d. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

WEEK 48[a]/PREMATURE DISCONTINUATION:

INTERVIEW	# AE assessment # Concomitant therapy	# Review and document continued compliance with pregnancy avoidance recommendations in the source records with females of childbearing potential
PRO	• PGA Skin Pain[b] • HSSA[c]	• Collect ePRO device
EXAM	• Weight • Vital signs • Physical examination	
LOCAL LAB	#,+ Urine pregnancy test[d,e]	
CENTRAL LAB	+ Hematology + Blood chemistry + Urinalysis + HBV testing, where required[f] • hsCRP + Total cholesterol, HDL-C, LDL-C, and triglycerides (fasting)	• Optional blood samples for biomarkers: whole blood RNA, plasma/serum proteomic, and IgG and B cell subsets

NOTES:

a. Subjects will be brought back to their original visit schedule (calculated from Baseline) if they are out of the visit window, for all visits indicated.

b. PGA Skin Pain is collected daily from at least 7 consecutive days prior to Baseline through Week 16 and then daily for 7 consecutive days prior to the Week 24, Week 32, Week 40, and Week 48/PD visits.

c. HSSA data collection for 7 consecutive days prior to Baseline, Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, and Week 48/PD visits.

d. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

e. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

f. Where mandated by local requirements, subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccine and HBs Ab+ and HBc Ab–.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall Post-Treatment Period Activity Schedule.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

30-Day Follow-Up Visit/Call[a]:

INTERVIEW	# AE assessment # Concomitant therapy
LOCAL LAB	#,+ Urine pregnancy test[b,c]

NOTES

a. A Follow-Up Visit will occur approximately 30 days after the last dose of study drug to obtain additional safety information. For subjects that prematurely discontinued study participation and are willing to provide additional information, this visit may be a telephone call if a site visit is not possible. The Follow-Up visit is not applicable for subjects who discontinued study drug and continued study participation with completion of at least one study visit occurring at least 30 days after last dose of study drug.

b. For all females of childbearing potential, collect urine for pregnancy test (refer to Section 3.19 for additional details).

f. If urine pregnancy tests cannot be performed on-site or at home due to COVID-19, urine pregnancy tests may be performed by a local lab.

3 STUDY PROCEDURES

3.1 Screening Period

Within 35 days prior to the Baseline Visit, subjects will receive a full explanation of the study design and study procedures, provide a written informed consent, and undergo the screening procedures outlined in Section 2.1. With the exception of the QuantiFERON tuberculosis (TB)-Gold Plus and purified protein derivative (tuberculin) (PPD) tests (requirements outlined in Section 3.19), exclusionary laboratory values can be re-tested once during the Screening Period. If the retested lab value(s) remain(s) exclusionary, the subject will be considered a screen failure. Redrawing samples, if previous samples were unable to be analyzed, would not count as a retest since previous result was never obtained.

3.2 Rescreening

Subjects who initially screen-fail for the study are permitted to be re-screened once following reconsent. For additional re-screening, AbbVie Therapeutic Area Medical Director (TA MD)/Scientific Director approval is required. All screening procedures with the exceptions noted below will be repeated during rescreening. The subject must meet all eligibility criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study.

If the subject had an initial screening evaluation including the following assessments, these tests will not be required to be repeated for re-screening, provided the conditions noted in Protocol Section 5.1 are met (Eligibility Criteria) and no more than 90 days have passed:

- HBV, HCV, and HIV serology

- QuantiFERON TB Gold Plus or equivalent and/or a PPD test (or both if required per local guidelines)
- CXR
- ECG
- Beta-D-glucan (Japan only)

If a subject is being re-screened within 14 days (≤ 14 days have passed) from the collection date of the previous screening testing, it is not required to repeat Screening testing for chemistry, hematology, urinalysis, and serum pregnancy provided that the subject's health status has not changed to warrant a repeat test.

3.3 Study Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Optional biomarker research samples will only be collected if the subject has voluntarily signed and dated a written consent form describing the exploratory research. The written consent may be part of the main consent form. If the subject does not consent to providing optional samples, the subject will still be allowed to participate in the study.

In cases of state of emergency or pandemic situations, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

3.4 Eligibility Criteria

Subjects will be evaluated to ensure they meet all eligibility criteria at both Screening and Baseline Visits.

3.5 Medical History

A complete non-study disease-related medical and surgical history, including demographics and history of alcohol and nicotine use, will be taken from each subject during the Screening Visit. Additionally, a list of each subject's specific disease-related medical and surgical history will be recorded at Screening. History of herpes zoster, herpes zoster vaccination, and hepatitis B vaccination status will be recorded as part of the medical history. The subject's medical history will be updated at the Study Day 1 visit. This updated medical history will serve as the baseline for clinical assessment.

3.6 Adverse Event Assessment

Please refer to Section 4.2.

3.7 Patient-Reported Outcomes

Data Collection

Subjects will complete self-administered patient-reported outcome (PRO) instruments. Subjects should be instructed to follow the instructions provided with the instrument(s) and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Site personnel will encourage completion of the instrument at all specified time points and will ensure that a response is entered for all items.

PRO instruments that are administered at the site should be completed prior to drug administration and prior to any discussion of AEs or any review of laboratory findings. The subject should complete the questionnaire(s) before site personnel perform any clinical assessments and before any other interaction with site personnel has occurred to avoid biasing the subject's response.

From at least 7 consecutive days prior to the Baseline visit and up to the Week 16 visit, PGA Skin Pain will be collected from subjects using an electronic daily diary and analgesic use using a paper diary. After the Week 16 visit, PGA Skin Pain will be collected for 7 consecutive days leading up to the next scheduled visits as specified in Section 2.1. HSSA will be collected for 7 consecutive days prior to visits specified in Section 2.1. PGA Skin Pain will be collected from subjects electronically every evening using a handheld device provided to the subject at Screening. All data entered on the device will be immediately stored to the device itself, as well as automatically uploaded to a central server. Analgesic use for HS-related pain will be collected from subjects during the same timeframe by completing a paper diary. Data from the pain medication diary will be transcribed into the electronic data capture (EDC) system by study site staff.

Data from the DLQI and HSIA will be collected electronically at the visits specified in Section 2.1. Subjects will use a tablet device at the site to enter the required pieces of information. The electronic tablet device will be programmed to allow data entry for only the visits specified in the protocol and will not allow subjects to complete more than one of the same assessment at any one visit. All data entered on the tablet device will be immediately stored to the devise itself and automatically uploaded to a central server.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

During a state emergency or pandemic situation, subject visits may be conducted via phone or video conference. Patient-reported outcomes (DLQI and HSIA) are eligible for completion at these virtual visits, except Baseline and Week 12. If conducted by phone or video conference, sites will read the PRO questions and response options to the subject and record the subject's responses. The subject's ability to view the PRO to understand the questions and response options should be preserved. Sites may send the questionnaires (email or hard copy) to the subjects to allow them to read/understand the questions and responses when the subject is providing responses over the phone. The date and time of PRO data collection should be recorded along with who collected the information.

Patient's Global Assessment of Skin Pain

The PGA Skin Pain (Appendix 7.1) will be used to assess the worst skin pain due to HS. The scoring for PGA Skin Pain is based on an 11-point numerical rating scale (NRS), with ratings for the item ranging from 0 (i.e., no skin pain) to 10 (i.e., skin pain as bad as you can imagine). Patients are asked to respond to the items based on a recall period of "the last 24 hours." The weekly average score is calculated based on the 7 available daily scores from the days within each visit window that were closest to the nominal day.

Hidradenitis Suppurativa Symptom Assessment Questionnaire

The HSSA (24-hour recall) is a 9-item PRO questionnaire (Appendix 7.2) developed to assess the primary symptoms of HS in the 7 consecutive days prior to assessments. Each item of the HSSA is scored on an 11-point (0 to 10) NRS, where 0 represents no symptoms and 10 represents extreme symptom experience. In this way, item scores can be generated to characterize the subject's experience at a symptom level. Additionally, Items 1 – 9 can be scored together to create a Total Symptom Score to characterize an overall symptom experience by averaging the scores collected from the non-missing items collected at the same assessment. The weekly average score is calculated based on the 7 available daily scores from the days within each visit window that were closest to the nominal day.

Hidradenitis Suppurativa Impact Assessment Questionnaire

The HSIA is an 18-item PRO questionnaire (Section 7.3) developed to assess the impact of HS on the daily lives of subjects in the 7 days prior to the assessment. Items 1 – 16 of the HSIA are scored on a 0 to 10 NRS, where 0 represents no impact and 10 represents extreme impact. In this way, item scores can be generated to characterize the subject's experience at an individual impact level. Additionally, Items 1 – 16 characterize the overall impact of HS and can be scored together to create a weekly Overall HSIA score. The Overall HSIA score is generated by summing the completed individual impact, item-level scores collected on the same day, and dividing that sum by the total number of completed responses (i.e., the Overall HSIA score is an average). The Overall HSIA score will only be derived if eight or more (i.e., at least 50%) of responses are available (and adjusting the denominator to match the number of completed items). Items 17 and 18 utilize an open field where patients are asked to fill in a number, and are not included in the Overall HSIA score. Instead, a separate mean score for the hours worked (Item 17) or hours missed at school or work (Item 18) will be calculated. If the response is "Not Applicable" for any of the Items 13 – 14 or 16 – 18 then the subject will be deemed as "not applicable" for calculating scores.

Dermatology Life Quality Index

The DLQI is a 10-item validated questionnaire (Section 7.4) used to assess the impact of HS disease symptoms and treatment on quality of life (QoL). It consists of 10 questions evaluating impact of skin diseases on different aspects of a subject's QoL over the prior week, including symptoms and feelings, daily activities, leisure, work or school, personal relationships, and the side effects of treatment. Each item is scored on a 4-point scale (0 = not at all/not relevant; 1 = a little; 2 = a lot; and 3 = very much). Item scores are added to provide a total score, ranging from 0 to 30, with higher scores indicating greater impairment of QoL. For general inflammatory skin conditions, a change in DLQI score of at least 4 points is considered the minimum clinically important difference (MCID).

3.8 Inflammatory Lesion Counts

The number of inflammatory nodules, abscesses, and draining fistulas, as well as the respective physical location (right/left axilla, right/left inframammary, intermammary, right/left buttock, right/left inguino-crural fold, perianal, perineal, other) will be recorded at designated study visits outlined in Section 2.1.

3.9 Hurley Stage

The investigator will determine the Hurley Stage in each affected anatomical region at designated study visits outlined in Section 2.1. Hurley stages are described as follows:

- Stage I - Abscess formation, single or multiple, without sinus tracts and cicatrization
- Stage II - Single or multiple, widely separated, recurrent abscesses with tract formation and cicatrization
- Stage III - Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area

If more than one stage is present in a region, the worst stage in each region should be entered. The site should make every attempt to have the same investigator conduct these assessments throughout the study for each subject.

3.10 Pharmacokinetic Sampling

Blood samples for the analysis of upadacitinib plasma concentrations will be collected from subjects throughout the treatment period on the study days specified in Section 2.1.

At Week 2 and Week 8 visits, pharmacokinetic (PK) samples should be collected prior to dosing and the subjects should take the study drug dose at the clinic after collecting the PK blood sample. However, if the subject normally takes the study drug dose at a time that is after the time of the scheduled study visit, the subject should follow the regular dosing schedule and the PK sample will be collected at any time during the visit.

For all PK samples, the date and accurate time of the PK sample collection will be recorded on the lab requisition form. The date and accurate time of the last 2 study drug doses will be recorded on the electronic case report form (eCRF) to the nearest minute.

Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

Measurement Method

Plasma concentrations of upadacitinib will be determined by the Bioanalysis Department at AbbVie using a validated liquid chromatography/mass spectrometry method.

3.11 Biomarker Research Sampling

Optional blood samples will be collected for biomarker research. Refer to Section 2.1 for the schedule of biomarker research sample collections. All biomarker samples should be collected pre-dose. All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on upadacitinib (or drugs of this class) or HS and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

3.12 12-Lead Electrocardiogram

For all subjects, a resting 12-lead ECG will be performed at Screening, and if clinically indicated at any time during the study at the investigator's discretion. A qualified physician will interpret the clinical significance of any abnormal finding, sign, and date each ECG. If there are findings that are considered to be clinically significant by the investigator, the investigator must contact the AbbVie TA MD before enrolling the subject. In addition, any clinically significant findings will be documented in the source documents and later transcribed on to the appropriate eCRF.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol-required source documentation is available and provided nothing has changed in the subject's health status or medical history to warrant a repeat ECG.

3.13 Chest X-ray

CXR (posterior-anterior and lateral views) is required for all subjects at Screening to rule out the presence of TB or other clinically relevant findings. The CXR will not be required if the subject had a previous normal CXR (posterior-anterior and lateral views) within 90 days of Screening, provided all source documentation is available at the site, as outlined below, and provided nothing has changed in the subject's medical history to warrant a repeat test.

Subjects can have a repeat CXR at any time during a study as warranted based on the opinion of the Investigator or as required per local guidelines.

A radiologist or pulmonologist must perform and document an assessment of the CXR. The Principal Investigator will indicate the clinical significance of any findings and will sign and date the report. In the assessment of the CXR, the Principal Investigator or their delegate must indicate the presence or absence of (1) calcified granulomas, (2) pleural scarring/thickening, and (3) signs of active TB. If the CXR demonstrates changes suggestive of previous TB (e.g., calcified nodule, fibrotic scar, apical or basilar pleural thickening) or other findings that are clinically significant, the Principal Investigator should contact the AbbVie TA MD before enrolling the subject.

The AbbVie TA MD may approve substitution of computed tomography or MRI of the chest for the CXR in individual subjects.

3.14 Height and Weight

Height will be measured at the Screening Visit only (with shoes off). Body weight will be measured at all scheduled visits, as specified in Section 2.1. All measurements will be recorded in metric units where applicable.

3.15 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure in sitting position, pulse rate, respiratory rate, and body temperature will be obtained at visits specified in Section 2.1. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed.

3.16 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2.1. The physical examination at the Baseline Visit will serve as the Baseline physical examination for the entire study. Physical examination abnormalities noted by the investigator at Baseline prior to the first dose of study drug will be recorded in the subject's medical history; abnormalities noted after the first dose of study drug will be evaluated and documented by the investigator as to whether or not the abnormality is an AE. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

3.17 Handheld ePRO Device

During the Screening Visit, subjects will be dispensed a handheld ePRO device to collect information about PGA Skin Pain and HSSA. PGA Skin Pain information will be collected daily from at least 7 consecutive days before the Baseline visit through the Week 16 visit. Post-Week 16 visit, PGA Skin Pain will be collected for 7 consecutive days prior to the scheduled visits outlined in Section 2.1. HSSA will be collected daily for 7 consecutive days prior to the scheduled visits outlined in Section 2.1. At

each visit, site representatives should check to see that subjects have performed the required assessments between study visits.

3.18 Dispense Study Drug

Study drug will be dispensed to subjects beginning at Baseline (Day 1) and as specified in Section 2.1. The first dose of study drug will be administered after all other baseline (Day 1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review and retain a copy of the dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

Study drug will be taken orally once daily, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day, with or without food.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

Study drug may be shipped from the study site directly to the study subject's home if all of the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
    - Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of PROs). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; this may be provided by the courier after delivery if social distancing measures are in place. Documentation of the shipment is to be retained by the clinical site.
    - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

3.19 Clinical Laboratory Tests

Samples will be obtained for the clinical laboratory tests listed in Table 1. Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per investigator's discretion. A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests.

The central laboratory chosen for this study will provide instructions regarding the collection, processing, and shipping of these samples.

Blood samples will be obtained for the laboratory tests at visits specified in Section 2.1. Blood draws should be performed after all questionnaires, clinical assessments, and vital sign determinations are obtained.

For blood sampling, subjects should be fasting (a minimum 8-hour fast). If a subject is not able to fast the non-fasting status will be recorded in study source documentation.

For any laboratory test value outside the reference range that the investigator considers to be clinically significant, the investigator should apply the standard of care for medical evaluation and treatment per local guidelines:

- The investigator will repeat the test to verify the out-of-range value.
- The investigator will follow the out-of-range value to a satisfactory clinical resolution.

A laboratory test value that requires a subject to be discontinued from study drug or requires a subject to receive treatment will be recorded as an AE.

Table 1. Clinical Laboratory Tests

Hematology (Central Lab)	**Clinical Chemistry (Central Lab)**	**Urinalysis (Central Lab)**	**Other Laboratory Tests**
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Reticulocyte count Platelet count	Blood urea nitrogen (BUN) Creatinine Total bilirubin Alanine transaminase (ALT) Aspartate transaminase (AST) Alkaline phosphatase Sodium Potassium Chloride Bicarbonate Calcium Inorganic phosphate Total protein Albumin Glucose Uric acid Total cholesterol Low density lipoprotein cholesterol (LDL-C) High density lipoprotein cholesterol (HDL-C) Triglycerides	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocytes Nitrites Microscopic examination, if needed	<u>Central Lab Tests:</u> Estimated glomerular filtration rate International normalized ratio (INR) Serum pregnancy (beta human chorionic gonadotropin [bHCG]) test Beta-D-glucan (Japan only) (if the result from the central lab is indeterminate or otherwise not interpretable, a local lab may be used) hsCRP Follicle stimulating hormone (FSH) Human immunodeficiency virus antibody (HIV Ab) QuantiFERON-TB Gold Plus <u>Hepatitis Screening:</u> Hepatitis B surface antigen (HBs Ag)

Hematology (Central Lab)	Clinical Chemistry (Central Lab)	Urinalysis (Central Lab)	Other Laboratory Tests
			Hepatitis B surface antibody (HBs Ab) Hepatitis B core antibody (HBc Ab) Hepatitis B virus deoxyribonucleic acid polymerase chain reaction (HBV DNA PCR) Hepatitis C virus antibody (HCV Ab) Hepatitis C virus ribonucleic acid (HCV RNA [reflex only]) <u>Local Lab Tests:</u> Urine pregnancy test Varicella antibody, if indicated QuantiFERON-TB Gold Plus Beta-D-glucan (Japan only) Purified protein derivative (PPD)

Pregnancy Tests (Serum and Urine)

A pregnant or breastfeeding female will not be eligible to enter the study or be allowed to continue study drug.

As described in the Contraception Recommendations section of the Protocol, females considered to be of non-childbearing potential should not have pregnancy testing performed.

A quantitative serum pregnancy test will be performed at the Screening Visit and if any urine pregnancy test is positive.

The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility. If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;
- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

A urine pregnancy test will be performed for all females of childbearing potential at the Baseline Visit prior to the first dose of study drug (local practices may require serum pregnancy testing at Baseline). Additional urine pregnancy tests will be performed (as indicated in the Activities Schedule) at a minimum of monthly intervals (either at study visits or at home or at unscheduled visits between scheduled study visits). The results of at home tests must be communicated to the site and recorded in source documentation. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the Baseline urine pregnancy test is negative, then dosing with study drug may begin.
- If the Baseline or post-Baseline urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required (as stated above).

At each visit, the study staff should review the pregnancy avoidance recommendations with each female of childbearing potential and document this discussion in the subject's source records.

Follicle Stimulating Hormone (FSH)

FSH should be tested at the Screening Visit for female subjects who are ≤ 55 years of age AND have had no menses for 12 months AND have no history of permanent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

Urinalysis

Urine samples will be obtained for urinalysis testing at visits specified in Section 2.1. The central laboratory will be responsible for performing a macroscopic urinalysis (urine dipstick) on the collected urine specimens. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

International Normalized Ratio

International normalized ratio (INR) will only be measured if ALT and/or AST > 3 × ULN. A separate blood sample for INR testing will be needed to measure INR at the time of repeat testing for ALT or AST.

Hepatitis Screening

All subjects will be tested for the presence of HBV and HCV at Screening.

HBV:

Subjects will be tested for the presence of HBV at Screening using the following tests:

- HBs Ag
- HBc Ab/anti-HBc
- HBs Ab/anti-HBs

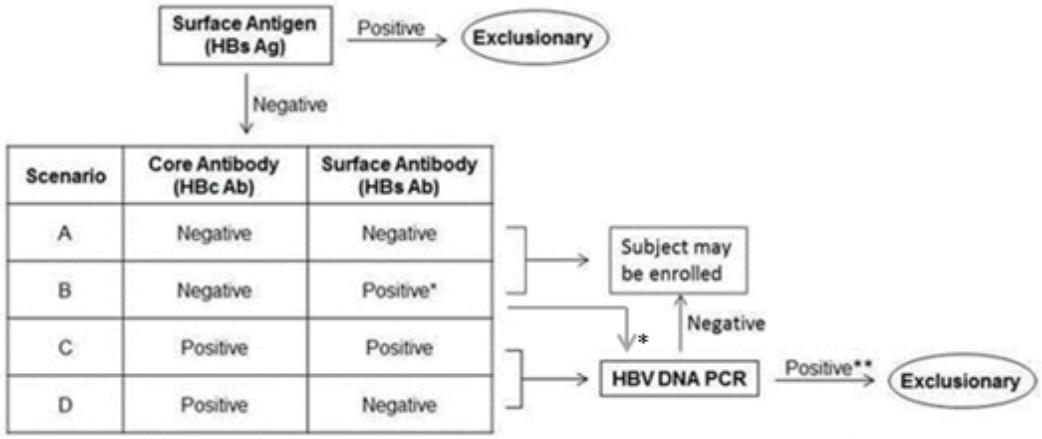
A positive result for HBs Ag will be exclusionary.

A negative result for HBs Ag will trigger automatic reflex testing for HBc Ab and HBs Ab.

- A negative test result for HBc Ab does not require HBV DNA PCR qualitative testing and the subject may be enrolled (Figure 1, Scenarios A and B).
- For a subject who has had a HBV vaccination (should document in the medical history), a positive test result for HBs Ab is expected, the HBV DNA PCR qualitative testing is not required and the subject may be enrolled (Figure 1, Scenario B).*
- For subjects without a history of HBV vaccination (and where mandated by local requirements) a positive result for HBs Ab requires HBV DNA PCR testing (automatic reflex testing; Figure 1, Scenario B).

A positive test result for HBc Ab requires HBV DNA PCR testing (automatic reflex testing) (Figure 1, Scenarios C and D). A result for HBV DNA that exceeds detection sensitivity will be considered positive and will be exclusionary. A subject with a negative result for HBV DNA may be enrolled.

Figure 1. Interpretation and Management of HBV Serologic Test Results



* Subjects who have had an HBV vaccination are expected to have a positive test result for HBs Ab and do not require HBV DNA PCR testing. For subjects without a history of HBV vaccination (and where mandated by local requirements), a positive result for HBs Ab requires HBV DNA PCR testing.

** Where mandated by local requirements, subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at Screening should have HBV DNA PCR testing performed approximately every 12 weeks. HBV DNA PCR testing every 12 weeks is not necessary when the subject has a history of HBV vaccination and is HBs Ab+ and HBc Ab–. If necessary, HBV DNA PCR may be tested at unscheduled visits.

HCV:

Blood samples for HCV serology will be obtained at the Screening Visit. A positive HCV Ab will trigger a HCV RNA test. A subject will not be eligible for study participation if test results indicate active Hepatitis C (HCV RNA detectable in any subject with anti HCV Ab).

Human Immunodeficiency Virus (HIV) Screening

Subjects with HIV infection (positive HIV test) are excluded from study participation. An anti-HIV antibody (Ab) test will be performed at Screening, unless prohibited by local regulations. The

investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. AbbVie will not receive results from the testing and will not be made aware of any positive result.

High-Sensitivity C-Reactive Protein (hsCRP)

During the study the hsCRP results starting after Baseline (Day 1) will not be reported to the Sponsor, investigator, study site personnel, and/or to the subject. Results of hsCRP may unblind the treatment assignment or introduce bias, and the results may be blunted in subjects taking a JAK inhibitor, thereby limiting clinical utility in the setting of a safety assessment or AE management. Any local testing of hsCRP or CRP during the study is therefore strongly discouraged and any local hsCRP or CRP tests reported to the investigator during the study will be recorded as protocol deviations.

Tuberculosis (TB) Testing/TB Prophylaxis

All subjects must be evaluated for TB at Screening. The results of the TB screening must be interpreted in the context of the subject's epidemiology, history, exam findings, etc., and it is the responsibility of the investigator to determine if a subject has previous, active, or latent TB.

At Screening, all subjects will be assessed for evidence of increased risk for TB by a risk assessment questionnaire (Section 7.5) and tested for TB infection as described below. The site staff will complete the TB risk assessment questionnaire in its entirety (Part I and Part II) and enter the data into the appropriate eCRF.

Subjects with a negative TB test and CXR not suggestive of active TB may be enrolled. Subjects with history of active TB may be enrolled if it has been adequately treated with no evidence of current active TB; subjects with inadequate documentation of treatment should be cleared by a TB specialist prior to enrollment.

Subjects with a positive TB test must be assessed for evidence of active TB versus latent TB, including signs and symptoms and CXR. Subjects with latent TB (positive TB test with no signs or symptoms and a CXR not suggestive of active TB) may be enrolled after initiation of TB prophylaxis (see below).

Subjects with evidence of active TB must not be enrolled.

TB Testing:

- The QuantiFERON-TB Gold Plus test should be performed at Screening on all subjects unless the subject is considered to be TB test positive prior to Screening. The PPD skin test (also known as TB Skin Test or Mantoux test) should be utilized when the QuantiFERON-TB Gold Plus test is not possible or if both tests are required per local guidelines.
- If a subject had a QuantiFERON-TB Gold Plus test within 90 days prior to Screening and source documentation is available TB testing does not need to be performed by the central laboratory at Screening provided nothing has changed in the subject's medical history to warrant a repeat test.

- For subjects with only a negative PPD Skin Test available within 90 days prior to Screening a QuantiFERON-TB Gold Plus test is required at Screening. If the QuantiFERON-TB Gold Plus test is not possible and source documentation is available, the PPD Skin Test does not need to be repeated provided nothing has changed in the subject's medical history to warrant a repeat test.
- For regions that require both PPD and QuantiFERON-TB Gold Plus testing, both will be performed. If either PPD or QuantiFERON-TB Gold Plus is positive, the TB test is considered positive.
- Subjects with documentation of prior positive result of QuantiFERON-TB Gold Plus Test, PPD skin test, and/or history of latent or active TB are not required to repeat a TB test at Screening or during the study and should be considered TB test positive.
    - If TB testing is done at Screening for subjects with a prior positive TB test and a positive result is reported the subject is considered TB test positive.
    - If TB testing is done at Screening in subjects considered at low risk for TB as described below and a positive or indeterminate result is reported the procedure for "Interpretation of a positive TB test in low risk subjects" should be followed OR either prior or concomitant treatment for latent TB is required.
- If performed, the PPD should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test. The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm" not "negative."
- Subjects who have had an ulcerating reaction to PPD in the past should not be re-exposed and the PPD should be considered positive and do not require subsequent testing with either PPD or QuantiFERON-TB Gold Plus.
- If the QuantiFERON-TB Gold Plus test is indeterminate, then the investigator should perform a local QuantiFERON-TB Gold Plus test (or through the central laboratory if not locally available) to rule out a positive test result. If testing remains indeterminate or is positive, then the subject is considered to be positive for the purpose of this study. If the testing result is negative, then the patient is considered to be negative.
- Interpretation of a positive TB test in low risk subjects: In cases where the QuantiFERON-TB Gold Plus test by the central laboratory is positive and the investigator considers the subject at low risk for TB (i.e., no risk factors identified using the Part I and Part II questions of the TB risk assessment questionnaire at Screening) and has no clinical suspicion of TB, the investigator may perform a local QuantiFERON-TB Gold Plus test (or repeat testing through the central laboratory if not locally available) to confirm the positive test result. If the repeat testing result is negative, the investigator may consider the test to be negative based on his/her clinical judgment; if the repeat testing result is positive or indeterminate, the test is considered positive.
- An equivalent Interferon Gamma Release Assay (IGRA) (such as T-SPOT TB test) may be substituted for the QuantiFERON-TB Gold Plus.
- TB test(s) results will be retained at the site as the original source documentation.

If the subject is experiencing signs or symptoms suspicious for TB or something has changed in the subject's medical history to warrant investigation and a repeat test during the study, the case (including the TB test results) should be discussed with the AbbVie TA MD.

TB Prophylaxis:

Note: Rifampicin and Rifapentine are not allowed for TB prophylaxis while on study drug.

At Screening, if the subject has evidence of latent TB infection, prophylactic treatment with isoniazid must be initiated at least 2 weeks prior to administration of study drug (or per local guidelines, whichever is longer). If receiving isoniazid prophylaxis during the study at least 6 months must be completed; however, the full course of prophylaxis does not need to be completed prior to the first dose of study drug.

Subjects with a prior history of active or latent TB that have documented completion of a full course of anti-TB therapy will be allowed to enter the study provided nothing has changed in the subject's medical history to warrant repeat treatment. Prior to the study, a full course of latent TB prophylaxis may be achieved with at least 4 months of rifampin, at least 6 months of isoniazid, or at least 3 months of combination rifapentine and isoniazid. Rifampin and rifapentine must be completed at least 30 days prior to baseline. For subjects with completion of a full course of anti-TB therapy, but insufficient documentation, the investigator should consult with the AbbVie TA MD.

During the study, subjects with new evidence of latent TB must initiate prophylactic treatment with isoniazid immediately and complete at least 6 months of prophylaxis. Study drug should not be withheld. Two to four weeks later, the subject should be re-evaluated (unscheduled visit) for signs and symptoms as well as laboratory assessment of toxicity to TB prophylaxis.

At Screening newly diagnosed latent TB should be entered in the TB Screening eCRF; prior history of latent or active TB should be entered into the medical history eCRF. Any positive TB test after the patient has started the study should be reported as an AE of latent TB or active TB (as applicable). Newly initiated prophylactic treatment and prior therapy should be captured in the concomitant/prior medications eCRF as appropriate.

State of Emergency or Pandemic-Related Acceptable Protocol Modifications

During a state of emergency or pandemic situation, if travel restrictions or other changes in local regulations prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the subject has at least 1 post Baseline visit and the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. Laboratory draws should be obtained as close as possible to the scheduled visit.

3.20 Subject Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject should be treated in accordance with the investigator's best clinical judgment irrespective of whether the subject decides to continue participation in the study.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

Subjects may withdraw from the study completely (discontinuation of study drug treatment and study participation; withdrawal of informed consent) for any reason at any time. If a subject prematurely discontinues study participation, the procedures outlined for the Premature Discontinuation visit (PD visit) should be completed as soon as possible, preferably within 2 weeks of study drug discontinuation. In addition, a 30-day follow-up visit (or phone call if a visit is not possible) should occur to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs. Subjects who discontinue the study prematurely after randomization will not be replaced.

Discontinuation of Study Drug and Continuation of Study Participation

Subjects may discontinue study drug treatment but may choose to continue to participate in the study.

Subjects who prematurely discontinue study drug should complete a Premature Discontinuation visit (PD visit) as soon as possible, preferably within 2 weeks. Afterwards, subjects should follow the regular visit schedule as outlined in the Protocol Study Activities Table and adhere to all study procedures except for dispensing study drug, PK sample collection, and blood sample collection for optional exploratory research and validation studies. Female subjects who discontinue study drug due to pregnancy will not undergo additional imaging tests. Once the subject has discontinued study drug, subjects should be treated per standard of care. If at any point a subject no longer wants to provide assessments (withdrawal of informed consent) following discontinuation of study drug, a second PD visit is not required.

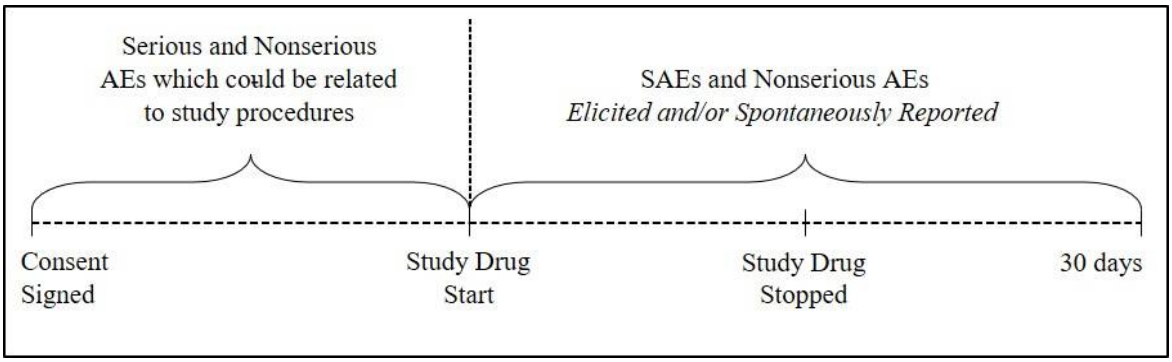
4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All AEs reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. Subjects who discontinue study drug treatment but continue to participate in the study will have AEs collected for the remainder of study participation. In addition, SAEs and protocol-related nonserious AEs (AEs due to study procedures) will be collected from the time the subject signed the study-specific informed consent.

AE information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



Note: Subjects who discontinue study drug but continue to participate in the study will have SAEs and non serious AEs collected for the remainder of study participation.

In the case of any of the following reported events, a supplemental eCRF should be completed:

- Cardiac events;
- Myocardial infarction or unstable angina;
- Heart failure;
- Cerebral vascular accident and transient ischemic attack;
- Cardiovascular procedures (SAE Supplemental Procedure eCRF);
- Embolic and/or thrombotic event (non-cardiac, non-central nervous system);
- Herpes zoster infection;
- COVID-19.

4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT) and compared between arms using Fisher's exact test. The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team Bldg. AP51-3
1 North Waukegan Road
North Chicago, Illinois 60064, USA
Office: +1 847-938-8737
Email: GPRD_SafetyManagement_Immunology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **MD**
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064, USA

Contact Information:

Office: [redacted]
Mobile:
Fax:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

In Japan, the principal investigator will provide documentation of all SAEs to the Director of the investigative site and the Sponsor.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

6 STUDY DRUG

6.1 Treatments Administered

Study drug will be taken orally once daily, beginning on Day 1 (Baseline), and should be taken at approximately the same time each day, with or without food.

Study drug includes the investigational product of upadacitinib and matching upadacitinib placebo. Details regarding study drug dosing and administration are provided in the Study Drug section of the Protocol. The study drug will be dispensed at the visits listed in Section 2.1.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature D/C visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

AbbVie will not supply any disease-related concomitant medication (indication) therapy taken during the course of the study.

6.2 Packaging and Labeling

All study drugs will be supplied in bottles. Each bottle will be labeled per local requirements. The labels must remain affixed to the bottles. All blank spaces should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Study drug must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of

this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

This study is a randomized, placebo-controlled, double-blind study. All eligible subjects will receive study drug for up to 48 weeks.

At the screening visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must access the IRT system and identify the subject as a screen failure.

As subjects are enrolled into a study, they will receive a subject number that will be retained throughout the remainder of the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system. Contact information and user guidelines for IRT use will be provided to each site.

Additional information on randomization and drug assignment are provided in the Randomization/Drug Assignment section of the Protocol.

6.4 Selection and Timing of Dose for Each Subject

Subjects should take study drug as outlined in Section 3.18.

Each subject's dosing schedule should be closely monitored by the site at each study visit by drug accountability data. This will ensure that all subjects enrolled into the study maintain their original dosing schedule beginning with the first dose of study drug (Baseline/Day 1).

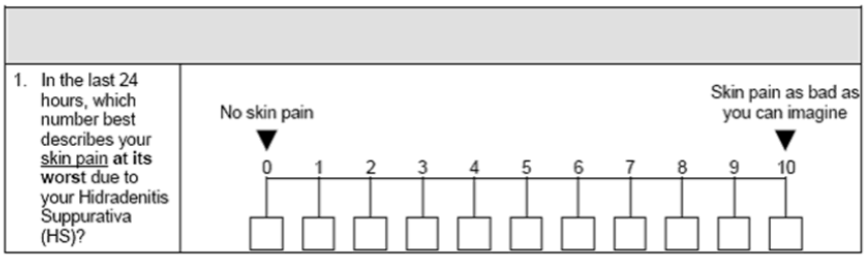
If a subject should forget to take their study drug dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember the dose was missed as long as it is at least 10 hours before their next scheduled dose. If a subject only remembers the missed dose within 10 hours before next scheduled dose, the subject should skip the missed dose and take the next dose at the scheduled time.

7 Appendices

7.1 PATIENT'S GLOBAL ASSESSMENT OF SKIN PAIN

Patient Global Assessment of Skin Pain

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



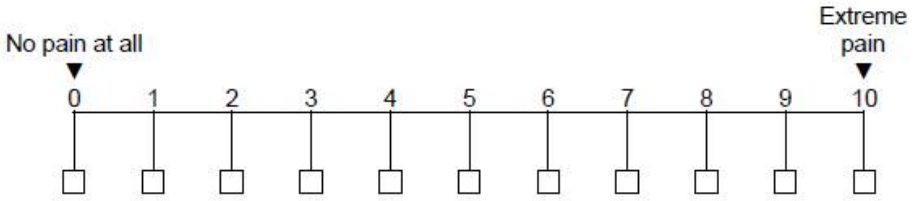
7.2 HIDRADENITIS SUPPURATIVA SYMPTOM ASSESSMENT QUESTIONNAIRE

Hidradenitis Suppurativa Symptom Assessment (HSSA)

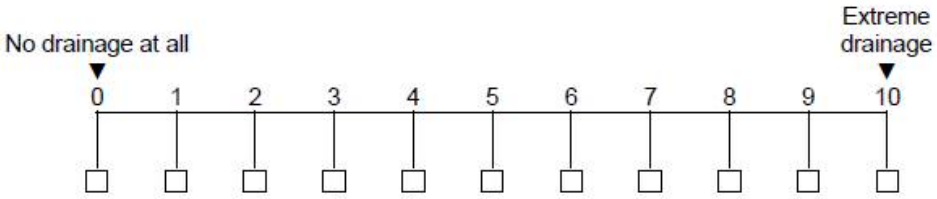
Instructions: This questionnaire includes nine questions about the symptoms you may experience associated with your Hidradenitis Suppurativa (HS). Hidradenitis Suppurativa is a skin condition that affects areas with sweat glands such as the underarms, breasts, inner thighs, groin, and buttocks. People often refer to their HS as boils, cysts, or lesions on their skin.

Please clearly mark an "x" in the box (☒) that best describes how severe your HS symptoms were in the **past 24 hours.** There are no right or wrong answers to any of the questions.

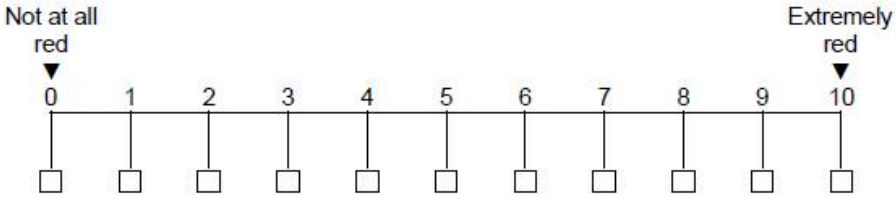
1. In the **past 24 hours**, what was the worst pain you felt in the area(s) affected by your HS?



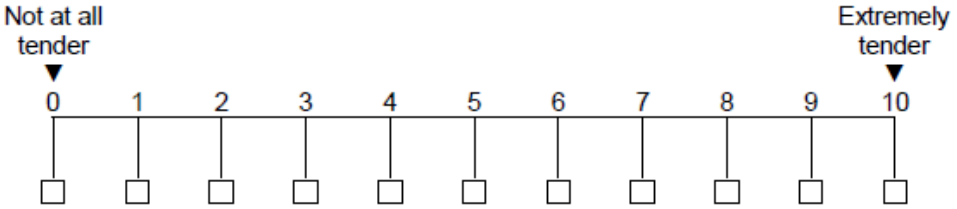
2. In the **past 24 hours**, what was the worst drainage you had in the area(s) affected by your HS?



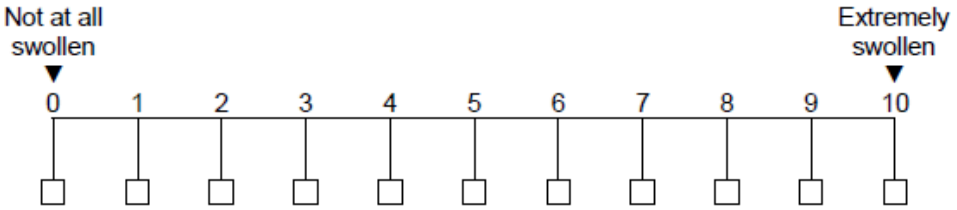
3. In the **past 24 hours**, how red was your skin in the area(s) affected by your HS?



4. In the **past 24 hours**, how tender was your skin in the area(s) affected by your HS?

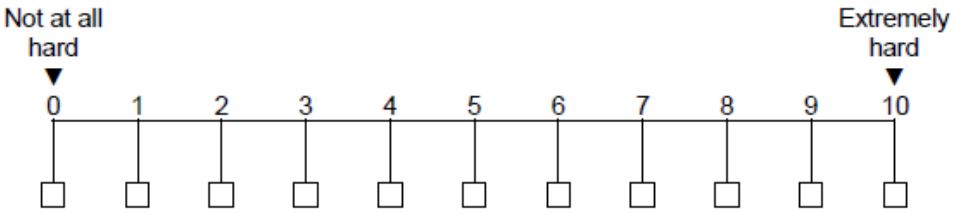


5. In the **past 24 hours**, how swollen was your skin in the area(s) affected by your HS?

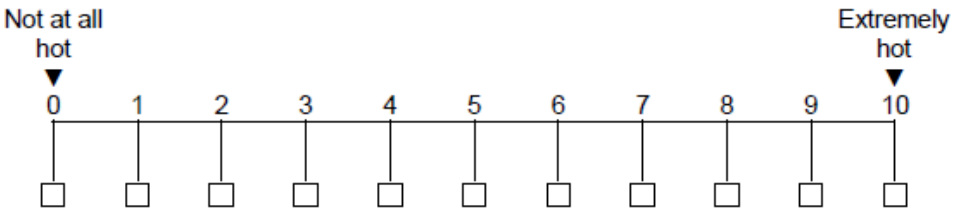


6. In the **past 24 hours**, how hard did your skin feel in the area(s) affected by your HS?

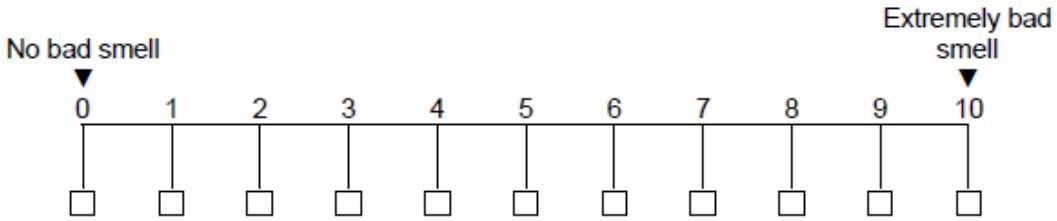
   Note: Please do not consider any hardness that you may have from the scars left on your skin from HS.



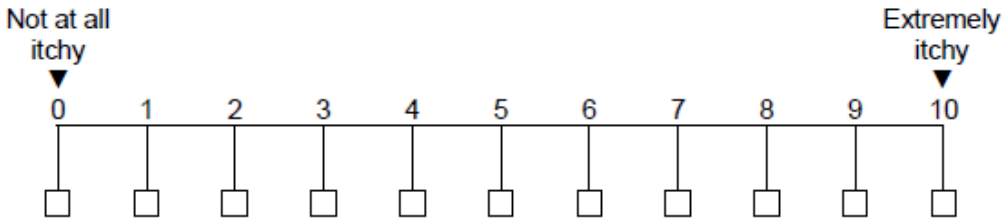
7. In the **past 24 hours**, how hot was your skin in the area(s) affected by your HS?



8. In the **past 24 hours**, how bad was the smell coming from the area(s) affected by your HS?



9. In the **past 24 hours**, how itchy was your skin in the area(s) affected by your HS?



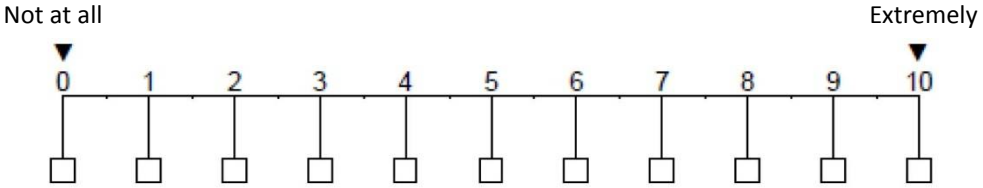
7.3 HIDRADENITIS SUPPURATIVA IMPACT ASSESSMENT QUESTIONNAIRE

Hidradenitis Suppurativa Impact Assessment (HSIA)

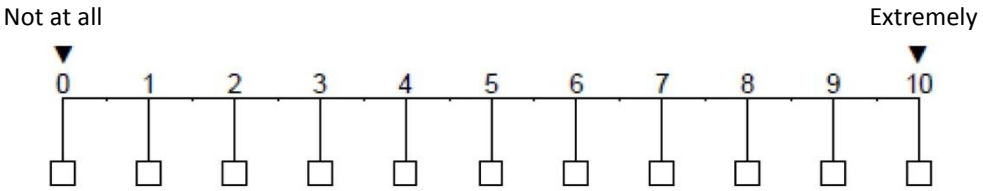
Instructions: This questionnaire includes 18 questions about the impacts that you may experience associated with your Hidradenitis Suppurativa (HS). Hidradenitis Suppurativa is a skin condition that affects areas with sweat glands such as the underarms, breasts, inner thighs, groin, and buttocks. People often refer to their HS as boils, cysts, or lesions on their skin.

Please clearly mark an "**x**" **in the box** (☒) that best describes how you have been affected by your **HS** in the **past 7 days**. There are no right or wrong answers to any of the questions.

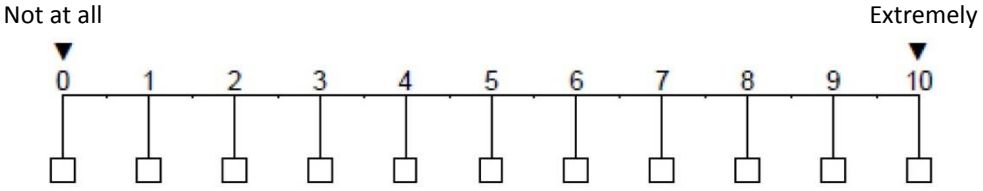
1. Over the **past 7 days**, how uncomfortable did your clothing make you feel because of your HS?



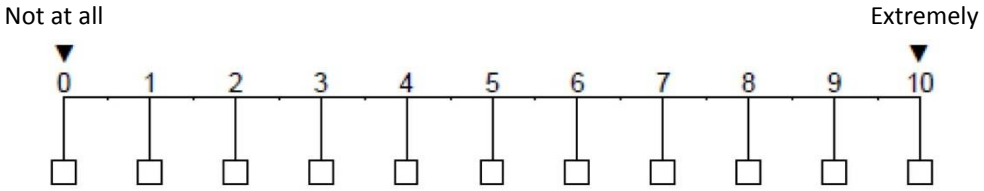
2. Over the **past 7 days**, how hard was it for you to move your arms because of your HS?



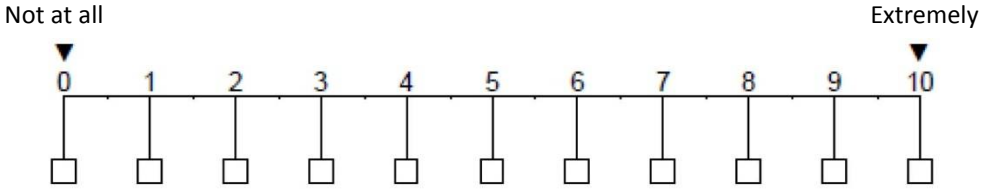
3. Over the **past 7 days**, how hard was it for you to exercise (for example, play sports, work out) because of your HS?
   Note: If you **did not exercise** because of your HS please mark a "10."



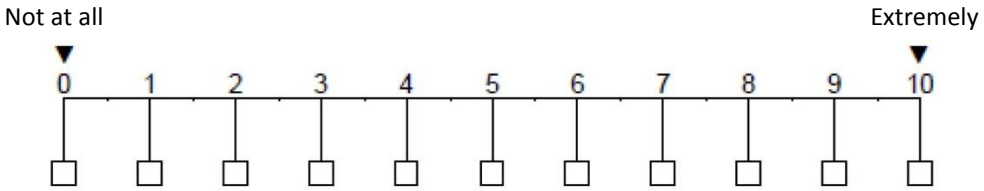
4. Over the **past 7 days**, how hard was it for you to walk because of your HS?
   Note: If you **did not walk** because of your HS please mark a "10."



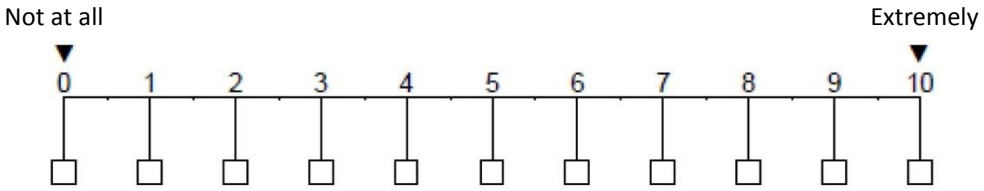
5. Over the **past 7 days**, how hard was it for you to sit because of your HS?
   Note: If you **did not sit** down because of your HS please mark a "10."



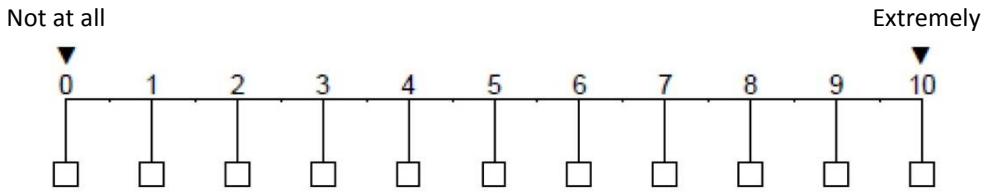
6. Over the **past 7 days**, how much did your HS interfere with your wanting to be around other people (for example, going to a party, being with friends or family)?



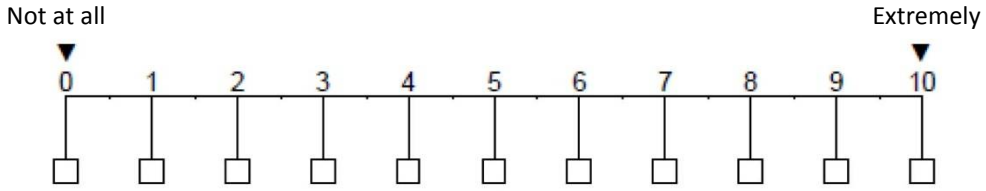
7. Over the **past 7 days**, how much did your HS interfere with your ability to do things around the house (for example, cleaning, cooking, yard work)?



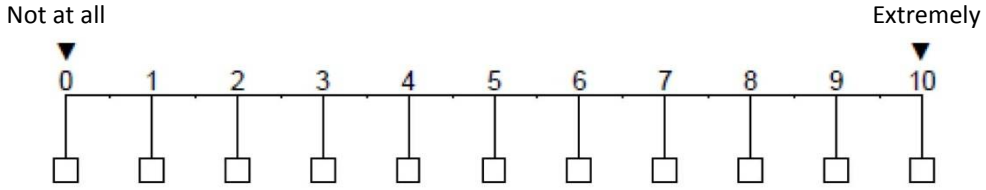
8. Over the **past 7 days**, how self-conscious did you feel because of your HS?



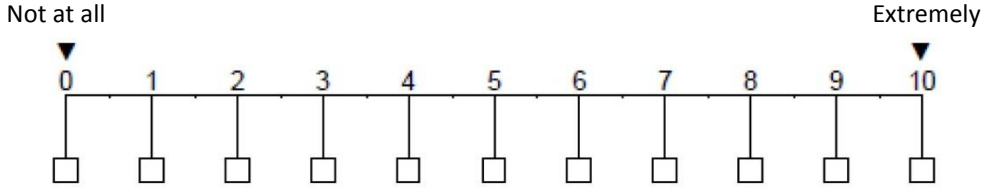
9. Over the **past 7 days**, how embarrassed did you feel because of your HS?



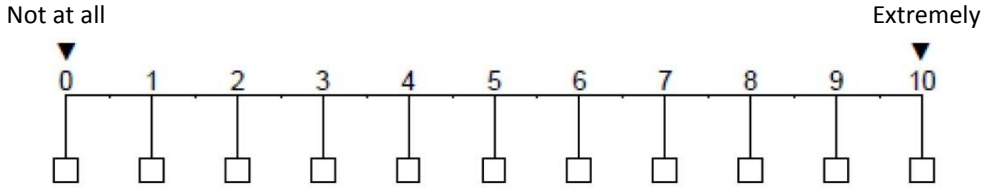
10. Over the **past 7 days**, how sad did you feel because of your HS?



11. Over the **past 7 days**, how worried did you feel because of your HS?

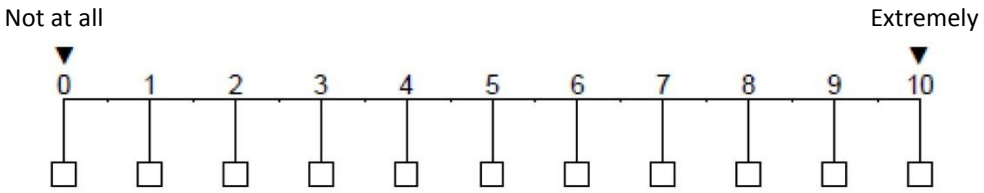


12. Over the **past 7 days**, how bothered did you feel because of your HS?



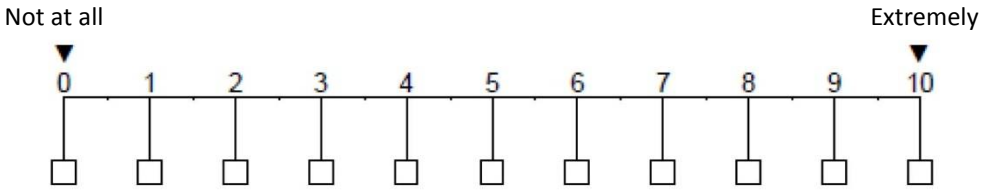
13. Over the **past 7 days**, how much did your feelings about your HS limit your desire to have sex (for example, because you felt unattractive, embarrassed, self-conscious, etc.)?

If this question is not applicable for you, please press "next."

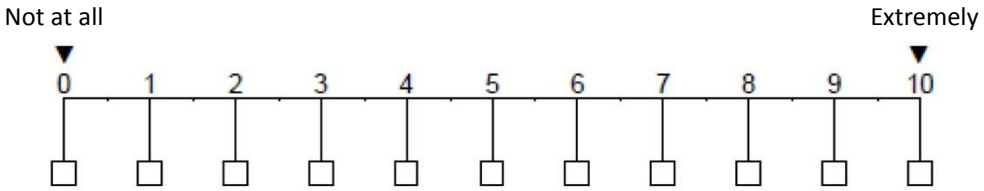


14. Over the **past 7 days**, how much was your ability to have sex limited because of your HS symptoms (for example, pain, cysts, drainage, flare ups, bleeding, etc.)?

    If this question is not applicable for you, please press "next."

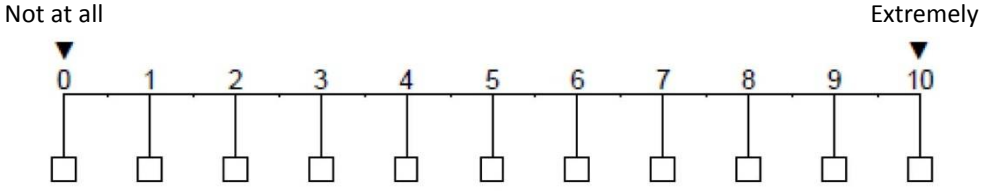


15. Over the **past 7 days**, how satisfied have you been with your HS medications?



16. Over the **past 7 days**, how bothered did you feel by the scars from your past HS surgery/surgeries?

    If this question is not applicable for you as you have not had surgery for your HS, please press "next."



17. Over the **past 7 days**, how many hours did you spend at work or school?

If this question is not applicable for you as you are not employed nor do you attend school, please press "next."

_____ Hours

18. Over the **past 7 days**, how many hours did you miss from work or school because of your HS? Include hours you missed on sick days, times you went in late, left early, etc., because of your HS.

    If this question is not applicable for you as you are not employed nor do you attend school, please press "next."

    _____ Hours

Source: AO-AV141778-HSIA-English-USA-Version 2-for electronic use; 03 Feb 2020

7.4 DERMATOLOGY LIFE QUALITY INDEX

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score: ☐

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

1.	Over the last week, how **itchy, sore, painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you.

7.5 SCREENING TB RISK ASSESSMENT QUESTIONNAIRE

For Screening TB risk assessment, ask Part I and Part II questions.

Part 1

1. Has an immediate family member or other close contact been newly diagnosed with or treated for active or latent tuberculosis during the last 3 months?
2. Within the past year, have you, or an immediate family member, had any of the following problems lasting for 3 weeks or longer which remained unexplained:
    - Chronic Cough
    - Production of Sputum
    - Blood-Streaked Sputum
    - Weight Loss
    - Fever
    - Fatigue/Tiredness
    - Night Sweats
    - Shortness of Breath
    - (Reference: https://www.cdc.gov/tb/topic/testing/diagnosingltbi.htm)

Part II

3. Have you ever been diagnosed or treated for active or latent tuberculosis?
4. Have you lived in or had prolonged travels to any of the following TB endemic regions?

Angola	China	India	Mozambique	Papua New Guinea	Thailand
Bangladesh	Congo	Indonesia	Myanmar	Philippines	UR Tanzania
Brazil	DPR Korea	Kenya	Namibia	Russian Federation	Viet Nam
Cambodia	DR Congo	Lesotho	Nigeria	Sierra Leone	Zambia
Central African Republic	Ethiopia	Liberia	Pakistan	South Africa	Zimbabwe

(Reference: World Health Organization Global Tuberculosis Report 2018. Available from: https://www.who.int/tb/publications/global_report/en/)

5. Have you lived or worked in a prison, refugee camp, homeless shelter, immigration center, or nursing home?