abbvie

Protocol for Study M16-833

Hidradenitis Suppurativa: Risankizumab versus Placebo for Adult Subjects with Moderate to Severe Hidradenitis Suppurativa

VERSION:	5.0	DATE:	15 December 2020
SPONSOR:	AbbVie	NUMBER OF SITES:	Approximately 60
ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab	EUDRACT:	2019-000122-21

FULL TITLE: A Phase 2, Multicenter, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety and Efficacy of Risankizumab in Adult Subjects with Moderate to Severe Hidradenitis Suppurativa

Incorporating Versions 1.0, 1.1, 2.0, 3.0, 4.0, and 5.0

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

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted]
AbbVie
Immunology Clinical Development
1 North Waukegan Road
[redacted]
North Chicago, IL 60064 USA

Office:
Mobile:
Email: [redacted]
EMERGENCY 24 hour Number: +1 973-784-6402

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information can be found in the Operations Manual (Appendix F).

abbvie

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 the Safety and Efficacy of Risankizumab 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. This study will provide essential data for risankizumab registration as treatment for patients with moderate to severe HS, as there is still a high unmet need for new safe and efficacious HS therapies. The primary hypothesis for the study is that risankizumab will provide superior efficacy compared to placebo and will be well tolerated in subjects with HS.
Objective(s) and Endpoint(s):	The primary objective of this study is to assess the safety and efficacy of risankizumab 180 mg and 360 mg versus placebo for the treatment of signs and symptoms of moderate to severe HS in adult subjects diagnosed for at least one year before the Baseline visit. The primary endpoint is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 16. HiSCR is defined as at least a 50% reduction in the total abscess and inflammatory nodule [AN] count with no increase in abscess count and no increase in draining fistula count relative to Baseline. The following ranked secondary endpoints will be evaluated at the time points listed. 1. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of Skin Pain (PGA Skin Pain) at Week 8 among subjects with Baseline Numerical Rating Scale (NRS) ≥ 3. NRS30 is based on worst skin pain in a 24-hour recall period (maximal daily pain). 2. Proportion of subjects achieving NRS30 in PGA Skin Pain at Week 16 among subjects with Baseline NRS ≥ 3. 3. Proportion of subjects who experience at least 25% increase in AN counts with a minimum increase of 2 relative to Baseline during Period A. 4. Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 16. 5. Change from Baseline in HS-related swelling – assessed based on the Hidradenitis Suppurativa Symptom Assessment (HSSA) at Week 16. 6. Change from Baseline in HS-related odor – assessed based on the HSSA at Week 16. 7. Change from Baseline in HS-related worst drainage – assessed based on the HSSA at Week 16.
Investigator(s):	Multicenter

Study Site(s):	Approximately 60 sites in the US, EU, Canada, Japan, and Australia
Study Population and Number of Subjects to be Enrolled:	The study is designed to enroll approximately 220 adult subjects with moderate to severe HS for at least 1 year prior to Baseline, as determined by the investigator.
Investigational Plan:	This is a Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of 2 dose levels of risankizumab in adult subjects with moderate to severe HS diagnosed at least 1 year before the Baseline visit. The duration of the study will be up to 85 weeks and will include an approximately 35-day screening period followed by 2 treatment periods. In Period A, subjects who meet the study's eligibility criteria will be randomized at the Baseline visit to receive either risankizumab 180 mg or 360 mg via a subcutaneous (SC) injection, or matching placebo up to Week 16. The final efficacy evaluation of Period A will be at Week 16. In Period B, subjects initially randomized to placebo will receive blinded risankizumab 360 mg at Weeks 16, 17, and 18, while subjects initially randomized to risankizumab will receive blinded matching placebo at the same time points to keep the treatment of Period A blinded. Starting at Week 20, all subjects will receive open-label risankizumab 360 mg every eight weeks (q8w) until Week 60. The final efficacy evaluation of Period B will take place at Week 68. A follow up call will be conducted approximately 20 weeks after last dose of study drug.
Key Eligibility Criteria:	Subjects must be ≥ 18 years old at Screening with a clinical diagnosis of 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) for at least 1 year prior to Baseline, as determined by the investigator (i.e., through medical history, interview of subject). Subjects must have a history of inadequate response or intolerance to an adequate trial of oral antibiotics for treatment of HS as determined by local guidelines.
Study Drug and Duration of Treatment:	Subjects will be randomized to receive either risankizumab 180 mg or 360 mg as an SC injection or matching placebo up to Week 16 in a 1:1:1 ratio. Study drug administration for Period A will occur at Weeks 0 (Baseline), 1, 2, 4, and 12, with study site staff administering study drug as follows: • Risankizumab 180 mg SC (2 × 90 mg pre-filled syringe [PFS] and 2 × placebo PFS) • Risankizumab 360 mg SC (4 × 90 mg PFS), or • Matching placebo SC (4 × placebo PFS). At Weeks 16, 17, and 18 in Period B, subjects who were originally randomized to receive risankizumab 180 mg or 360 mg in Period A will receive placebo. Subjects who were originally randomized to receive placebo will receive risankizumab 360 mg. Beginning with Week 20 in

	Period B, study site staff will administer open-label risankizumab 360 mg q8w at Weeks 20, 28, 36, 44, 52, and 60.
Date of Protocol Synopsis:	15 December 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

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

Hidradenitis suppurativa 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] Important differential diagnoses of HS are furuncles, carbuncles, abscesses, cutaneous Crohn's disease, and acne.[8] 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.[9]

Hidradenitis suppurativa lesions (i.e., nodules, abscesses, and sinuses) are characterized by painful lesions located in the intertriginous areas, which can be malodorous and have purulent discharge. This constellation results in substantial disability and social stigma of the patients and a profound impact on the quality of life.[10] Depression, anxiety, and an increased suicide risk may be seen in patients with HS, as well as an adverse influence on a patient's sexual health.[11-15] Patients may have several comorbidities, such as obesity, metabolic syndrome, diabetes, arthritis, Crohn's disease, and polycystic ovary disease.[2,16] Patients with HS have an increased risk of adverse cardiovascular (CV) outcomes and all-cause mortality, and their risk of CV-associated death was shown to be higher than in psoriasis patients.[17]

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).[18] However, 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 TNF-α inhibitor that demonstrated in 2 Phase 3, multicenter, double-blind, placebo controlled studies (PIONEER I and PIONEER II) its safe and efficacious use in this patient population. The primary endpoint in these studies was the Hidradenitis Suppurativa Clinical Response (HiSCR), which is defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase in abscess count and no increase in draining fistula count relative to Baseline. At Week 12, HiSCR was achieved by 41.8% (PIONEER I) and 58.9% (PIONEER II) of subjects treated with adalimumab, respectively, in comparison to 26% (PIONEER I) and 27.6% (PIONEER II) of subjects treated with placebo.[19] In the context of this single HS-approved treatment option, there is still a high unmet need for new safe and efficacious HS therapies.

Hidradenitis suppurativa is a disease of unknown etiology characterized by a perifollicular lymphocytic infiltrate with subsequent sebaceous gland loss.[20] It is hypothesized that this process may be the result

of local immune system deregulation.[20,21] As HS progresses, increased levels of interleukin (IL)-1, tumor necrosis factor (TNF), IL-17, S100A8, S100A9, caspase-1, and IL-10 appear in the tissue accompanied by an influx of immune competent cells.[21-23] Macrophages are the most numerous inflammatory cells found in HS infiltrates and release numerous pro-inflammatory cytokines such as IL-23, IL-1β, and TNF-α, exacerbating the inflammation and contributing to the pathogenesis of HS.[24] IL-23 and IL-1β help differentiate T helper 17 (Th17) cells, which lead to abundant production of IL-17 in HS lesions. Macrophages that infiltrate the papillary and reticular dermis of HS lesions showed the expression of high amounts of IL-23 compared to skin of patients who do not have HS.[25] In accordance with the high expression of IL-23 and its important role in the development of Th17 cells, IL-17-producing T helper cells were found to distinctly infiltrate lesional dermis, suggesting that the IL-23/Th17 pathway is involved in HS.[25]

In a small uncontrolled, open-label, investigator-initiated study using standard weight-based psoriasis dosing of ustekinumab (Stelara®), a monoclonal antibody (mAb) that inhibits the p40 subunit of both the IL-12 and IL-23 receptor, 82% of the enrolled patients had moderate to marked improvements of the modified Sartorius score (a clinical scoring system for HS) at Week 40.[26] In a small, 28-week open-label, investigator-initiated pilot study investigating 300mg of secukinumab, a mAb that inhibits IL-17A, 78% of patients achieved HiSCR and a 40% decrease in mean Sartorius score at Week 24.[27] These results suggest that a targeted inhibition of IL-23 mediated inflammation with risankizumab may improve the signs and symptoms of the patients with HS.

Risankizumab is a humanized mAb of the IgG1 subclass directed towards IL 23p19. The antibody (Ab) has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23 and is currently being developed for the treatment of psoriasis (Phase 3 studies concluded and under registration review), Crohn's disease (in Phase 3 studies), psoriatic arthritis (in Phase 3 studies), ulcerative colitis (in Phase 2/3 studies), and atopic dermatitis (in a Phase 2 study). Risankizumab may also address the current needs for subjects with HS.

Clinical Hypothesis

Risankizumab will provide superior efficacy compared to placebo and will be well tolerated in subjects with HS.

2.2 Benefits and Risks to Subjects

This study is required to learn more about the potential treatment effect of risankizumab in HS.

As with many immune modulating agents, risankizumab may impair immune function, resulting in a risk of infection. This will be monitored by collection of all adverse events (AEs) during the treatment and observation periods. In addition, subjects with active systemic infection or clinically important infection will not be included in the study.

Subjects with a positive QuantiFERON®-TB (or interferon gamma release assay [IGRA] equivalent)/tuberculosis (TB) skin test result for TB must fulfill entry criteria as specified in Section 5.1 of this protocol. IL-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[28,29] Subjects with positive QuantiFERON-TB testing (or IGRA

equivalent)/TB skin test who have latent TB and are considered at low risk for reactivation (defined by local guidelines and investigator judgment) are not required to be treated with TB prophylaxis prior to receiving risankizumab, but should be carefully monitored for any sign of TB reactivation.

Published literature indicates that inhibition of IL-23 is unlikely to increase the risk for cancer. Expression of IL-23 is increased in human tumors.[30-32] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models. However, while there is not enough clinical information at this time to rule out a risk of cancer with risankizumab, this risk is considered small.

Although rare, a potential for hepatic AEs is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety.

Increases in major adverse cardiovascular (MACE) events, including myocardial infarction (MI), cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or nonserious) observed in this study will be adjudicated by an independent Cardiovascular Adjudication Committee (CAC), which will adjudicate all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation (Section 6.3).

Local reactions to subcutaneously-administered biologic therapies are usually limited to redness, swelling, or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during study drug administration. An independent Anaphylaxis Adjudication Committee (AAC) will adjudicate observed systemic hypersensitivity and anaphylactic events. The AAC will remain blinded to treatment allocation (Section 6.4).

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development.[33] Based on data from the integrated safety analyses, risankizumab is safe and well-tolerated and demonstrates a favorable benefit-risk profile.

For further details, please see findings from completed studies, including safety data in the current risankizumab Investigator's Brochure (IB).

In view of the coronavirus disease of 2019 (COVID-19) pandemic, the benefit-risk profile of various immunomodulatory therapies on COVID-19 is being evaluated based on real world and clinical trial data. At this time, the effects of risankizumab on the course of COVID-19 are not well defined.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The primary objective of this study is to assess the safety and efficacy of risankizumab 180 mg and 360 mg versus placebo for the treatment of signs and symptoms of moderate to severe HS in adult subjects diagnosed for at least one year before the Baseline visit.

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response (HiSCR) at Week 16. 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.

3.3 Secondary Endpoints

Key Secondary Endpoints

The following ranked secondary endpoints will be evaluated at the time points listed.

1. Proportion of subjects achieving at least 30% reduction and at least 1 unit reduction from Baseline in Numerical Rating Scale (NRS30) in Patient's Global Assessment of Skin Pain (PGA Skin Pain) at Week 8 among subjects with Baseline Numerical Rating Scale (NRS) ≥ 3. NRS30 is based on worst skin pain in a 24-hour recall period (maximal daily pain).
2. Proportion of subjects achieving NRS30 in PGA Skin Pain at Week 16 among subjects with Baseline NRS ≥ 3.
3. Proportion of subjects who experience at least 25% increase in AN counts with a minimum increase of 2 relative to Baseline during Period A.
4. Change from Baseline in Dermatology Life Quality Index (DLQI) at Week 16.
5. Change from Baseline in HS-related swelling – assessed based on the Hidradenitis Suppurativa Symptom Assessment (HSSA) at Week 16.
6. Change from Baseline in HS-related odor – assessed based on the HSSA at Week 16.
7. Change from Baseline in HS-related worst drainage – assessed based on the HSSA at Week 16.

Additional Endpoints

All variables listed as primary or ranked secondary endpoints will also be analyzed at all visits collected in addition to those listed above. The following endpoints will also be evaluated at all visits collected:

- Change and percent change from Baseline in PGA Skin Pain at worst (maximal daily pain), among subjects who have Baseline NRS ≥ 3.
- Proportion of subjects achieving a total AN count of 0, 1, or 2.
- Proportion of subjects achieving complete elimination of inflammatory lesions by lesion type, among subjects who had the corresponding lesion type at Baseline.
- Proportion of subjects who experience at least 25% increase in inflammatory lesion counts with a minimum increase of 2 relative to Baseline, by lesion type.
- Change from Baseline in inflammatory lesion counts by lesion type.
- Percent change from Baseline in lesion counts by inflammatory lesion type, among subjects who had at least 3 of the corresponding lesion type at Baseline.
- Proportion of subjects achieving DLQI = 0 or 1.

- Proportion of subjects achieving a DLQI improvement (reduction) of ≥ 4 points among subjects with DLQI ≥ 4 at Baseline.
- Change from Baseline in symptoms assessed based on HSSA questionnaire.
- Change from Baseline in Hidradenitis Suppurativa Impact Assessment (HSIA) questionnaire.
- Change from Baseline in EuroQol 5 Dimensions 5 Levels Health State Instrument (EQ-5D-5L).
- Change from Baseline in Work Productivity and Activity Impairment (WPAI).
- Proportion of subjects achieving at least 1 grade improvement from Baseline in Patient Global Impression of Severity (PGIS) scale among subjects with Baseline PGIS of at least "Minimal."
- Proportion of subjects who report symptoms to be "Minimal" or "Absent" on the PGIS scale.
- Proportion of subjects achieving "much improved" or "very much improved" on the Patient Global Impression of Change (PGIC) scale.
- Change from Baseline in Hospital Anxiety and Depression Scale (HADS).
- Change from Baseline in high-sensitivity C-reactive protein (hsCRP).
- Proportion of subjects who experience worsening by at least 1 Hurley Stage in at least 1 affected anatomic region.

3.4 Safety Endpoints

The following safety evaluations will be performed during the study: treatment emergent adverse events (TEAEs), serious adverse events (SAEs), areas of safety interest (ASI), and AEs leading to discontinuation; vital signs; and laboratory tests.

3.5 Pharmacokinetic and Immunogenicity Endpoints

Serum risankizumab concentrations, antidrug antibodies (ADA), and neutralizing antibodies (NAb) will be determined from blood collected by venipuncture at the visits indicated in the Activity Schedule.

3.6 Biomarker Research

Optional blood samples will be collected to investigate changes in biomarkers following treatment with risankizumab, such as proteins and/or genes involved in the IL-23 pathways and biomarkers of HS disease activity. Prognostic, surrogate, predictive and pharmacodynamics biomarkers may be investigated. Samples for different applications, potentially including but not limited to pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomic, metagenomic, phenotypic, functional and targeted investigations will be collected at various time points. Assessments may include but may not be limited to nucleic acids, proteins, metabolites, or lipids. 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

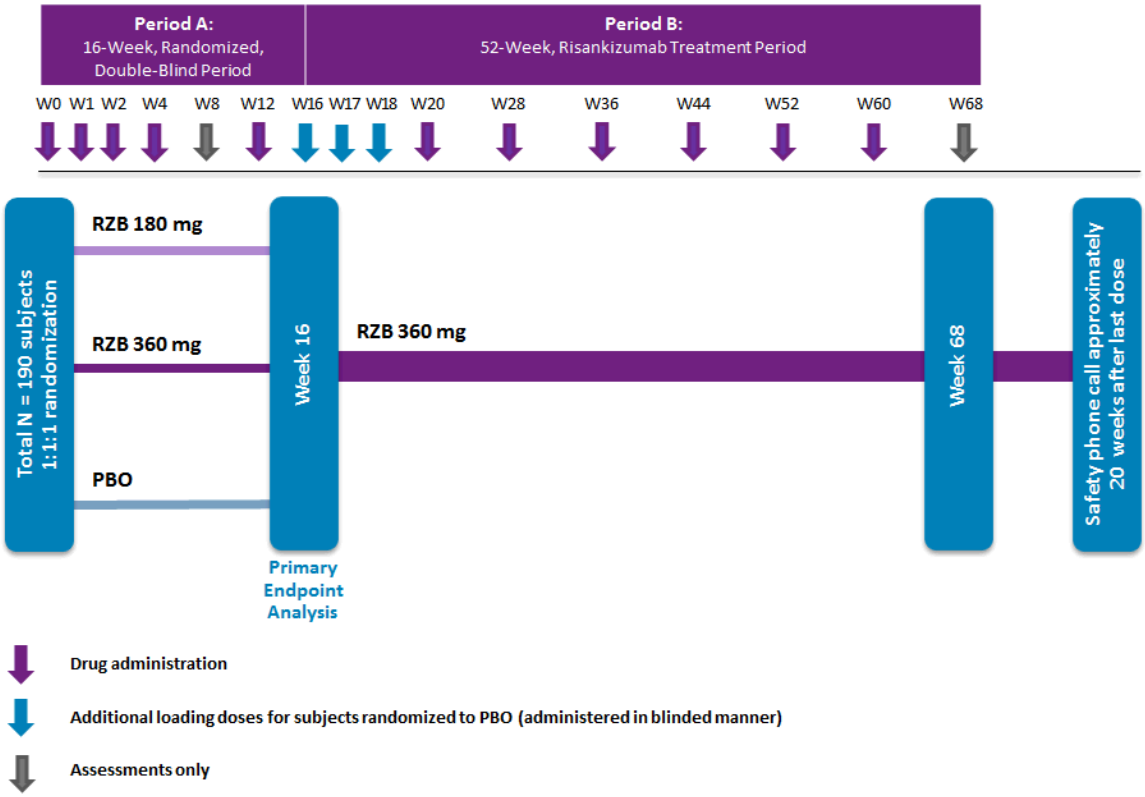
This is a Phase 2, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety and efficacy of 2 dose levels of risankizumab in adult subjects with moderate to severe HS diagnosed at least 1 year before the Baseline visit.

The duration of the study will be up to 85 weeks and will include an approximately 35-day screening period followed by 2 treatment periods. In Period A, subjects who meet the study's eligibility criteria (Section 5.1) will be randomized at the Baseline visit, in a 1:1:1 ratio, to receive either risankizumab 180 mg or 360 mg via a subcutaneous (SC) injection, or matching placebo up to Week 16. Study drug administration for Period A will occur at visits Weeks 0 (Baseline), 1, 2, 4, and 12. The final efficacy evaluation of Period A will be at Week 16.

In Period B, subjects who were initially randomized to placebo will then receive blinded risankizumab 360 mg at Weeks 16, 17, and 18, while subjects who were initially randomized to risankizumab will receive blinded matching placebo at the same time points to keep the treatment of Period A blinded. Starting at Week 20, all subjects will receive open-label risankizumab 360 mg every eight weeks (q8w), at Weeks 20, 28, 36, 44, 52, and 60. The final efficacy evaluation of Period B will take place at Week 68. A follow up call will be conducted approximately 20 weeks after last dose of study drug.

A schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

Figure 1. Study Schematic



PBO = placebo; RZB = risankizumab; W = week

This study plans to enroll approximately 220 subjects from approximately 60 sites in the US, EU, Canada, Japan, and Australia, although the number, allocation, and location of sites may vary depending on operational aspects of the study.

Once a sufficient number of subjects to fulfill the enrollment target have entered the screening process, no further subjects will be screened. Once 220 subjects have been randomized, subjects who have started screening but have not yet been randomized will be allowed to enroll in the study if eligible.

The study team will remain blinded until the Week 16 Primary Analysis. In addition, the study will have an external independent data monitoring committee (IDMC) to review unblinded safety data (Section 6.2). Independent committees to assess cardio- and cerebro-vascular events (Cardiovascular Adjudication Committee [CAC]) and suspected anaphylactic reactions (Anaphylaxis Adjudication Committee [AAC]) will also be formed (Section 6).

4.2 Discussion of Study Design

Choice of Control Group

A placebo control has been selected as the appropriate control group for this study to establish an unbiased efficacy and safety profile of risankizumab in subjects with HS.

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 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) for at least 1 year prior to Baseline, as determined by the investigator are eligible for this study. The criteria relating to safety have been selected to allow subjects to be safely enrolled and treated with risankizumab based on the current knowledge of this drug. The study population selected reflects a standard population for moderate to severe HS studies with new treatment intervention.

Selection of Doses in the Study

Hidradenitis suppurativa is considered a high inflammatory disease with deep-seated lesions and an abundance of innate and adaptive immune cells. Two doses of risankizumab (180 mg and 360 mg) were selected for evaluation in this study. A 180 mg SC dose administered q8w has maintained efficacy in the Phase 2 Crohn's disease study and is likely to be efficacious in subjects with HS. The additional higher dose of 360 mg SC is also being tested as the high-maintenance dose level in the Phase 3 Crohn's disease studies based on the preliminary exposure-response analyses of the Phase 2 Crohn's disease study, indicating greater efficacy at a higher dose above 180 mg. Evaluating both doses in this study is expected to provide dose/exposure-response data and to allow for evaluation if an efficacy plateau can be achieved at 360 mg dose level. Both doses are within the range of doses safely administered in previous risankizumab clinical studies.

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 or their legally authorized representative 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.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old and functionally able to read and understand study questionnaires.
- 3. **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;
  - Serum total bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
  - Total white blood cell (WBC) count > 3,000/µL;
  - Absolute neutrophil count (ANC) > 1,500/µL;
  - Platelet count > 100,000/µL;
  - Hemoglobin > 8.0 g/dL.
- 4. Subjects are willing or able to comply with procedures required in this protocol.
- 5. Subject is not an employee or a family member of the sponsor and/or study sites.

Disease Activity

- 6. Adults with moderate to severe HS for at least 1 year prior to Baseline, as determined by the investigator (i.e., through medical history, interview of subject).
- 7. Subject must have a total AN count of ≥ 5 at Baseline.
- 8. HS lesions must be present in at least 2 distinct anatomic areas.
- 9. Draining fistula count of ≤ 20 at Baseline.
- 10. Inadequate response (or intolerant) to an adequate trial of oral antibiotics for treatment of HS as determined by local guidelines.

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. No evidence of **hepatitis B virus (HBV) or hepatitis C virus (HCV) infection**, defined as:
  - HBV: Hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV DNA polymerase chain reaction (PCR) qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+) (and for hepatitis B surface antibody [HBs Ab] positive [+] subjects where mandated by local requirements).
  - HCV: HCV RNA detectable in any subject with anti-HCV antibody (HCV Ab).

- 13. No evidence of **HIV**, defined as confirmed positive anti-HIV antibody (HIV Ab) test. (Note: In case a screened subject has a confirmed positive HIV Ab test, Eligibility Criterion #22 should be selected in the eCRF for documentation of reason for screening failure.)
- 14. No **active TB or concurrent treatment for latent TB**. (Note: TB antibiotic prophylaxis is prohibited due to potential impact on efficacy assessments.) Subjects with a positive QuantiFERON® TB gold test (or IGRA equivalent) or purified protein derivative (PPD) test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB and the subject does not require the use of prophylactic anti-TB therapy during the conduct of the study. If anti-TB therapy has been previously completed by the subject, the last dose of anti-TB therapy must have been completed at least 4 weeks prior to the Baseline visit.
- 15. No history of **active systemic infection** during the last 2 weeks prior to the Baseline visit (exception: common cold), as assessed by the Investigator.
- 16. No documented **active or suspected malignancy** or **history of any malignancy within the last 5 years** except for successfully treated non-melanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
- 17. No history of organ transplantation.
- 18. No **major surgery** performed within 12 weeks prior to randomization or planned during the conduct of the study (e.g., hip replacement, aneurysm removal, stomach ligation).
- 19. No history or concurrent clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition that in the opinion of the Investigator would compromise the safety or **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the protocol; as well as being permanently wheelchair-bound or bedridden or having very poor functional status that is preventing the ability to perform self-care.
- 20. No history of clinically significant (per Investigator's judgment) **drug or alcohol abuse** within the last 6 months, including medicinal or recreational cannabis or cannabinoids.
- 21. No 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.
- 22. Subject is judged to be in good general health, as determined by the Principal Investigator based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead electrocardiogram (ECG) performed during the Screening period.

Contraception

- 23. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening visit and a negative urine pregnancy test at Baseline prior to the first dose of study drug.
- 24. If female, subject must be of non-childbearing potential OR a female of childbearing potential practicing at least 1 protocol-specified **method of birth control**, that is effective from Baseline through at least 140 days (20 weeks or as guided by the local risankizumab label if approved, whichever is longer) after the last dose of study drug (local practices may require 2 methods of birth control).

- 25. Female is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or for approximately 140 days (20 weeks or as guided by the local risankizumab label if approved, whichever is longer) after the last dose of study drug.

Prior Medication Restrictions

- 26. Subjects with prior exposure to **biologic agents** that block IL-12/23 (e.g., ustekinumab), IL-23 (e.g., risankizumab, guselkumab), or IL-17 (e.g., secukinumab) are eligible, provided that the last drug administration occurred at least 6 months prior to Baseline. Overall, no more than 10% of the study population will be subjects with prior exposure to these biologic agents.
- 27. Subjects who have had prior exposure to anti-TNF therapy (e.g., adalimumab, infliximab) for any indication are not eligible, unless they received anti-TNF therapy for HS and demonstrated inadequate response (TNF-IR). The last anti-TNF treatment administration must have occurred at least 2 months prior to Baseline.
- 28.No exposure to other immunomodulatory biologic therapies, including anti-IL-1 (e.g., anakinra, canakinumab), within 3 months or 5 half-lives, whichever is longer, prior to Baseline.
- 29. 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.
- 30. No use of traditional Chinese medicines within 4 weeks prior to the Baseline visit.
- 31. 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.
- 32. Subjects must not have received systemic non-biologic therapies (e.g., spironolactone) that can also be used to treat HS within 4 weeks prior to the Baseline visit.
- 33. Subjects must not have received any systemic (including oral) antibiotic treatment for HS or any other inflammatory disorder within 4 weeks prior to the Baseline visit.
- 34. Subjects are required to use a daily antiseptic wash on their HS lesions starting at least 14 days (2 weeks) 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.
- 35. For HS and non-HS related pain, subjects must not have received oral concomitant analgesics (including opioids) within 14 days prior to the Baseline visit.

  Exception: Subjects may continue on non-opioid analgesics provided that the dose and dosing regimen have been stable for at least 14 days preceding the Baseline visit and are expected to remain stable at least until Week 16 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 (Section 5.4).
- 36. Subject must not have received **any live vaccine** within 6 weeks prior to the first dose of study drug (Baseline), or expect the need for live vaccination during study participation including at least 140 days (20 weeks or as guided by the local risankizumab label if approved, whichever is longer) after the last dose of study drug.

- 37. Subject must not have been treated with **any other investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.

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(s) and for at least 140 days (20 weeks or as guided by the local risankizumab label if approved, whichever is longer) after the last dose of study drug.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, injectable, transdermal) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline;
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline;
    - Bilateral tubal occlusion/ligation [can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure];
    - Intrauterine device (IUD);
    - Intrauterine hormone-releasing system (IUS);
    - Vasectomized sexual partner(s) (provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the study subject);
    - True abstinence: 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 guidelines, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

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

5.3 Prohibited Concomitant Medications and Therapy

Use of the following treatments is prohibited throughout the study:

1. Use of any biologic immunomodulation agent, including but not limited to anti-TNF (e.g., adalimumab, infliximab), anti-IL-1 (e.g., anakinra, canakinumab), anti-IL-12/23 (e.g., ustekinumab), other anti-IL-23 (e.g., guselkumab), or anti-IL-17 (e.g., secukinumab) throughout the study.
2. Any other systemic therapy that can also be used to treat HS, including but not limited to apremilast, corticosteroids, methotrexate (MTX), cyclosporine, retinoids, acitretin/etretinate, hormonal therapy (except for contraception), zinc gluconate, intramuscular gamma-globulin, colchicine, metformin (except for continuous treatment of pre-existing diabetes), and fumaric acid esters throughout the study.
3. Injectable corticosteroids. Exception: Rescue treatment (intralesional triamcinolone acetonide injection) initiated after Week 16 assessment.
4. Non-antibiotic topical therapies or changes in the concentration/frequency of such treatments that may be used to treat HS (e.g., zinc pyrithione, resorcinol, dapsone, and delgocitinib). Other non-antibiotic topical treatments (e.g., corticosteroids, antifungals, etc.) are permitted, provided these are not being used in anatomic regions where HS lesions are located.
5. 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 is prohibited. Exception: Rescue treatment (local incision/draining) performed after Week 16 assessment.
6. Any antibiotic therapy (topical and/or systemic) during study participation. Systemic and/or topical antibiotic use is only allowed for the treatment of acute, non-HS related infections.
7. Use of any treatments for HS-related pain, other than ibuprofen or acetaminophen (paracetamol), including but not limited to antiepileptics (e.g., gabapentin), tricyclics (e.g., nortriptyline), or selective serotonin norepinephrine reuptake inhibitors (e.g., duloxetine, venlafaxine). Use of any opioid is prohibited, regardless of the indication.
8. Over-the-counter topical antiseptic washes, creams, ointments, gels, and liquids containing antibacterial agents to treat HS, other than those allowed as per concomitant therapy section.
9. Phototherapy treatment (ultraviolet B [UVB] or ultraviolet A [UVA] phototherapy, including psoralen and ultraviolet A [PUVA]), tanning booth, or extended sun exposure.
10. Receipt of any live vaccine expected during study participation, including at least 140 days (20 weeks or as guided by the local risankizumab label if approved, whichever is longer) after the last dose of study drug.

11. Live attenuated vaccines are not permitted during study participation and including up to 140 days (20 weeks or as guided by the local risankizumab label if approved, whichever is longer) after the last dose of study drug. Examples of live attenuated vaccines include, but are not limited to, the following:
    - Bacille Calmette-Guérin (BCG)
    - Zoster vaccine live (Zostavax)
    - Measles-mumps-rubella or measles mumps rubella varicella
    - Monovalent live attenuated influenza A (intranasal)
    - Oral polio vaccine
    - Rotavirus
    - Seasonal trivalent live attenuated influenza (intranasal)
    - Smallpox
    - Oral typhoid vaccine
    - Varicella (chicken pox)
    - Yellow fever
    - Dengue (Dengvaxia®)
12. Treatment with any investigational drug.
13. Medicinal and recreational cannabis or cannabinoid use.
14. Traditional Chinese medicines.

5.4 Prior and Concomitant Therapy

Required Concomitant Medications/Therapies

Subjects are required to use a daily antiseptic wash on their HS lesions. Allowable antiseptic washes are limited to one of the following: chlorhexidine gluconate, benzoyl peroxide, benzalkonium chloride, benzethonium chloride, or dilute bleach in bath water.

Allowed Concomitant Medications/Therapies

Stable doses of other concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the subject from participation, are permissible. All concomitant medications should be carefully evaluated by the investigator.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject has received from 4 weeks prior to screening 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).

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with risankizumab can be located in the risankizumab IB.

Subjects must be able to safely discontinue any prohibited medications as specified in the eligibility criteria; where not specified, discontinuation must occur 5 half-lives or 4 weeks, whichever is longer, prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

The following categories of concomitant medications/therapies are allowed during the study:

- **Antibiotics.** Concomitant use of oral antibiotics is only allowed for the treatment of acute non-HS related infections. Dosing and/or frequency need to be reported in the eCRF documentation; "as needed" (PRN) use is not permitted. Use of topical or systemic antibiotics to treat HS or other chronic inflammatory disorders is prohibited. Subjects who receive antibiotics for HS-related infections will be considered treatment failures; however they will continue to receive the study treatment assigned at randomization.
- **Over-the-counter shampoos and soaps containing antibacterial agents.**
- **Wound care.** Use of wound care dressings on HS wounds is allowed. Recommended options include alginates, hydrocolloids, and hydrogels.
- **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 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. 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 in the context of this study.

  Subjects will complete a daily diary of their HS-related analgesic use. Subjects will be required to record their analgesic use daily through Week 16; after Week 16, subjects will fill out analgesic use information for 7 days leading up to the visit. Any changes in dosing and/or frequency need to be reported in the daily diary; documentation of only PRN use is not permitted. Dose adjustments of ibuprofen or acetaminophen for HS-related pain up to the maximum permitted dose and frequency per local label are allowed during the study.

  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 at least until the Week 16 assessment.

Rescue Medications/Therapy

Rescue treatment is allowed to start only after the Week 16 assessments. Rescue treatment is limited to an injection with intralesional triamcinolone acetonide suspension OR local incision and draining.

In the event that an acutely painful HS lesion that requires immediate intervention occurs after the Week 16 assessment, 2 protocol-allowed interventions per subject are permissible for the remainder of

the study. An intervention can occur at a maximum on 2 different lesions at the same visit or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same visit.

All study visit evaluations have to occur before interventions are performed. If incision and draining is performed, antiseptic creams/liquids are allowed to be administered on the specific lesions upon which an intervention had been performed for as many days as considered medically necessary by the investigator.

When counting the total lesions in each body region, the site will be required to count any lesion that undergoes an intervention as permanently present from the date of the intervention, regardless of the outcome of the intervention performed.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study drug and/or study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory result(s) or AE(s) that preclude continuation of the study medication, as determined by the Investigator and the TA MD (as applicable).
- The Investigator believes withdrawal from the study is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation(s) are noted after the subject started study drug, if continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD, after consultation with the Investigator.
- Introduction of prohibited medications and continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Subject develops active TB at any time during the study.
- Subject becomes pregnant while participating in the study.
- Subject is diagnosed with a malignancy. Exception: Localized NMSC or carcinoma in-situ of the cervix, where discontinuation is at the discretion of the Investigator.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the study.
- Subject requires > 2 protocol-allowed HS interventions.
- Post-Baseline occurrence of one or more of the following hepatic test abnormalities (confirmed on a second separate sample at least 48 hours apart):
  - ALT or AST > 8 × ULN;
  - ALT or AST > 5 × ULN for more than 2 weeks;
  - ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5;
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

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.

AbbVie may terminate this study prematurely, either in its entirety or at any site. 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.

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID 19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix F for details on how to handle study activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

For subjects with documented COVID-19, the timing of next administration of study drug or possibility of premature discontinuation from study drug should be discussed with the AbbVie Medical Contact. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug.

5.6 Follow-Up for Subject Withdrawal from Study

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, unless subjects have decided to discontinue the 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.

If a subject prematurely discontinues study participation, 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 and has not withdrawn consent, a 20-week follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

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, 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 optional biomarker research, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Information about the study drug and placebo used in this study is presented in (Table 1).

Table 1. Identity of Investigational Product

Study Drug	Dosage Form	Formulation	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Solution for injection in pre-filled syringe (PFS)	90 mg/mL	SC injection	Boehringer-Ingelheim Pharma GmbH & Co. KG
Placebo for risankizumab (ABBV-066)	Solution for injection in PFS	N/A	SC injection	Boehringer-Ingelheim Pharma GmbH & Co. KG

N/A = not applicable; PFS = pre-filled syringe; SC = subcutaneous

Through Week 12 of Period A, study site staff will administer study drug subcutaneously as follows:

- Risankizumab 180 mg (2 × 90 mg PFS and 2 × placebo PFS)
- Risankizumab 360 mg (4 × 90 mg PFS), or
- Matching placebo (4 × placebo PFS).

At Weeks 16, 17, and 18 in Period B, subjects who were originally randomized to receive risankizumab 180 mg or 360 mg in Period A will receive placebo. Subjects who were originally randomized to receive placebo will receive risankizumab 360 mg.

Beginning with Week 20 in Period B, study site staff will administer open-label risankizumab 360 mg subcutaneously as described above q8w until the end of the study.

Risankizumab and matching placebo 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 kept in the original packaging in a secured limited access storage area according to the recommended storage conditions on the medication label. No extemporaneous dose preparation is required.

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.

AbbVie will not supply drug other than risankizumab and matching placebo, and study drug will only be used for the conduct of this study. AbbVie-provided study drug should not be substituted or alternately sourced unless otherwise directed by AbbVie.

5.8 Randomization/Drug Assignment

Each subject 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. Subjects may only be rescreened one time. 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 who meet the study's eligibility criteria will be initially randomized to receive either risankizumab 180 mg or 360 mg as an SC injection or matching placebo up to Week 16 in a 1:1:1 ratio.

Subjects who have been treated with anti-TNF therapy and had inadequate response to this therapy (TNF- IR) will be eligible. Subjects will be randomized by their anti-TNF use (yes or no) prior to Baseline. TNF-naïve (no) subjects will be further stratified by the worst Hurley stage across all affected anatomic regions. Therefore, there will be 4 strata in total:

- Prior exposure to anti-TNF (yes)
- Prior exposure to anti-TNF (no) with the worst Hurley Stage as I
- Prior exposure to anti-TNF (no) with the worst Hurley Stage as II
- Prior exposure to anti-TNF (no) with the worst Hurley Stage as III

All AbbVie personnel with direct oversight of the conduct and management of the study (with the exception of AbbVie Drug Supply Management Team) will remain blinded until the Primary Analysis at Week 16 is available. The investigator, study site personnel, and the subject will remain blinded to each subject's initial treatment throughout the study. To maintain the blind, the risankizumab kits and placebo kits provided for the study will be identical in appearance. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

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 adverse event 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 an AE only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria, and/or the investigator considers it to be an AE.

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 as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual 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 20 weeks (140 days) after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related 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 (SUSAR) 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.

Areas of Safety Interest/Safety Topics of Interest

Subjects will be screened and monitored throughout the study for ASI/Safety Topics of Interest. Screening procedures are outlined in the Activity Schedule (Appendix D). In consideration of the ASI, the following supplemental eCRFs must be completed if AEs in any of the following areas are reported during the study (Table 2).

Table 2. Supplemental Adverse Events eCRFs

Adverse Event	Supplemental eCRF
Cardiac events **Myocardial infarction or unstable angina** **Cerebral vascular accident** **Cardiovascular death**	• Cardiovascular History and CV Risk Factors eCRF • Cardiovascular (Cardiac) AE eCRF • Myocardial Infarction and Unstable Angina AE eCRF • Heart Failure AE eCRF • Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF • Combination Thrombotic Event AE eCRF • Arrhythmia AE eCRF
Discontinuation or interruption of study drug due to a **Hepatic-related AE** **Hepatic-related SAE**	• Hepatic AE eCRF
Suspected anaphylactic/systemic hypersensitivity reactions	• Hypersensitivity Reaction Signs and Symptoms eCRF
TB Subjects will be screened for TB (using the TB Screening Form) and those with active TB will be excluded from participation in the study. Subjects with events of latent TB or suspected active TB after initiation of study drug should have a TB Supplemental Form completed.	• TB Screening eCRF • TB Supplemental eCRF
Death	• Death eCRF

AE = adverse event; CV = cardiovascular; eCRF = electronic case report form; SAE = serious adverse event; TB = tuberculosis

Adverse Event Severity and Relationship to Study Drug

Adverse events must be graded to the 5 criteria described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.[34]

If no specific criteria per CTCAE Version 5 guidelines are available for the reported event, the event should be graded per the investigator's judgment:

- **Grade 1 (Mild):** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- **Grade 2 (Moderate):** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- **Grade 3 (Severe):** Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4 (Severe):** Life-threatening consequences; urgent intervention indicated.
- **Grade 5 (Severe):** 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.

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. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

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 after the site becomes aware of the event.

6.2 Independent Data Monitoring Committee

An external IDMC will review unblinded safety data on a cohort level, at approximate 6-month intervals throughout the course of the study.

- A separate IDMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the IDMC members, frequency and triggers of data reviews, and relevant safety data to be assessed. Unblinded adjudicated cardio-cerebrovascular events will be presented to the IDMC for review on a periodic basis.
- Communications from the IDMC to the Study Teams will not contain information that could potentially unblind the team to subject treatment assignments.

6.3 Cardiovascular Adjudication Committee

An independent adjudication committee will be adjudicating all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation. The events that are adjudicated and the adjudication process will be detailed in the CAC Charter. Dedicated eCRFs will be used as outlined in Table 2.

In addition, the site may be contacted for additional source documentation for relevant events.

6.4 Anaphylaxis Adjudication Committee

While no concerns with systemic hypersensitivity have been identified with the use of risankizumab, the sponsor has established the AAC to adjudicate events of anaphylaxis based on pre-specified definitions. This independent, external committee will adjudicate suspected anaphylactic reactions and will remain blinded to treatment allocation. The event terms to be adjudicated and the adjudication process are detailed in the AAC Charter. A supplemental Hypersensitivity Reactions Signs and Symptoms eCRF will be used to collect information pertinent to the events (Table 2). In addition, the site may be contacted for additional source documentation for relevant events.

If a suspected systemic hypersensitivity reaction occurs at the investigative site, subjects should be tested for tryptase and histamine levels. In addition to testing tryptase and histamine levels, pharmacokinetic (PK) and ADA/NAb samples will also be collected. If a systemic hypersensitivity reaction such as anaphylaxis is suspected while the subject is not at the investigative site, every effort should be made to obtain tryptase and histamine levels from the treating facility to help better characterize the diagnosis.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The Primary Analysis will be conducted after all continuing subjects complete Week 16 and all data pertaining to Period A are cleaned. This will be the only and final analysis for efficacy in Period A. Study sites and subjects will remain blinded to their initial treatment assignment for the duration of the entire study.

The statistical analysis will be described and fully documented in the SAP, which will be finalized prior to the start of the study. All statistical tests, between each risankizumab dose and placebo, will be performed at a two-sided alpha level of 0.025.

The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The intent-to-treat (ITT) Population, which includes all randomized subjects, will be used for all efficacy analyses. Subjects who are randomized to placebo in Period A and do not continue into Period B will be excluded from the analysis in Period B.

In order to evaluate the impact of major protocol deviations on the primary efficacy endpoint, additional sensitivity analyses may be performed on a per-protocol population, which excludes subjects with major protocol deviations that potentially affect the primary efficacy endpoint. If it is decided that this analysis should be performed, the criteria for exclusion of subjects from the per-protocol population will be fully defined in the classification plan, and the exclusion of subjects from the per-protocol population will be finalized before blind break and before the database lock for the primary analysis.

The following populations will be used for the safety analysis:

- The Safety Population in Period A (Safety_A) is defined as all subjects who are randomized and received at least one dose of study drug in Period A.
- The Safety Population in Period B (Safety_B) is defined as all subjects who received at least one dose of study drug in Period B.
- The all risankizumab treated (ALL_RZB) Population is defined as subjects who received at least one dose of risankizumab in the study. This population will be used to provide a comprehensive summary of safety.

7.3 Statistical Analyses for Efficacy

Analysis of all efficacy endpoints in Period A will be conducted on the ITT Population, based on treatment as randomized for Period A. In addition, the primary efficacy endpoint will be analyzed in the per-protocol population, if defined.

Comparison of the primary endpoint will be made between each risankizumab dose and placebo using the Cochran-Mantel-Haenszel (CMH) test, adjusting for stratification factors. Non-responder imputation (NRI) will be the primary approach to handle missing values. To account for impact of COVID-19 pandemic, the NRI will be adjusted to NRI-C, Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19.

The overall type-I error rate will be strongly controlled using a graphical multiple testing procedure. The primary and ranked secondary endpoints will be first tested in the ranked order specified in Section 3 between each risankizumab dose and placebo, with a 2-sided significance level of 0.025. Continued testing will follow a pre-specified α transfer path which includes downstream transfer along the endpoint sequence. More details of the graphical procedure will be specified in the SAP.

Details on the primary and other efficacy analyses will be provided in the SAP.

Sample Size Estimation

Under the study design with a 1:1:1 randomization, with the assumed Week 16 HiSCR response rate as summarized in Table 3, a total sample size of 222 subjects will provide 80% to 90% power to detect at least one risankizumab dose is different from placebo (with a 2-sided significance level of 0.025 for the test of each risankizumab dose versus placebo).

Table 3. Power with a 1:1:1 Randomization

Assumed Dose Response Model	Assumed HiSCR Rate at Week 16 (%)			Power[1]
	Placebo (N = 74)	Risankizumab 180 mg (N = 74)	Risankizumab 360 mg (N = 74)	
Linear	26%	39.5%	53%	83.9%
EMax	26%	46.5%	53%	87.6%
EMax (with early plateau)	26%	50%	53%	90.6%

HiSCR = Hidradenitis Suppurativa Clinical Response

1. Power to detect at least one risankizumab dose is different from placebo, under a 2-sided significance level of 0.025 for each risankizumab dose.

7.4 Statistical Analyses for Safety

All safety analyses will be performed on the Safety populations. Subjects will be analyzed based on the first dose of treatment received after randomization. A TEAE is defined as an event with onset or worsening after the first dose of study drug and within 20 weeks (140 days) after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT), as well as by severity and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100-PYs) of SAEs, deaths, and AEs leading to discontinuation will be provided as well. Pre-treatment AEs will be summarized separately. For selected lab parameters, a listing of all subjects with any laboratory value above Grade 3 of Common Toxicity Criteria (CTC) 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 Analyses of Pharmacokinetics and Immunogenicity

Serum risankizumab concentrations will be summarized at each sampling time point for each dose group using descriptive statistics. Population PK analyses combining data from this study and other studies of risankizumab may be performed and reported separately. The relationship between risankizumab concentrations and certain efficacy and/or safety variables of interest may be explored.

ADA titers will be tabulated for each subject at the respective study visits. The number and percentage of subjects with ADA and NAb will be calculated by dose group. As appropriate, the effect of ADAs on risankizumab PK, efficacy, and/or safety variable(s), and/or any additional analyses may be explored.

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 of Technical Requirements for Pharmaceuticals for Human Use (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 the event of a state of emergency due to the COVID-19 pandemic 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 study visit schedule modification. Refer to the Operations Manual in Appendix F for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if 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). During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

Supplemental study case report forms should be completed in the event of COVID -19-related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

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 contact, which will be a follow-up phone call 20 weeks after the last dose.

12 REFERENCES

1. Zouboulis CC, Del Marmol V, Mrowietz U, et al. Hidradenitis suppurativa/acne inversa: criteria for diagnosis, severity assessment, classification and disease evaluation. Dermatology. 2015;231(2):184-90.

2. Fimmel S, Zouboulis CC. Comorbidities of hidradenitis suppurativa (acne inversa). Dermatoendocrinol. 2010;2(1):9-16.

3. Fitzsimmons JS, Guilbert PR, Fitzsimmons EM. Evidence of genetic factors in hidradenitis suppurativa. Br J Dermatol. 1985;113(1):1-8.

4. Jemec GB. The symptomatology of hidradenitis suppurativa in women. Br J Dermatol. 1988;119(3):345-50.

5. Lookingbill DP. Yield from a complete skin examination: findings in 1157 new dermatology patients. J Am Acad Dermatol. 1988;18(1 Pt 1):31-7.

6. Jemec GB, Heidenheim M, Nielsen NH. The prevalence of hidradenitis suppurativa and its potential precursor lesions. J Am Acad Dermatol. 1996;35(2 Pt 1):191-4.

7. Revuz JE, Canoui-Poitrine F, Wolkenstein P, et al. Prevalence and factors associated with hidradenitis suppurativa: results from two case-control studies. J Am Acad Dermatol. 2008;59(4):596-601.

8. Saunte DML, Jemec GBE. Hidradenitis suppurativa: advances in diagnosis and treatment. JAMA. 2017;318(20):2019-32.

9. Saunte DM, Boer J, Stratigos A, et al. Diagnostic delay in hidradenitis suppurativa is a global problem. Br J Dermatol. 2015;173(6):1546-9.

10. von der Werth JM, Jemec GB. Morbidity in patients with hidradenitis suppurativa. Br J Dermatol. 2001;144(4):809-13.

11. Sampogna F, Abeni D, Gieler U, et al. Impairment of sexual life in 3,485 dermatological outpatients from a multicentre study in 13 European countries. Acta Derm Venereol. 2017;97(4):478-82.

12. Janse IC, Deckers IE, van der Maten AD, et al. Sexual health and quality of life are impaired in hidradenitis suppurativa: a multicentre cross-sectional study. Br J Dermatol. 2017;176(4):1042-7.

13. Thorlacius L, Cohen AD, Gislason GH, et al. Increased suicide risk in patients with hidradenitis suppurativa. J Invest Dermatol. 2018;138(1):52-7.

14. Vangipuram R, Vaidya T, Jandarov R, et al. Factors contributing to depression and chronic pain in patients with hidradenitis suppurativa: results from a single-center retrospective review. Dermatology. 2016;232(6):692-5.

15. Shavit E, Dreiher J, Freud T, et al. Psychiatric comorbidities in 3207 patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol. 2015;29(2):371-6.

16. Miller IM, McAndrew RJ, Hamzavi I. Prevalence, risk factors, and comorbidities of hidradenitis suppurativa. Dermatol Clin. 2016;34(1):7-16.

17. Egeberg A, Gislason GH, Hansen PR. Risk of major adverse cardiovascular events and all-cause mortality in patients with hidradenitis suppurativa. Jama dermatol. 2016;152(4):429-34.

18. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol. 2015;29(4):619-44.

19. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. N Engl J Med. 2016;375(5):422-34.

20. Prens E, Deckers I. Pathophysiology of hidradenitis suppurativa: an update. J Am Acad Dermatol. 2015;73(5 Suppl 1):S8-11.

21. Hotz C, Boniotto M, Guguin A, et al. Intrinsic defect in keratinocyte function leads to inflammation in hidradenitis suppurativa. J Invest Dermatol. 2016;136(9):1768-80.

22. van der Zee HH, de Ruiter L, van den Broecke DG, et al. Elevated levels of tumour necrosis factor (TNF)-alpha, interleukin (IL)-1beta and IL-10 in hidradenitis suppurativa skin: a rationale for targeting TNF-alpha and IL-1beta. Br J Dermatol. 2011;164(6):1292-8.

23. Kelly G, Hughes R, McGarry T, et al. Dysregulated cytokine expression in lesional and nonlesional skin in hidradenitis suppurativa. Br J Dermatol. 2015;173(6):1431-9.

24. Shah A, Alhusayen R, Amini-Nik S. The critical role of macrophages in the pathogenesis of hidradenitis suppurativa. Inflamm Res. 2017;66(11):931-45.

25. Schlapbach C, Hanni T, Yawalkar N, et al. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol. 2011;65(4):790-8.

26. Blok JL, Li K, Brodmerkel C, et al. Ustekinumab in hidradenitis suppurativa: clinical results and a search for potential biomarkers in serum. Br J Dermatol. 2016;174(4):839-46.

27. Prussick L, Rothstein B, Joshipura D, et al. Secukinumab for patients with moderate-to-severe hidradenitis suppurativa. Abstract #610. In: Program and abstracts from IID 2018, International Investigative Dermatology Meeting; Orlando, FL:May 16-19, 2018.

28. Khader SA, Pearl JE, Sakamoto K, et al. IL-23 compensates for the absence of IL-12p70 and is essential for the IL-17 response during tuberculosis but is dispensable for protection and antigen-specific IFN-gamma responses if IL-12p70 is available. J Immunol. 2005;175(2):788-95.

29. O'Garra A, Redford PS, McNab FW, et al. The immune response in tuberculosis. Annu Rev Immunol. 2013;31:475-527.

30. Qian X, Gu L, Ning H, et al. Increased Th17 cells in the tumor microenvironment is mediated by IL-23 via tumor-secreted prostaglandin E2. J Immunol. 2013;190(11):5894-902.

31. Baird AM, Leonard J, Naicker KM, et al. IL-23 is pro-proliferative, epigenetically regulated and modulated by chemotherapy in non-small cell lung cancer. Lung Cancer. 2013;79(1):83-90.

32. Hu WH, Chen HH, Yen SL, et al. Increased expression of interleukin-23 associated with progression of colorectal cancer. J Surg Oncol. 2017;115(2):208-12.

33. AbbVie. Data on File, RRT165055.

34. US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 27 November 2017 [Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAC	Anaphylaxis Adjudication Committee
Ab	antibody
ADA	antidrug antibody
AE	adverse event
Ag	antigen
ALT	alanine transaminase
AN	abscess and inflammatory nodule
ANC	absolute neutrophil count
ASI	areas of special interest
AST	aspartate transaminase
BCG	Bacilli Calmette-Guérin
CAC	Cardiovascular Adjudication Committee
CMH	Cochran-Mantel-Haenszel
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
COVID-19	Coronavirus Disease – 2019
CV	cardiovascular
DLQI	Dermatology Life Quality Index
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
EU	European Union
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HB	hepatitis B
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HiSCR	Hidradenitis Suppurativa Clinical Response

HIV	human immunodeficiency virus
HIV Ab	HIV antibody
HS	hidradenitis suppurativa
hsCRP	high-sensitivity C-reactive protein
HSIA	Hidradenitis Suppurativa Impact Assessment
HSSA	Hidradenitis Suppurativa Symptom Assessment
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IGRA	interferon gamma release assay
IL	interleukin
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
IUD	intrauterine device
IUS	Intrauterine hormone-releasing system
mAb	monoclonal antibody
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MTX	methotrexate
NAb	neutralizing antibody
NCI	National Cancer Institute
NMSC	non-melanoma skin cancer
NRI	non-responder imputation
NRS	numerical rating scale
NRS30	at least 30% reduction and at least 1 unit reduction from Baseline in Patient's Global Assessment of Skin Pain
NSAID	nonsteroidal anti-inflammatory drug
PCR	polymerase chain reaction

PFS	pre-filled syringe
PGA	Patient's Global Assessment of Skin Pain
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PPD	purified protein derivative
PRN	as needed
PT	preferred term
PRO	patient-reported outcome
PUVA	psoralen and ultraviolet A
q8w	every 8 weeks
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SOC	system organ class
STEEP	skin-tissue-saving excision with electrosurgical peeling
SUSAR	suspected unexpected serious adverse reaction
TA MD	Therapeutic Area Medical Director
TB	tuberculosis
TEAE	treatment-emergent adverse event
Th17	T helper 17
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
UVA	ultraviolet A
UVB	ultraviolet B
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-833 - Hidradenitis Suppurativa: Risankizumab versus Placebo for Adult Subjects with Moderate to Severe Hidradenitis Suppurativa

Protocol Date: 15 December 2020

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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]		Pharmaceutical Development
		Pharmaceutical Development
		Pharmacovigilance and Patient Safety
		Clinical Program Development
		Data and Statistical Sciences
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology & Pharmacometrics
		Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the Screening, 6 Period A, 10 Period B, and Study Follow-up subject encounters. The individual activities and allowed modifications due to COVID-19 are described in detail in the **Operations Manual**.

Activity	Screening	Period A						Period B									Follow Up Call
		Baseline/Week 0	*Week 1*	*Week 2*	*Week 4*	Week 8	*Week 12*	*Week 16*	*Week 17 & 18*	*Week 20*	*Week 28*	*Week 36*	*Week 44*	*Week 52*	*Week 60*	Week 68/Premature Discontinuation	
	Day –35 to Day –1	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	Days 120 & 127	Day 141	Day 197	Day 253	Day 309	Day 365	Day 421	Day 477	20 Weeks after Last Dose
Visit window			+/– 3 days								+/– 7 days						
INTERVIEWS & QUESTIONNAIRES																	
Subject information and informed consent	✓																
Eligibility criteria	✓	✓															
Medical history	✓	✓															
HS history	✓	✓															
Demographics	✓																
Drug, tobacco (including e-cigarettes), and alcohol history	✓																
AE assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy (including prior use of biologics)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TB screening	✓													✓			
Patient Reported Outcomes (PGA Skin Pain and Analgesic Use)	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓			✓		✓	
Patient Reported Outcome (HSSA)	✓	✓		✓	✓	✓	✓	✓			✓			✓		✓	
Patient Reported Outcome (HSIA)		✓				✓		✓			✓			✓		✓	

Activity	Screening	Period A						Period B									Follow Up Call
		Baseline/Week 0	*Week 1*	*Week 2*	*Week 4*	Week 8	*Week 12*	*Week 16*	*Week 17 & 18*	*Week 20*	*Week 28*	*Week 36*	*Week 44*	*Week 52*	*Week 60*	Week 68/Premature Discontinuation	
	Day –35 to Day –1	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	Days 120 & 127	Day 141	Day 197	Day 253	Day 309	Day 365	Day 421	Day 477	20 Weeks after Last Dose
Visit window			+/– 3 days								+/– 7 days						
Patient Reported Outcomes (DLQI, EQ-5D-5L, WPAI, HADS)		✓						✓						✓		✓	
Patient Reported Outcome (PGIS)		✓				✓		✓			✓			✓			
Patient Reported Outcome (PGIC)			✓	✓	✓	✓	✓	✓			✓			✓			
Dispense handheld ePRO device	✓																
Collect handheld ePRO device																✓	
LOCAL LABS & EXAMS																	
Inflammatory lesion count (abscess, inflammatory nodule, and draining fistula count)	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	
Hurley Stage	✓	✓						✓						✓		✓	
12-lead ECG	✓																
Height	✓																
Weight and waist circumference	✓															✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination	✓	✓														✓	

Activity	Screening	Period A						Period B									Follow Up Call
		Baseline/Week 0	*Week 1*	*Week 2*	*Week 4*	Week 8	*Week 12*	*Week 16*	*Week 17 & 18*	*Week 20*	*Week 28*	*Week 36*	*Week 44*	*Week 52*	*Week 60*	Week 68/Premature Discontinuation	
	Day –35 to Day –1	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	Days 120 & 127	Day 141	Day 197	Day 253	Day 309	Day 365	Day 421	Day 477	20 Weeks after Last Dose
Visit window			+/– 3 days								+/– 7 days						
Urine pregnancy test (Females of childbearing potential)		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
CENTRAL LABS																	
FSH (if applicable, per operations manual)	✓																
Serum pregnancy test (Females of childbearing potential)	✓																
TB test (QuantiFERON-TB Gold test [or IGRA equivalent] and/or local purified protein derivative [PPD] skin test)	✓													✓			
HIV, HBV, and HCV screening	✓																
Hematology, clinical chemistry (including hsCRP), and urinalysis	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	
Total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, and glucose (Baseline only)		✓														✓	
Blood samples for ADA assay and NAb assay		✓			✓			✓								✓	
Blood samples for PK assay					✓		✓	✓								✓	

Activity	Screening	Period A						Period B									Follow Up Call
		Baseline/Week 0	*Week 1*	*Week 2*	*Week 4*	Week 8	*Week 12*	*Week 16*	*Week 17 & 18*	*Week 20*	*Week 28*	*Week 36*	*Week 44*	*Week 52*	*Week 60*	Week 68/Premature Discontinuation	
	Day –35 to Day –1	Day 1	Day 8	Day 15	Day 29	Day 57	Day 85	Day 113	Days 120 & 127	Day 141	Day 197	Day 253	Day 309	Day 365	Day 421	Day 477	20 Weeks after Last Dose
Visit window			+/– 3 days								+/– 7 days						
Optional biomarker samples: Whole blood (plasma/serum/PG-RNA)		✓			✓			✓				✓		✓		✓	
Optional biomarker sample: Whole blood (PG-DNA)		✓															
℞ TREATMENT																	
Randomization/drug assignment		✓															
Administer study drug to subjects		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		
In-clinic post-dose monitoring		✓	✓	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		

NOTE: Column headers in *underlined italic* font style denote dosing visits.

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	04 March 2019
Version 1.1 (VHP countries only)	28 June 2019
Version 2.0	19 August 2019
Version 3.0	26 March 2020
Version 4.0	09 June 2020

The purpose of Protocol Version 5.0 is to update the following sections below and incorporate necessary protocol modifications due to the COVID-19 pandemic and per revised Risankizumab Safety Standards (v7.0) 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.*

- Modify the following sections to account for state-emergency or pandemic situations:
  - Update Section 5.5 to permit mitigation strategies for withdrawal/interruption/discontinuation of study drug.
  - Update Section 5.9 to define protocol deviations to include those due to the COVID-19 pandemic.
  - Updated Section 7.3 to clarify that in the efficacy analysis, Non-Responder Imputation incorporating multiple imputation will be utilized to handle missing data due to COVID-19.
  - 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.*

- 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 details in Section 2.1 specifying virtual visits that may be performed and modifications for laboratory and central testing.
  - Update Section 3.1 to clarify subject information and informed consent in case of state-of emergency or pandemic situations.
  - Update Section 3.4 to clarify patient reported outcomes (PROs) that 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 3.13 with instructions on performing laboratory work in the case of a state-of emergency or pandemic situation.
  - Update Section 4.3 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

- In the Synopsis and Section 2.1, replaced the term/abbreviation "inflammatory nodule (AN)" with "abscess and inflammatory nodule (AN)."

  Rationale: *To align with the full term/abbreviation defined in Appendix A.*

- In the Section 2.2, updated that subjects with active systemic infection or clinically important infection will not be included in the study.

  Rationale: *To update benefit-risk text according to revised risankizumab safety standard language.*

- In the Section 2.2, removed text stating that there are no cases of active TB, including no reactivation of TB in subjects diagnosed with latent TB, across the entire risankizumab development program to date.

  Rationale: *To update benefit-risk text according to revised risankizumab safety standard language.*

- In the Section 2.2, updated that subjects with positive QuantiFERON-TB testing/TB skin test who have latent TB and are considered at low risk for reactivation are not required to be treated with TB prophylaxis.

  Rationale: *To update benefit-risk text according to revised risankizumab safety standard language.*

- Clarified in Section 3.3 that the additional endpoint with respect to the proportion of subjects achieving at least 1 grade improvement from Baseline in PGIS scale is among subjects with Baseline PGIS of at least "minimal."

Rationale: *To clarify this additional endpoint is only applicable among subjects with Baseline PGIS of at least "minimal" (i.e., who have room for "at least 1 grade improvement").*

- In Section 5.3, removed text for new topical therapies and clarified the use of non-antibiotic topical therapies or changes in the concentration/frequency of such treatments for the treatment of HS.

  Rationale: *To clarify the restriction regarding non-antibiotic topical therapies and changes the in the concentration/frequency of topical therapies.*

- In Section 5.3, added in addition to systemic antibiotic use, "and/or topical" antibiotic use is only allowed for the treatment of acute, non-HS related infections.

  Rationale: *To clarify the restriction of both systemic and/or topical antibiotic use is only allowed for the treatment of acute, non-HS related infections.*

- In Section 5.3, added Dengue (Dengvaxia®) to the list of examples of live attenuated vaccines that are not permitted during study participation and including up to 140 days after the last dose of study drug.

  Rationale: *To clarify the restriction of live attenuated vaccines as prohibited concomitant medications and therapies according to revised risankizumab safety standard language.*

- In Section 5.5, added hepatic test abnormalities confirmed by a second sample should be at least 48 hours apart.

  Rationale: *To clarify the minimum timing between samples for hepatic test abnormalities that would constitute withdrawal of subject from study drug and/or study according to revised risankizumab safety standard language.*

- In Section 6.1 for product complaints and pregnancies, replaced the reporting period from '1 business day' or '1 working day' (respectively) to '24 hours.'

  Rationale: *To update the safety reporting period according to revised risankizumab safety standard language.*

- In Section 6.1, update the text 'areas of safety interest' to 'areas of safety interest/safety topics of interest' and rename Table 2 'Areas of Safety Interest' to 'Supplemental Adverse Events eCRFs.'

  Rationale: *To update the safety reporting terms according to revised risankizumab safety standard language.*

- In Section 6.1, removed text that infections, especially opportunistic infections, are a potential risk with immunomodulators.

  Rationale: *To update the areas of safety interest text according to revised risankizumab safety standard language.*

- In Appendix C, updated protocol signatories and titles.

  Rationale: *To update due to personnel changes for this protocol amendment.*

- In Appendix D, removed "PGA Skin Pain and Analgesic Use" as an assessment performed at the Week 36 visit.

  Rationale: *To correct a typographical error.*

Operations Manual

- In Section 1 and Section 4.3, updated the safety team contact information.

  Rationale: *To correct per current safety contact information.*