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Protocol for Study M23-702

Genital or Scalp Psoriasis: Risankizumab for Adult Subjects with Moderate to Severe Genital or Moderate to Severe Scalp Psoriasis

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FULL TITLE: A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis

Incorporating Versions 1.0 and 2.0

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

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1 SYNOPSIS

Title: A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis	
Background and Rationale:	Risankizumab is a humanized mAb of the immunoglobin (Ig) G1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement-binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23. Risankizumab is currently approved for marketing in the United States (US), the European Union (EU), Japan, and other countries for the treatment of moderate to severe plaque psoriasis, active psoriatic arthritis, and moderately to severely active Crohn's disease. Risankizumab is also being developed for the treatment of ulcerative colitis. This study is designed to evaluate the treatment effect of risankizumab in moderate to severe genital psoriasis and moderate to severe scalp psoriasis.
Objective(s) and Endpoint(s):	The primary objective of the study is to evaluate the efficacy and safety of risankizumab for the treatment of moderate to severe genital psoriasis (Study-G) or moderate to severe scalp psoriasis (Study-S) in adults who are candidates for systemic therapy. The primary endpoints are: • Study-G: Achievement of static Physician Global Assessment of Genitalia (sPGA-G) of 0 or 1 at Week 16 • Study-S: Achievement of scalp Investigator Global Assessment (IGA) of 0 or 1 at Week 16 Ranked secondary endpoints are: Study-G 1. Achievement of sPGA-G of 0 at Week 16 2. Achievement of Dermatology Life Quality Index (DLQI) of 0 or 1 at Week 16 3. Achievement of clinically meaningful (≥ 4-point) improvement from baseline on the Genital Psoriasis Itch Numerical rating scale (NRS) at Week 16 among subjects with baseline scores ≥ 4 4. Achievement of Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ) item 2 score of 0 or 1 at Week 16 among subjects with baseline scores ≥ 2 Study-S 1. Achievement of ≥ 90% improvement from baseline in Psoriasis Scalp Severity Index (PSSI) 90 at Week 16 2. Achievement of PSSI 75 (≥ 75% improvement from baseline in PSSI) response at Week 16 3. Change from baseline in Psoriasis Symptom Scale (PSS) at Week 16

	4. Achievement of PSSI 100 (100% improvement from baseline in PSSI) response at Week 16 5. Achievement of PSS of 0 at Week 16
Investigator(s):	Multicenter.
Study Site(s):	45 sites in France, Germany, Italy, Poland, Spain, and United States
Study Population and Number of Subjects to be Enrolled:	The study is designed to randomize approximately 200 adult subjects (100 in Study-G and 100 in Study-S). Subjects must have a current diagnosis of moderate to severe genital psoriasis (Study-G) defined as sPGA-G ≥ 3 or moderate to severe scalp psoriasis (Study-S) defined as PSSI ≥ 12, scalp IGA ≥ 3, and ≥ 30% of the scalp affected.
Investigational Plan:	This is a Phase 4, international, multicenter, randomized, double-blind, placebo-controlled study in subjects with moderate to severe genital psoriasis (Study-G) or moderate to severe scalp psoriasis (Study-S). Each study comprises a 30-day Screening Period, a 16-week double-blind placebo-controlled treatment period (Period A), a 36-week open-label treatment period (Period B), and an 8-week Follow-up Period with a follow-up phone call 20 weeks after last dose of study drug. Eligible subjects within each study will be randomized to receive risankizumab or placebo in a 1:1 ratio. Participants will receive double-blind risankizumab (for those randomized to risankizumab) or matching placebo (for those randomized to placebo) during Period A; all subjects will receive open-label risankizumab during Period B. The primary analysis will be performed after all ongoing subjects have completed Week 16 of Study-G and Study-S and all data pertaining to Period A are cleaned. This will be the only and final analysis for efficacy in Period A for each study, respectively. The final analysis will be conducted upon study completion.
Key Eligibility Criteria:	Subjects must be at least 18 years old (and also meet the legal age of majority per local law) with a clinical diagnosis of chronic plaque psoriasis with or without psoriatic arthritis for at least 6 months before the Baseline Visit. Subjects must have a current diagnosis of moderate to severe genital psoriasis (Study-G) defined as sPGA-G ≥ 3 or moderate to severe scalp psoriasis (Study-S) defined as PSSI ≥ 12, scalp IGA ≥ 3, and ≥ 30% of the scalp affected. Subjects must have body surface area (BSA) ≥ 1% with at least 60% of subjects having BSA ≥ 10%; sPGA ≥ 3; inadequate control of psoriasis and/or intolerance to topical treatment, phototherapy and/or systemic therapy; and be candidates for systemic therapy or phototherapy as assessed by the investigator.

Study Drug and Duration of Treatment:	Study drug will be provided as a solution for injection SC: risankizumab 150 mg/1 mL in pre-filled syringe and matching placebo. Participants will receive a single injection SC of risankizumab (150 mg total dose for those randomized to risankizumab) or matching placebo (for those randomized to placebo), at Baseline/Day 1 and Week 4. Subjects will receive 1 injection SC of risankizumab (150 mg total dosage) at Weeks 16, 28, and 40.
Date of Protocol Synopsis:	07 June 2023

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Psoriasis is a chronic debilitating immune-mediated disease characterized by marked inflammation of the skin that results in thick, erythematous, scaly plaques involving the skin. In most developed countries, prevalence is between 1.5 and 5%.[1] Twenty-five percent of patients have moderate to severe disease with a considerable negative impact on psychosocial and economic status.[2] Psoriasis is more than a superficial disease, with up to 30% of patients having joint involvement and a high correlation between psoriasis and obesity, diabetes, depression, metabolic syndrome, and cardiovascular disease.[3] Topical therapies are used for limited disease or as an adjunct to systemic therapy or phototherapy for moderate to severe psoriasis.[4] For more widespread disease, phototherapy is a consideration. Systemic therapies, including methotrexate, cyclosporine[5], synthetic retinoids[6], apremilast[7], and fumaric acid esters can also be used in patients with moderate or severe disease, though known side effect profiles may limit their use.[8,9]

Biologics have emerged as a preferred alternative treatment option for patients with psoriasis and are now routinely used when traditional systemic agents fail, are not tolerated, or are contraindicated due to comorbid conditions.[4] These biologic agents include TNF-alpha inhibitors (etanercept[10,11], infliximab[12,13], certolizumab pegol[14,15], and adalimumab[16,17]), the IL-12/23 inhibitor (ustekinumab[18,19]), IL-17A inhibitors (secukinumab[20,21], brodalumab[22,23], and ixekizumab[24,25]), and IL-23p19 inhibitors (guselkumab[26,27], tildrakizumab[28,29], and risankizumab[30,31]).

IL-23 plays a critical role in the differentiation and function of Th17 cells, which are an important T-cell subpopulation involved in the pathogenesis of immune mediated disorders.[32]

There is still clinical need for increased efficacy as the most effective anti-TNF and anti-IL-12/23 agents provide approximately 75% improvement in psoriasis in about 50 to 80% of patients and these responses can be lost over time. While the anti-IL-17A, -IL-17RA, and -IL-23p19 agents (i.e., secukinumab, ixekizumab, brodalumab and guselkumab) may provide better efficacy than anti-TNF therapies and ustekinumab, they require monthly or every other month injections.[33-36] Studies show patients prefer less frequent dosing intervals for biologics in psoriasis management.[37]

Psoriasis often manifests in areas that are difficult to treat, such as the genitals (14% – 43%) and scalp (43% – 65%).[38-43] Scalp psoriasis is characterized by demarcated erythematosquamous chronic plaques that often advance beyond the hairline into the face and retroauricolar region. Due to its visibility, scaling of the scalp negatively impacts quality of life, often causing embarrassment and psychosocial handicap. Topical treatments are less effective on the scalp than other body areas because the scalp is relatively inaccessible and hair making adherence and the use of ointments and cream-based products challenging, often leading to poor compliance.[44]

Genital psoriasis frequently remains undiagnosed in patients due to insufficient evaluation of genital involvement and a reluctance of patients and healthcare providers to discuss genital psoriasis.[45] Psoriasis affecting genital areas may be associated with considerable morbidity, discomfort and embarrassment and may significantly impair the quality of life and psychosexual wellbeing of

patients.[46] Many standard topical or ultraviolet-based treatments for psoriasis are either contraindicated or not well tolerated on sensitive genital skin, limiting treatment options. Systemic therapies are indicated by current treatment guidelines for areas that are difficult to treat such as genital psoriasis or scalp psoriasis, even in patients with lower BSA involvement.[47]

Risankizumab is currently approved for marketing in the US, the EU, Japan, and other countries for the treatment of moderate to severe plaque psoriasis, active psoriatic arthritis, and moderately to severely active Crohn's disease. Risankizumab is also being developed for the treatment of ulcerative colitis.

Risankizumab is a humanized mAb of the Ig G1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. Risankizumab binds with high affinity to human IL-23.

The risankizumab clinical program assessed the efficacy and safety versus placebo and other commonly used biological therapies such as adalimumab, ustekinumab, and secukinumab up to 1 year. Risankizumab showed high levels of sustained clearance in these clinical trials and demonstrated superior efficacy relative to comparators at the assessed primary endpoints.

2.2 Benefits and Risks to Subjects

Risankizumab is a humanized Ig G1 mAb directed against the p19 subunit of the human cytokine IL-23. IL-23 is implicated in the pathophysiology of immune-mediated inflammatory diseases.

The Phase 3 pivotal program with risankizumab demonstrated efficacy for improvement in signs and symptoms of plaque psoriasis and the safety results were consistent with those known to be associated with mechanism of action or other appropriate safety findings. Taken together, the safety and efficacy data from the Phase 3 program support further development of risankizumab in subjects with psoriasis.

This study is designed to evaluate the treatment effect of risankizumab in moderate to severe genital psoriasis and moderate to severe scalp psoriasis.

As with any immune modulating agent, risankizumab may impair immune function resulting in a risk of infection. This will be monitored by collection of all AEs during the treatment and observation periods. In addition, subjects with clinically important active infection will not be included in the study. The safety profile in the global pivotal trials was consistent with that observed in Phase 2 clinical trials, with no important identified risks for risankizumab through 4.5 years of continuous risankizumab treatment in an ongoing open-label extension study.

Subjects with a positive QuantiFERON®-TB (or IGRA equivalent)/TB skin test result 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.[48,49] Subjects with positive QuantiFERON-TB testing (or IGRA equivalent)/TB skin test who have latent TB (defined by local guidelines) should be treated as per local guidelines or by investigator judgement with TB prophylaxis prior to receiving risankizumab and 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.[50-52] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models.[53]

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 is designed to enable timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety.

Increases in MACE, including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents such as ustekinumab have not been observed in longer-term studies with risankizumab. While the likelihood of increased MACE is small, all suspected cardiovascular or cerebrovascular events (serious or nonserious) observed in this study will be adjudicated by an independent CAC. The committee will remain blinded to treatment allocation (Section 6.2).

Local reactions to subcutaneously administered biologic therapies are usually limited to redness, swelling, or induration at the injection site. Manifestations of systemic hypersensitivity reactions may include anaphylaxis, generalized urticaria, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are typically readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored during study drug administration. An independent AAC will adjudicate observed systemic hypersensitivity and anaphylactic events. The AAC will remain blinded to treatment allocation (Section 6.3).

There are no important identified risks for risankizumab.[54]

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development.[55] 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 risankizumab Investigator Brochure.[54]

In view of the 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 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

The primary objective of the study is to evaluate the efficacy and safety of risankizumab for the treatment of moderate to severe genital psoriasis (Study-G) or moderate to severe scalp psoriasis (Study-S) in adults who are candidates for systemic therapy.

Hypotheses and Estimand for the Primary Objective

The primary endpoints are achievement of static sPGA-G of 0 or 1 at Week 16 for subjects in Study-G, and achievement of scalp IGA of 0 or 1 at Week 16 for subjects in Study-S.

The hypotheses corresponding to the primary efficacy objective are:

- The proportion of subjects achieving sPGA-G of 0 or 1 at Week 16 in subjects treated with risankizumab is greater than those treated with placebo in Study-G.
- The proportion of subjects achieving scalp IGA of 0 or 1 at Week 16 in subjects treated with risankizumab is greater than those treated with placebo in Study-S.

The estimand corresponding to the primary endpoints in Study-G and Study-S are defined as follows:

- Study-G: Difference in the proportion of subjects achieving sPGA-G of 0 or 1 at Week 16, regardless of premature discontinuation of study drug, in the risankizumab group compared with the placebo group among adult subjects with moderate to severe genital psoriasis who are candidates for systemic therapy.
- Study-S: Difference in the proportion of subjects achieving scalp IGA of 0 or 1 at Week 16, regardless of premature discontinuation of study drug, in the risankizumab group in compared with the placebo group among adult subjects with moderate to severe scalp psoriasis who are candidates for systemic therapy.

Intercurrent events handling: No intercurrent event is considered.

The ranked secondary endpoints are as defined in Section 3.3.

The estimands corresponding to these ranked secondary endpoints are:

- Binary endpoints: The estimand is defined as the difference in the proportion of subjects achieving each endpoint, regardless of premature discontinuation of study drug, in the risankizumab group versus the placebo group in subjects with moderate to severe genital psoriasis in Study-G or in subjects with moderate to severe scalp psoriasis in Study-S.
- Continuous endpoint (change from Baseline in PSS for Study-S): The estimand is defined as the difference in mean change from Baseline in PSS at Week 16, regardless of premature discontinuation of study drug, in the risankizumab group versus the placebo group in subjects with moderate to severe scalp psoriasis in Study-S.

Intercurrent events handling: No intercurrent event is considered.

3.2 Primary Endpoints

The primary endpoints are:

- Study-G: Achievement of sPGA-G of 0 or 1 at Week 16
- Study-S: Achievement of scalp IGA of 0 or 1 at Week 16

3.3 Secondary Endpoint

Ranked Secondary Endpoints

Study-G

1. Achievement of sPGA-G of 0 at Week 16
2. Achievement of DLQI of 0 or 1 at Week 16
3. Achievement of clinically meaningful (≥ 4-point) improvement from baseline on the Genital Psoriasis Itch NRS at Week 16 among subjects with a baseline score ≥ 4
4. Achievement of GenPs-SFQ item 2 score of 0 or 1 at Week 16 among subjects with a baseline score ≥ 2

Study-S

1. Achievement of ≥ 90% improvement from baseline in PSSI 90 at Week 16
2. Achievement of PSSI 75 (≥ 75% improvement from baseline in PSSI) response at Week 16
3. Change from baseline in PSS at Week 16
4. Achievement of PSSI 100 (100% improvement from baseline in PSSI) response at Week 16
5. Achievement of PSS of 0 at Week 16

3.4 Additional Efficacy Endpoints

All variables listed above as primary or secondary endpoints will be evaluated at all scheduled visits for the respective study.

The following endpoints will also be evaluated at all scheduled visits during which the assessments are measured as noted in the Study Activities Table (Appendix D), unless otherwise noted.

Study-G

- Achievement of sPGA of 0 or 1
- Achievement of sPGA of 0
- Change from Baseline in the GPSS (itch, pain, discomfort, stinging, burning, redness, scaling, cracking and total) scores
- Achievement of at least 2-point reduction on PatGA-Genital among subjects with a baseline score ≥ 2
- Change from Baseline in DLQI
- Change from Baseline in HADS D-Score
- Change from Baseline in HADS A-Score

Study-S

- Achievement of sPGA of 0 or 1
- Achievement of sPGA of 0
- Achievement of scalp IGA of 0
- Achievement of ≥ 4-point improvement (reduction) from baseline on the Scalp Itch NRS among subjects with baseline scores ≥ 4
- Achievement of DLQI of 0 or 1
- Achievement of PSS of 0 or 1
- Change from Baseline in HADS D-Score
- Change from Baseline in HADS A-Score
- Change from Baseline on the Scalp Itch NRS
- Change from Baseline in PSSI

3.5 Safety Endpoints

Safety evaluations include AEs, vital signs, physical examinations, ECGs, and clinical laboratory assessments (hematology, chemistry, and urinalysis) as measures of safety and tolerability throughout the study as specified in the study activities table (Appendix D).

3.6 Pharmacokinetic Endpoints

The PK and immunogenicity of risankizumab have been well characterized in subjects with plaque psoriasis. No samples will be collected for the purpose of PK and immunogenicity in this study, except in cases of systemic hypersensitivity reactions.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 4, international, multicenter, randomized, double-blind, placebo-controlled study examining the effect of risankizumab in subjects with moderate to severe genital psoriasis (Study G) or moderate to severe scalp psoriasis (Study-S).

This study is designed to randomize approximately 200 subjects, with approximately 100 subjects in Study-G (50 subjects/arm) and 100 subjects in Study-S (50 subjects/arm).

Eligible subjects within each study will be randomized to receive risankizumab or placebo in a 1:1 ratio. Subjects who meet the criteria for both Study-G and Study-S will first be randomized to either Study G or Study-S with equal probability and then will be randomized to receive either risankizumab or placebo in a 1:1 ratio.

Participants will receive 150 mg of risankizumab (for those randomized to risankizumab) or matching placebo (for those randomized to placebo) subcutaneously at Weeks 0 and 4. Starting at Week 16, all subjects will receive 150 mg of risankizumab every 12 weeks until the last dose at Week 40.

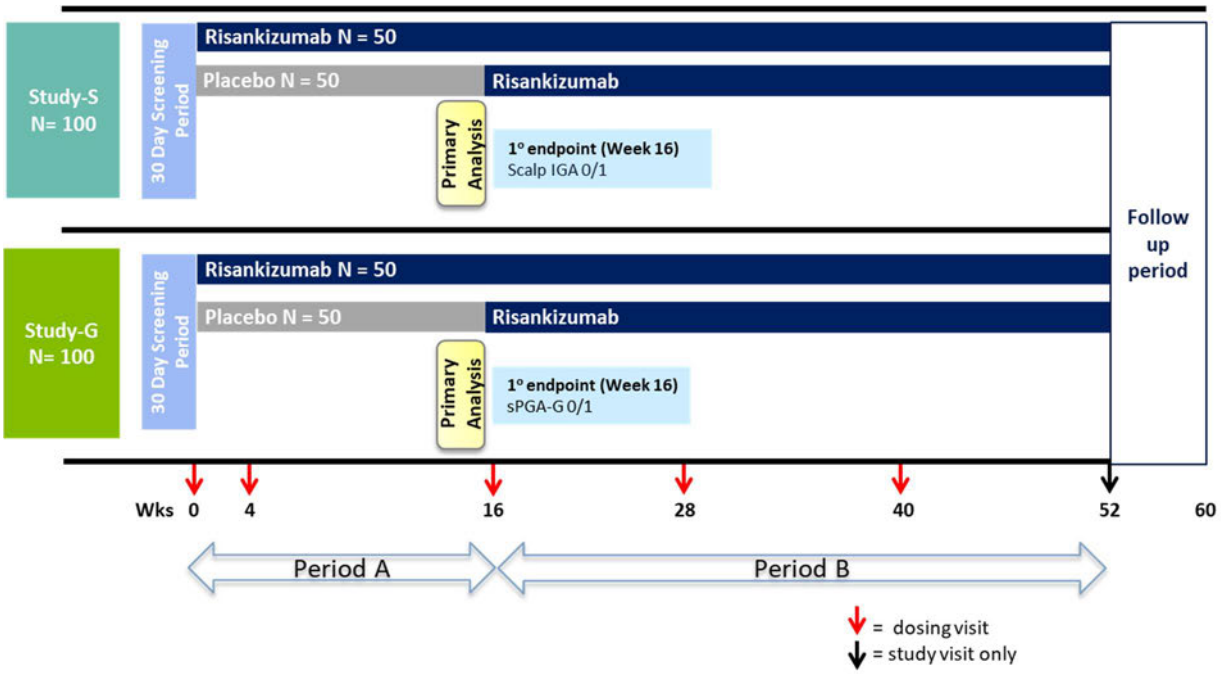
The duration of the studies will be approximately 64 weeks. Each study comprises a 30-day Screening Period, a 16-week double-blind placebo-controlled treatment period (Period A), a 36-week open-label treatment period (Period B), and an 8-week Follow-up Period. The follow-up phone call (20 weeks following the last dose of study drug) during the trial will not be required for any subject who initiates commercial risankizumab or continues under another AbbVie protocol for the purposes of continued treatment (i.e., CTE or CTTP OLE).

The primary analysis will be performed when all ongoing subjects complete Week 16 of Study-G and Study-S and all data pertaining to Period A are cleaned. The Week 16 analysis is the only and final analysis for the primary endpoints and ranked secondary endpoints at Week 16.

An independent CAC will adjudicate all cardio- and cerebro-vascular events as described in Section 6.2. An independent AAC will adjudicate events of anaphylaxis as described in Section 6.3.
The schematic of the study is shown in Figure 1 and study activities are listed in Appendix D. Further details regarding study procedures are located in the Operations Manual (Appendix G).

Subjects will be stratified by weight (≤ 100 kg vs. >100 kg) and number of prior biologic therapies for psoriasis (0 vs. ≥ 1) within each study. See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schema



4.2 Discussion of Study Design

Choice of Control Group

Placebo control will be used in this study to address potential confounding factors, such as placebo effect, potential investigator bias in safety and efficacy assessment, or regression to the mean in endpoint scoring.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with moderate to severe genital or scalp psoriasis. All clinical and laboratory procedures in this study are standard and generally accepted. All PRO measures in this study were adequately developed and validated to measure specific concepts of interest relevant to this study.

Suitability of Subject Population

Subjects must have moderate to severe genital psoriasis (sPGA-G ≥ 3) or moderate to severe scalp psoriasis (PSSI ≥ 12, scalp IGA ≥ 3, and ≥ 30% of the scalp affected) and must be eligible for systemic therapy or phototherapy. To qualify for the study, subjects must have ≥ 1% BSA psoriasis involvement and at least 60% of each study population must have ≥ 10% BSA psoriasis involvement at Screening and the Baseline Visit; and sPGA score of ≥ 3 at Screening and the Baseline Visit.

Selection of Doses in the Study

The selected risankizumab dosage for the current study is consistent with the dosing and the dosing schedule as per the approved risankizumab psoriasis dosing regimen for the treatment of moderate to severe plaque psoriasis.

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 IEC/IRB, prior to the initiation of any screening or study-specific procedures, and are eligible to participate per applicable local regulations.
- 2. Employees of the sponsor and/or study sites and their family members may not be enrolled in this study.
- 3. Subjects are willing and able to comply with procedures required in this protocol.

Demographic and Laboratory Assessments

- 4. Adult **individuals**, at least 18 years old (subjects must also meet the legal age of majority per local law).
- 5. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum AST ≤ 2 × ULN;
  - Serum ALT ≤ 2 × ULN;
  - Serum total bilirubin ≤ 2 × ULN, except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
  - Total WBC count > 3,000/µL;
  - ANC > 1,500/µL;
  - Platelet count > 100,000/µL;
  - Hemoglobin > 10 g/dL (100 g/L).

Disease/Condition Activity

- 6. Subject has **moderate to severe genital psoriasis** (Study-G) defined as sPGA-G ≥ 3 or **moderate to severe scalp psoriasis** (Study-S) defined as PSSI ≥ 12, scalp IGA ≥ 3, and ≥ 30% of the scalp affected at Screening and Baseline.
- 7. Subject has BSA ≥ 1% at Screening and Baseline. At least 60% of subjects within Study-G and within Study-S will each comprise subjects with Baseline BSA ≥ 10%.
- 8. Subject has an **overall sPGA** ≥ 3 ("moderate" or "severe") at Screening and Baseline.
- 9. Subject has inadequate control and/or intolerance to topical treatment, phototherapy and/or systemic therapy for the treatment of psoriasis affecting the genitalia (Study G) or scalp (Study-S).
- 10. Subject must be a candidate for systemic therapy or phototherapy as assessed by the investigator.
- 11. Subject has a clinical diagnosis of chronic plaque psoriasis with or without psoriatic arthritis for at least **6 months** before the Baseline Visit.
- 12. Subject has **stable** moderate to severe chronic plaque psoriasis with or without psoriatic arthritis.

Subject History

- 13. Subject is judged to be **in good general health**, as determined by the investigator based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead ECG performed during the Screening Period.
- 14. Subject must not have a history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.

- 15. Subject must not have a history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 16. Subject must not have had **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).
- 17. In subjects who tested positive for COVID-19, at least 5 days have passed since a COVID-19 positive test result in asymptomatic subjects. Subjects with mild/ moderate COVID-19 infection can be enrolled if resolution of fever without use of antipyretics for 24 hours and improvement in other symptoms or 5 days since the COVID-19 positive test result (whichever comes last). The subject may be rescreened if judged to be in good general health, as determined by the investigator based upon the medical history and physical.
- 18. Subject must not have evidence of:
  - **HBV or HCV infection**, defined as:
    - HBV: HBs Ag positive (+) test or detected sensitivity on the HBV DNA PCR qualitative test for subjects who are HBc Ab positive (+) (and for HBs Ab positive [+] subjects where mandated by local requirements).
    - HCV: HCV RNA detectable in any subject with HCV Ab.
  - **HIV**, defined as confirmed positive anti-HIV Ab test. Note: In case a screened subject has a confirmed positive HIV Ab test, Eligibility Criterion 13 should be selected in eCRF for documentation of screening failure.
  - **Active TB**. For subjects with latent TB, please see Section 3.12 of the Operations Manual.
  - **Active systemic infection/Clinically important infection** during the last 2 weeks prior to Baseline Visit as assessed by the investigator.
- 19. Subject must not have any of the following medical diseases or disorders:
  - Recent (within past 6 months) cerebrovascular accident or myocardial infarction.
  - History of an **organ transplant** that requires continued immunosuppression.
  - **Active or suspected malignancy** or history of **any malignancy** within the last 5 years except for successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix.
  - **Non-plaque forms of psoriasis** (including guttate, erythrodermic, or pustular) or current drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium).
  - **Active skin disease,** other than psoriasis, that could interfere with the assessment of psoriasis.

Contraception

- 20. 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.

- 21. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 1 through at least 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). Female subjects of non-childbearing potential do not need to use birth control.
- 22. Female subjects may not be **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.

Concomitant Medications

- 23. Subject must not have had **previous exposure to IL-23 inhibitors** including but not limited to guselkumab, tildrakizumab, ustekinumab, mirikizumab, or risankizumab.
- 24. Subject must not have received **any live viral or bacterial vaccine** (with the exception of replication deficient viral vaccines, [e.g., JYNNEOS®, Imvamune®, or Imvanex®] for the prevention of monkeypox disease) within 4 weeks prior to the first dose of study drug 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.
- 25. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or be currently enrolled in another interventional clinical study.
- 26. Subjects must be able to safely discontinue any **prohibited medications (including biologics)** 30 days or 5 half-lives (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. Subjects who need to discontinue therapy in order to comply with this inclusion criterion must have discontinued the listed therapy for the amount of time noted in Table 1.

Table 1. Prohibited Medications/Treatments and Restriction Duration

Medication, Class of Medications, or Treatment	Restriction Duration (through Week 52)
Guselkumab, tildrakizumab, risankizumab, ustekinumab, mirikizumab, investigational IL-23 inhibitors, (or biosimilar versions)	Not allowed any time prior to study participation
Secukinumab	6 months prior to randomization
Brodalumab, ixekizumab, bimekizumab	4 months prior to randomization
Infliximab (or biosimilar versions)	12 weeks prior to randomization
Etanercept (or biosimilar versions)	6 weeks prior to randomization
Any investigational device or product Other systemic immunomodulating treatments, e.g., methotrexate, cyclosporin A, corticosteroids,[a] cyclophosphamide, tofacitinib, apremilast, deucravacitinib Other systemic psoriasis treatment (e.g., retinoids, fumarates, any other drug known to possibly benefit psoriasis) Photochemotherapy (e.g., PUVA)	30 days prior to randomization
Phototherapy (e.g., UVA, UVB) Topical treatment for psoriasis or any other skin condition (e.g., corticosteroids,[b] vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, anthralin, α-hydroxy acid)	14 days prior to randomization

a. No restriction on corticosteroids with only a noncutaneous topical effect (e.g., inhaled corticosteroids or drops used in the eye or ear).

b. Exception: bland emollients and shampoos and/or low potency topical corticosteroids (US Class 6-7) on the palms, soles, face, and inframammary area only.

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:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral salpingectomy, bilateral oophorectomy.

- Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.

2. Postmenopausal female
   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level ≥ 30 IU/L.

- 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, transdermal, injectable) associated with inhibition of ovulation-initiated at least 30 days prior to study Baseline Day 1.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device.
    - Intrauterine hormone-releasing system.
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

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

5.3 Prohibited Medications and Therapy

Subjects must have discontinued biologic therapies prior to the first dose of study drug as specified in the washout procedures (Eligibility Criterion 26, Protocol Section 5.1). The required washout period is at least 5 times the mean terminal elimination half-life of the medication or 4 weeks (whichever is longer) prior to the first dose of study drug.

Prohibited medications and therapy through Week 52/Premature Discontinuation visit include the following:

1. Any systemic biologic therapy (other than the study drug).
2. Systemic non-biologic therapy known to have benefit in psoriasis, including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, apremilast, deucravacitinib, and fumaric acid derivatives.
3. Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect psoriasis disease severity or interfere with disease assessments.
4. Topical psoriasis treatments, including but not limited to corticosteroids, anthralin, topical vitamin D derivatives, retinoids, urea, alpha- or beta-hydroxyl acids, and medicated shampoos (for example, those that contain > 3% salicylic acid, corticosteroids, coal tar or vitamin D analogues).
    - Exception: Subjects are allowed to use bland (containing no active ingredient) emollients and shampoos and/or low potency topical corticosteroids (US Class 6-7) on the palms, soles, face, and inframammary area only.
5. Treatment with an experimental therapy.
6. Live vaccines (except non-replicating live vaccines e.g., JYNNEOS, Imvamune, or Imvanex monkeypox vaccine) are NOT allowed during the study through the Week 60 follow-up call (20 weeks after the last dose of risankizumab), (or as guided by the local risankizumab label [if approved], whichever is longer).

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

    - Bacille Calmette-Guérin (BCG)
    - Zoster vaccine live (Zostavax®)
    - Measles mumps rubella (MMR) or measles mumps rubella varicella
    - Monovalent live attenuated influenza A (intranasal)
    - Oral polio vaccine
    - Rotavirus
    - Seasonal trivalent live attenuated influenza (intranasal)
    - Smallpox/monkey pox vaccine capable of replicating (ACAM2000®)
    - Oral typhoid vaccine
    - Varicella (chicken pox)
    - Yellow fever
    - Dengue (Dengvaxia®)

5.4 Prior and Concomitant Therapy

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 eCRF.

A detailed history of all prior biologic use will be obtained in the EDC.

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 Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications (including biologics) 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.

Non-live vaccines may be administered during screening or treatment period, if not contraindicated or medically inappropriate.

When possible, first dose of study drug should be given at least ± 7 days from non-live SARS-CoV-2 vaccine administration. The potential impact of risankizumab on SARS-CoV-2 vaccination is unknown. The decision to receive a locally available non-live vaccine should be based on local guidance and an individual discussion between the treating physician and the subject and/or guardian. These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with psoriasis and as more data are collected in real-world scenarios and clinical trials Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

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

- The subject requests withdrawal from the study.
- The investigator believes it is in the best interest of the subject.
- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the sponsor.

- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Malignancy, except for localized non-melanoma skin cancer or carcinoma in-situ of the cervix where discontinuation is at the discretion of the investigator.
- The subject becomes pregnant while on study drug.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk.
- The investigator determines the subject is significantly noncompliant with study procedures.
- 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 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%).
- Subjects who meet any of the above criteria should be evaluated for an alternative etiology of the ALT or AST elevation and managed as medically appropriate. If applicable, the alternative etiology should be documented in the source documents. If after clinically appropriate evaluation, no alternative etiology for ALT or AST elevation is found or the ALT or AST elevation has not resolved or is not trending down toward normal, the subject should be discontinued from study drug.

For 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 their site if they have 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 G.

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

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

During the study drug dosing period, for a subject with confirmed (viral test positive) or suspected COVID-19 infection, the timing of next administration of study drug or possibility of premature discontinuation would be at the discretion of the investigator. Follow protocol Section 5.6 for subjects who discontinued study drug.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow protocol Section 5.6 for subjects who discontinued study drug.

5.6 Follow-Up After Subject Discontinuation of Study Drug or 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 (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a follow-up phone call 140 days (20 weeks) after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved. The 140-day (20-week) follow-up phone call following the last dose of risankizumab study drug during the trial will not be required for any subject who initiates commercially available risankizumab upon the study Completion Visit or Premature Discontinuation visit.

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

5.7 Study Drug

Study site staff will administer risankizumab 150 mg SC (1 × 150 mg PFS) or matching placebo (Table 2).

AbbVie will not supply drugs other than risankizumab and matching placebo.

Risankizumab and matching placebos will be packaged in quantities sufficient to accommodate the study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label in their original packaging and kept in a secure location. A temperature log must be maintained for documentation. Each kit will contain a

unique kit number. This kit number is assigned to a subject via IRT and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to administering to subjects. Study drug will only be used for the conduct of this study. Instructions for drug administration will be provided separately by AbbVie.

Table 2. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Storage Conditions
Risankizumab (ABBV-066)	Solution for injection in PFS	150 mg / 1 mL PFS	SC injection	Store at 2°C to 8°C (36°F to 46°F)
Placebo for Risankizumab	Solution for injection in PFS	NA (Placebo)	SC injection	Store at 2°C to 8°C (36°F to 46°F)

Upon completion of or discontinuation from study treatment, all original study drug units (containing unused study drugs)/devices will be returned to the sponsor (or designee) or destroyed on site. All return or destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug/device accountability procedures.

5.8 Randomization/Drug Assignment

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

Subjects who satisfy eligibility criteria for Study-G only or Study-S only will be assigned to Study-G or Study-S, respectively. Subjects who satisfy eligibility criteria for both Study-G and Study-S will be randomly assigned to Study-G or Study-S with a 1:1 ratio. After one of the two studies reaches 40 subjects in the BSA < 10% group, subjects with BSA <10% who are eligible for both studies will be automatically assigned to the other study until both studies reach 40 subjects in this BSA < 10% group.

Subjects within each study will be randomized to receive risankizumab or placebo in a 1:1 ratio. Randomization will be stratified by weight (≤ 100 kg vs. > 100 kg) and the number of prior biologic therapies for psoriasis (0 versus ≥ 1).

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Clinical 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 treatment throughout the study. To maintain the blind, the risankizumab PFS and matching placebo PFS 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

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

5.10 Data Monitoring Committee

No data monitoring committee is planned in the study.

5.11 Post-Trial Access to Risankizumab

Prior to the last study visit (Week 52), the investigator will discuss the appropriate subsequent treatment with the subject. If the subject and investigator determine continued therapy with risankizumab remains the best course of treatment, AbbVie will work with the investigator to evaluate a path for continued treatment in accordance with local regulations until such time when the subject has reasonable access to the treatment locally (Section 12 and Appendix E).

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 damage or 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.

Reporting will be done via EDC. The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for

reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/AEs and SAEs: Study Drug

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

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

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as an 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 study completion (see Section 11) will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for SAR and SUSAR:

SAR	Defined as all noxious and unintended responses to an IMP related to any dose administered that result in an SAE as defined above.
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable RSI) and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

AEs 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 (ASI)

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

Table 3. 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
In the case of any of the following AEs, the appropriate supplemental eCRFs should be completed: • **Discontinuation or interruption of study drug due to any hepatic-related AE** • **Any hepatic-related SAE** • **A subject experiencing an ALT or AST > 8 × ULN** • **A subject experiencing an ALT or AST > 3 × ULN in conjunction with a total bilirubin > 2 × ULN**	• Hepatic AE eCRF
Suspected anaphylactic/systemic hypersensitivity reactions	• Hypersensitivity Reaction Signs and Symptoms eCRF
TB Subjects with events of latent TB or suspected active TB after initiation of study drug should have a TB Supplemental Form completed.	• TB Supplemental eCRF
Death	• Death eCRF

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the NCI CTCAE Version 5.0.

Grades: Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this guideline:

- **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 Cardiovascular Adjudication Committee (CAC)

An independent CAC will adjudicate 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 3, Supplemental Adverse Events eCRFs.

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

6.3 Anaphylaxis Adjudication Committee (AAC)

While no concerns with anaphylaxis/systemic hypersensitivity have been identified with the use of risankizumab, the sponsor has established an independent, blinded, expert committee to adjudicate events of anaphylaxis based on pre-specified definitions. This independent external AAC 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. In addition, the site may be contacted for additional source documentation.

If a suspected systemic hypersensitivity reaction occurs at the investigative site, in addition to testing tryptase and histamine levels, PK, and ADA/NAb samples should also be collected. If a systemic hypersensitivity reaction such as anaphylaxis is observed or reported 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 statistical methods provided in this protocol will be focused on primary and ranked secondary analyses. Complete and specific details of the statistical analysis will be described in the SAP.

The primary analysis will be conducted after all subjects have completed Week 16 in Study-G and Study-S and all data pertaining to Period A are cleaned. This will be the only and final analysis for efficacy in Period A for each study, respectively.

The final analysis will be conducted upon study completion.

The statistical analyses will be described and fully documented in the SAP. All statistical tests will be performed at a two-sided alpha level of 0.05.

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

7.2 Definition for Analysis Populations

The analysis populations are defined as follows:

- ITT Populations:
  - ITT_G includes all subjects randomized in Study-G.
  - ITT_S includes all subjects randomized in Study-S.

  The ITT_G and ITT_S Populations will be used for all efficacy analyses in Study-G and Study-S, respectively. Subjects will be analyzed according to treatment as randomized.

- Safety Populations:
  - Safety_G includes all subjects randomized to Study-G and received at least 1 dose of study drug.
  - Safety_S includes all subjects randomized to Study-S and received at least 1 dose of study drug.

  For the Safety_G and Safety_S Populations, subjects will be analyzed according to treatment actually received, regardless of the treatment randomized.
- All Risankizumab Treated Populations:
  - ALL_RZB_G: all subjects who receive at least 1 dose of risankizumab as the study drug in Study-G.
  - ALL_RZB_S: all subjects who receive at least 1 dose of risankizumab as the study drug in Study-S.

  The all risankizumab treated populations will be utilized for a comprehensive safety summary of risankizumab.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

There are no intercurrent events considered in this study.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

Analysis of the primary endpoint will be conducted on the ITT_G and ITT_S Populations for Study-G and Study-S, respectively, based on treatment as randomized.

Comparison of the primary endpoint will be made between risankizumab and placebo using the CMH test adjusting for the actual values of stratification factors weight (≤ 100 kg vs. > 100 kg) and number of prior biologic therapies for psoriasis (0 vs. ≥ 1), with a 2-sided significance level of 0.05 for each study.

Handling of Missing Data

- Non-responder Imputation (NRI) will be the primary approach to handle missing values. In cases data missing at random can be reasonably assumed, NRI while incorporating multiple imputation to handle any missing data that can be reasonably assumed to be Missing at Random (NRI-MI) will be used.

Details for NRI, NRI-MI, and other sensitivity analysis (if applicable) will be provided in the SAP.

Summary and Analysis of Ranked Secondary Endpoints

Analysis of all ranked secondary efficacy endpoints will be conducted on the ITT_G and ITT_S Populations based on treatment as randomized respectively in each study.

The categorical endpoints will be analyzed using the CMH test described above.

The continuous endpoints will be analyzed using a MMRM, including baseline, adjusting for treatment, actual values of stratification factors, visit, and treatment by visit interaction.

Summary and Analysis of Additional Efficacy Endpoints

Details for the analyses of additional efficacy endpoints will be provided in the SAP.

Subgroup Analysis for Efficacy

To evaluate the consistency of the efficacy across demographic and other baseline characteristics, the number and percentage of subjects achieving sPGA-G of 0 or 1 at Week 16 (for ITT_G Population) and scalp IGA of 0 or 1 at Week 16 (for ITT_S Population) will be summarized among the following subgroups:

- BMI (normal: < 25; overweight: ≥ 25 to < 30; obese: ≥ 30)
- BSA (< 10%, ≥ 10%)
- Prior biologic therapies for psoriasis (0, ≥ 1)
- Weight (≤ 100 kg, > 100 kg)
- Baseline sPGA (3,4)
- Baseline sPGA-G (3,4) for Study-G only
- Baseline scalp IGA (3,4) for Study-S only
- Baseline PSSI (by median) for Study-S only

The BMI ≥ 30 subgroups will be combined with the adjacent subgroup when having fewer than 10% subjects.

7.5 Statistical Analyses for Safety

The safety analyses will be carried out using the Safety_G and Safety_S populations for Study-G and Study-S, respectively, and will be based on treatments the subjects actually received. Safety will be assessed by AEs, physical examination, laboratory assessments, and vital signs. Analysis details will be specified in the SAP.

TEAEs in each analysis period is defined as follows:

A TEAE in Period A for both Study-G and Study-S is defined as any AE with an onset date on or after the first dose of study drug in Period A and within the minimum of 140 days after the last dose of study drug in Period A and first dose of study drug in Period B.

A TEAE in Period B for both Study-G and Study-S is defined as any AE with an onset date on or after the first dose of study drug in Period B and within 140 days after the last dose of study drug in Period B.

A TEAE during the administration of risankizumab (i.e., among the ALL_RZB_G and ALL_RZB_S Population) is defined as any AE with an onset date on or after the first dose of risankizumab and within 140 days after the last dose of risankizumab.

The number and percentage of subjects experiencing TEAEs will be tabulated using the MedDRA SOC and preferred term, by severity, and by relationship to the study drug as assessed by the investigator. Summaries (including percentages and events per 100 patient-years) of SAEs, deaths, AEs leading to discontinuation and ASI will be provided as well. Pre-treatment SAEs will be summarized separately.

For laboratory tests and vital signs, mean change from baseline and percentage of subject with evaluations meeting predefined Potentially Clinically Significant criteria will be summarized. A listing of all subjects with any laboratory value that is above Grade 3 of CTCAE will be provided.

Additional details for the safety analysis will be provided in the SAP.

7.6 Interim Analysis

No interim analysis is planned for this study.

7.7 Overall Type I Error Control

For Study-G and Study-S, overall type-I error will be controlled under a two-sided significance level of 0.05 respectively for each study by testing the primary endpoint, followed by the ranked secondary endpoints, in a hierarchical order as described in Section 3.2 and Section 3.3.

7.8 Sample Size Determination

This study plans to enroll approximately 100 subjects into Study-G and 100 subjects into Study-S to be sufficiently powered to detect the treatment difference between risankizumab and placebo with respect to the primary endpoints within each study.

- In Study-G, assuming the treatment difference versus placebo (13%) in sPGA-G 0/1 at Week 16 is 53%, a total sample size of N = 100 subjects (risankizumab: 50; placebo: 50) will provide more than 90% power to detect the treatment difference between risankizumab and placebo, using a Chi-square test with a 2-sided significance level of 0.05.
- In Study-S, assuming the treatment difference versus placebo (11%) in Scalp IGA 0/1 at Week 16 is 37%, a total sample size of N = 100 subjects (risankizumab: 50; placebo: 50) will provide more than 90% power to detect the treatment difference between risankizumab and placebo, using a Chi-square test with a 2-sided significance level of 0.05.

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, 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. 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.

For personal data that AbbVie controls and maintains, AbbVie has developed a robust security program to protect subject personal data focused on due diligence in design, managed change, and information security governance. Information security policies govern the information security functions including identity and access management, operations, infrastructure, application, and third-party security requirements. The risk-based AbbVie Data Classification Tool dictates the level of scrutiny and control required for the relevant activities per AbbVie's information security policies taking into account the sensitivity of the data.

Before subject data are shared with AbbVie, the study doctor and staff will replace any information that could directly identify a subject (such as name, address, and contact information) with a generic code which AbbVie cannot link to that subject's identity to protect the confidentiality of the data.

AbbVie has a DPIA program to ensure and document the appropriate controls and safeguards stated above are in place for clinical trial data that it controls and maintains, and these processing activities respect the privacy of clinical trial subjects. AbbVie also maintains robust security incident response policies and procedures, including requirements for the containment of any data related incidents, the mitigation measures where needed, and notification to authorities or affected individuals where required.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

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 GCP, and applicable local regulatory requirement(s). During the COVID-19 pandemic and geo-political conflict in Ukraine and surrounding impacted regions, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

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

11 START AND COMPLETION OF THE STUDY

The start-of-study is defined as the date of the first site activated.

The end-of-study is defined as the date of the last follow-up call (20 weeks after last dose), as indicated in Appendix D in the last country where the study is conducted.

The completion of the study for a subject is defined as one following:

- The date of the follow-up call (20 weeks after the last dose), as applicable
- The date of the Week 52 visit (for subjects who enter the optional CTE)
- The date of the last study visit (for subjects who prematurely discontinue and do not consent and/or complete to the follow-up call)
- The date of commercial risankizumab initiation (for subjects who initiate commercial risankizumab)

12 OPTIONAL CONTINUOUS TREATMENT EXTENSION (CTE)

Purpose

To provide study completers with continuous treatment of risankizumab with the aim to ensure uninterrupted care in accordance with local regulations until commercially available and/or the subject has reasonable access to the treatment locally or transition to a separate CTTP OLE study.

Efficacy Variables

There are no defined efficacy endpoints for CTE.

Safety Endpoints

In the CTE, safety evaluation will include AE monitoring and concomitant medication updates. Additional procedures required for safety assessment will be conducted locally, per the investigator's discretion and local standard of care.

Overall Study Design and Plan

Eligible subjects may continue to receive open-label treatment with risankizumab in CTE to bridge the gap between completion of study and commercial availability and/or local treatment access to risankizumab or availability to enroll in a separate CTTP OLE study in the respective market. Continuing with CTE visits does not preclude a subject from being considered as completing the trial (Completion Visit at Week 52). CTE visits for the purposes of continued treatment are optional and occur following subject's completion of the trial.

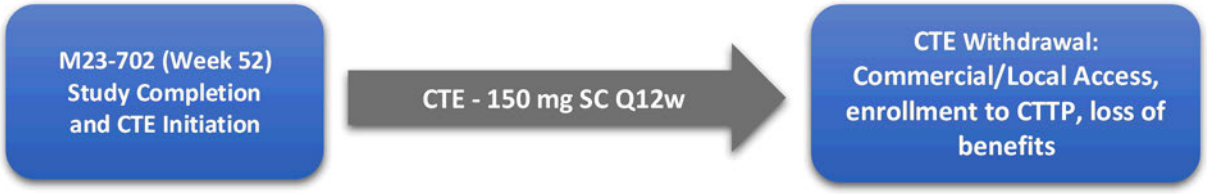
In the CTE, subjects will be evaluated per standard of care and will return every 12 weeks (± 14 days) to continue administration of risankizumab (where locally permitted), as well as evaluation of AEs, SAEs, and use of concomitant medications. Efficacy data will not be collected.

Open-label risankizumab will be administered every 12 weeks starting at Week 52.

The 20-week follow-up phone call following the last dose of risankizumab in CTE will not be required for any subject who initiates commercial risankizumab or transitions to CTTP OLE study.

If risankizumab treatment is not available commercially via local access or through a CTTP OLE study, CTE will continue until all participating subjects have an option available for continued treatment or no longer derive benefit from receiving risankizumab and are discontinued.

Figure 2. CTE Schematic



Concomitant Medications

For subjects who receive open-label treatment with risankizumab in the CTE starting at Week 52, addition or modification of concomitant medications can be made per the investigator's judgment.

Withdrawal and Discontinuation of Subjects

Subjects will be withdrawn from the CTE if any of the following occur in addition to what is stated in Section 5.5:

- A subject no longer derives benefit from risankizumab per investigator assessment.
- Subject has reasonable access to commercial risankizumab in the country of participation per investigator and/or sponsor assessment.
- Subject receives a live vaccine (with exception of non-replicating live vaccines).

Drug Assignment

Subjects will have the option to receive continued treatment with open-label risankizumab in CTE if they completed the study (Week 52) and continue to tolerate and derive benefit from risankizumab treatment, but do not have risankizumab commercially available and/or do not have reasonable access to risankizumab.

Safety Considerations

If any urine pregnancy test is positive, a serum pregnancy test will be performed locally. If the serum pregnancy test is positive, study drug must be permanently discontinued. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later. If the repeat serum pregnancy test is:

- Positive, the study drug must be permanently discontinued;
- Negative, the subject can continue in the study;
- Still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can continue in the study (unless prohibited locally) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

A pregnant or breastfeeding female will not be eligible for continuation or be allowed to continue study drug.

Independent Data Monitoring Committee, Cardiovascular Adjudication Committee, Anaphylaxis Adjudication Committee

Not applicable for CTE data.

Statistical Analysis for Safety

Safety analysis for the CTE may be conducted separately as needed.

Refer to Appendix E for additional information.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
A-Score	Anxiety Score
AAC	Anaphylaxis Adjudication Committee
Ab	Antibody
ADA	Anti-drug antibodies
AE	Adverse event
ALL_RZB_G	All Risankizumab Treated Population for Study-G
ALL_RZB_S	All Risankizumab Treated Population for Study-S
ALT	alanine transaminase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
ASI	Areas of Safety Interest
AST	Aspartate transaminase
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
BUN	Blood urea nitrogen
C	Celsius
CAC	Cardiovascular Adjudication Committee
CBC	Complete blood count
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CTE	Continuous Treatment Extension
CTTP	Continued Treatment for Trial Participants
CV	Cardiovascular
D-Score	Depression Score
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
DPIA	Data protection impact assessment

ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
EU	European Union
F	Fahrenheit
FSH	Follicle stimulating hormone
GCP	Good clinical practice
GenPs-SFQ	Genital Psoriasis Sexual Frequency Questionnaire
GGT	Gamma-glutamyl transferase
GPSS	Genital Psoriasis Symptom Scale
HADS	Hospital Anxiety and Depression Scale
HBc	Hepatitis B core
HBs Ab	Hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
Ig	Immunoglobin
IGA	Investigator Global Assessment
IGRA	Interferon gamma release assay
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
ITT_G	Intent-to-treat Population for Study-G

ITT_S	Intent-to-treat Population for Study-S
IU	International units
LDL-C	Low-density lipoprotein cholesterol
mAb	Monoclonal antibody
MACE	Major adverse cardiovascular events
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MMRM	Mixed-effect Model Repeat Measurement
NA	Not applicable
NAb	Neutralizing antibodies
NCI	National Cancer Institute
NCS	Not clinically significant
NRI	Non-responder Imputation
NRI-MI	Non-responder Imputation incorporating multiple imputation
NRS	Numerical rating scale
OLE	Open-Label Extension
PatGA-Genital	Patient Global Assessment for Genital Psoriasis
PCR	Polymerase chain reaction
PEF	Peak expiratory flow
PFS	Pre-filled syringe
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PRO	patient-reported outcome(s)
PSS	Psoriasis Symptom Scale
PSSI	Psoriasis Scalp Severity Index
PSSI 75/90/100	At least 75%/90%/100% reduction from Baseline in Psoriasis Scalp Severity Index
PT	Prothrombin
PUVA	Psoralen + ultraviolet light A
q12w	Every 12 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RNA	Ribonucleic acid
RSI	Reference Safety Information

SAE	Serious adverse event
Safety_G	Safety Population for Study-G
Safety_S	Safety Population for Study-S
SAP	Statistical analysis plan
SAR	Serious adverse reactions
SC	Subcutaneous
SOC	System Organ Class
sPGA	static Physician Global Assessment
sPGA-G	static Physician Global Assessment of Genitalia
Study-G	Genital psoriasis study
Study-S	Scalp psoriasis study
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Th17	T helper 17
TNF	Tumor necrosis factor
UACR	Urine albumin-to-creatinine ratio
ULN	upper limit of normal
US	United States
UVA	Ultraviolet light A
UVB	Ultraviolet light B
WBC	white blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M23-702: A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis

Protocol Date: 07 June 2023

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 laws and 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 (within 1 calendar day) to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
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]	[redacted]	Immunology, Clinical Development Data and Statistical Sciences

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the Screening and subsequent study visits. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 and/or the geo-political conflict in Ukraine and surrounding impacted regions are detailed within the Operations Manual.

The follow-up phone call is not required for any subject who initiates commercial risankizumab.

Study Activities Table

Activity	Screening	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52 / Premature Discontinuation	Follow-Up Call 20 Weeks after Last Dose
	Day –30 to Day –1	Day 1	Day 29	Day 113	Day 197	Day 281	Day 365	Day 421
Visit Window			± 3 Days		± 7 Days			
INTERVIEWS & QUESTIONNAIRES								
Informed consent	✓							
Demographics	✓							
Eligibility criteria	✓	✓						
Medical (including psoriasis)/surgical history	✓	✓						
Drug, tobacco (including e-cigarettes), and alcohol history	✓							
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓
Dispense handheld ePRO device	✓							
Collect handheld ePRO device				✓				
Patient Reported Outcomes Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI, and HADS Study-S: PSS, Scalp Itch NRS, DLQI, and HADS * GPSS and PSS collected DAILY from Screening to Week 16 and then at site visits. GenPs-SFQ collected WEEKLY from Screening to Week 16 and then at site visits. All other PROs collected at site visits from Baseline to Week 52.	✓*	✓*	✓*	✓*	✓*	✓*	✓*	
Latent TB risk assessment form	✓							

Activity	Screening	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52 / Premature Discontinuation	Follow-Up Call 20 Weeks after Last Dose
	Day –30 to Day –1	Day 1	Day 29	Day 113	Day 197	Day 281	Day 365	Day 421
Visit Window			± 3 Days		± 7 Days			
LOCAL LABS & EXAMS								
12-lead ECG	✓							
Height (screening only) and weight	✓						✓	
Vital signs	✓	✓	✓	✓	✓	✓	✓	
Physical examination (targeted physical exam possible at any time, if required)	✓	✓					✓	
Efficacy assessments Study-G: sPGA-G, sPGA Study-S: scalp IGA, PSSI, sPGA	✓	✓	✓	✓	✓	✓	✓	
BSA	✓	✓						
Urine pregnancy test (for females of childbearing potential only, performed prior to dosing)		✓	✓	✓	✓	✓		
Optional photography (not performed at Premature Discontinuation Visit)		✓	✓	✓	✓	✓	✓	
CENTRAL LABS								
HIV/HBV/HCV screening	✓							
Follicle-stimulating hormone (FSH) (if applicable, per operations manual)	✓							
Serum pregnancy test (for females of childbearing potential only)	✓							
TB test (QuantiFERON-TB Gold test [or IGRA equivalent] and/or local PPD skin test)	✓						✓	
Clinical chemistry, Hematology (including CBC)	✓	✓			✓		✓	
Urinalysis	✓							

Activity	Screening	Baseline	Week 4	Week 16	Week 28	Week 40	Week 52 / Premature Discontinuation	Follow-Up Call 20 Weeks after Last Dose
	Day –30 to Day –1	Day 1	Day 29	Day 113	Day 197	Day 281	Day 365	Day 421
Visit Window			± 3 Days		± 7 Days			
℞ TREATMENT								
Randomization/drug assignment in IRT		✓						
Study drug administration		✓	✓	✓	✓	✓		
In-clinic post-dose monitoring for hypersensitivity reactions		✓	✓	✓	✓	✓		

Optional Continuous Treatment Extension Study Activities Table

Activity	Week 52 of Main Study	Every 12 Weeks	CTE Withdrawal	Follow-Up Call 20 Weeks After Last Dose
		± 14 Day		
Informed consent	✓			
Adverse event assessment and concomitant medication	✓	✓	✓	✓
Pregnancy test	✓	✓	✓	
Risankizumab administration	✓	✓		

APPENDIX E. OPTIONAL CONTINUOUS TREATMENT EXTENSION FOR APPLICABLE COUNTRIES

Directions for sites in countries that require continued study drug provision to accommodate country-specific needs is found throughout this appendix. AbbVie will assess feasibility for continued access to the AbbVie treatment with the aim to ensure uninterrupted access in accordance with local regulations. AbbVie will work with the investigator to ensure a path for continued access until such time when AbbVie treatment is commercially available and/or the subject can access treatment locally.

INVESTIGATIONAL PLAN

Overall Study Design and Plan (for additional details please review main Protocol)

At the end of Week 52 study visit, eligible subjects may continue to receive open-label treatment with risankizumab 150 mg (1 × 150 mg PFS) subcutaneous injection q12w to bridge the gap between completion of study and commercial availability and/or local treatment access to risankizumab or availability to enroll in a CTTP OLE study in the respective market (CTE Activities Table in Appendix D). Note: These extension visits completed for purposes of post-Week 52 access to risankizumab are considered optional and do not preclude a subject from being considered as completing the trial (i.e., Week 52).

Participating sites in applicable countries will be provided with estimated dates of when the subjects' final visits are expected to occur for planning purposes. It is acknowledged that these dates may change at any time during the course of the regulatory approval/reimbursement process. The final visit dates will be communicated to the sites based on subject reasonable access to commercial risankizumab in the country of participation per investigator and/or sponsor. The investigator may 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. AbbVie reserves the right to terminate the study at any time.

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	29 March 2023

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol in addition to the following:

Protocol

- In Section 5.7, Table 2, removed the Manufacturer of the Investigational Product and added the storage conditions.

  Rationale: *The Investigational Product manufacturer information has been removed as alternate manufacturing sites might be used during the course of the study. The Storage Conditions have been added, to be clear on the storage requirements of the Investigational Product.*

- In Section 6.1, corrected the sentence "If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected." into "If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected."

  Rationale: *Information regarding the pregnancy of the partner of a study subject does not need to be collected, as risankizumab, an immunoglobulin, is not considered to be teratogenic given animal studies do not indicate harmful effects with risankizumab on pregnancy. Furthermore, risankizumab is not genotoxic and thus male-mediated developmental risk involving effects on the germ cell is considered low. Given risankizumab is a large molecule, amounts in seminal fluid transferred to the conceptus are negligible. Male-mediated seminal transfer of large molecule drugs like risankizumab do not present a health risk to the female partner.*

- In Section 7.4, updated details of the Handling of Missing Data section to remove caveat for missing data due to COVID-19. Any missing data for the binary endpoints will be handled with the NRI approach. In cases data missing at random can be reasonably assumed, NRI-MI will be used.

  Rationale: *Made missing data handling language more general to account for the ending of the COVID-19 pandemic emergency.*

Operations Manual

- In Section 3.6 of the Operations Manual (Appendix G), added that only subjects at prospectively selected sites in the US will be asked to have optional photographs taken.

  Rationale: *Only sites in the US will be asked to participate in the optional photography.*

APPENDIX G. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M23-702

Genital or Scalp Psoriasis: Risankizumab for Adult Subjects with Moderate to Severe Genital or Moderate to Severe Scalp Psoriasis

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab

FULL TITLE: A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis

1 CONTACTS

Sponsor/ Emergency Medical Contact	[redacted], MD PhD AbbVie 1 North Waukegan Road North Chicago, IL 60064, US **EMERGENCY 24 hour Number:** **+1 (973) 784-6402**	Office: Mobile: Fax: Email: [redacted]
Safety Questions	Immunology Safety Team	Email: SafetyManagement_Immunology@abbvie.com
SAE Reporting outside of EDC	Email: PPDINDPharmacovigilance.@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations and Product complaints	[redacted] AbbVie B.V. Wegalaan 9 2132JD Hoofddorp, The Netherlands	Phone: Email: [redacted]
Certified Clinical Lab	LabCorp 8211 Scicor Drive Indianapolis, IN 46214, US	Phone: +1 (866) 762-6209 (Toll free) +1 (317) 271-1200 (Local calls) Fax: +1 (317) 616-2362 For country specific toll-free numbers, please refer to Covance Lab Manual
PK Sample Lab	AbbVie Deutschland GmbH and Co KG Regulated Bioanalysis Knollstrasse 67061 Ludwigshafen, Germany	Phone: Email: [redacted] gprd_lupet@abbvie.com

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to logistical restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- Study visits and/or activities should be performed at the study site and as scheduled whenever possible. If a subject is unable to visit the study site due to COVID-19-related issues, the subject should perform the visit/related activities at the earliest feasible opportunity and as per the following modifications.
  - Reschedule study visits as soon as possible and contact AbbVie if out-of-window to obtain guidance on which visit should be performed once the subject's return to site has been confirmed.
  - Regardless of when the rescheduled onsite visit may occur, a phone call from the site to the enrolled subject should be conducted as close to the originally scheduled date of the study visit as possible to query for any adverse events and review concomitant medications.

2.1 Individual Treatment Period Visit Activities

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

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

SCREENING:

INTERVIEW	• Subject information and informed consent • Demographics • Eligibility criteria • Medical (including psoriasis)/surgical history	• Drug, tobacco (including e-cigarettes), and alcohol history • AE assessment • Prior/concomitant therapy • Latent TB risk assessment form
PRO	• Dispense handheld ePRO device	• GPSS and GenPs-SFQ for subjects with genital involvement • PSS for subjects with scalp involvement
EXAM	• 12-lead ECG • Height • Weight • Vital signs • Physical exam	• BSA • sPGA-G and sPGA for subjects with genital involvement • Scalp IGA, PSSI, and sPGA for subjects with scalp involvement
CENTRAL LAB	• HIV, HBV, and HCV screening • FSH (if applicable) • Serum pregnancy test (for all female subjects of childbearing potential)	• TB test (QuantiFERON-TB Gold test [or IGRA equivalent] and/or local PPD skin test) • Hematology (including CBC) • Clinical chemistry • Urinalysis

NOTES: All screening procedures must be performed onsite, with the exception of PRO assessments. GPSS and PSS will be assessed daily and GenPs-SFQ will be assessed weekly until Week 16.

Baseline/DAY 1:

INTERVIEW	• Eligibility criteria • Medical (including psoriasis)/surgical history	• AE assessment • Prior/concomitant therapy
PRO	• Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI, HADS	• Study-S: PSS, Scalp Itch NRS, DLQI, HADS
EXAM	• Vital signs • Physical exam • Photography (optional)	• BSA • Study-G: sPGA-G, sPGA • Study-S: scalp IGA, PSSI, sPGA
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology (including CBC)	• Clinical chemistry
TREATMENT	• Randomization/drug assignment • Administer study drug	• In-clinic post-dose monitoring for hypersensitivity reactions

NOTES: GPSS and PSS will be assessed daily and GenPs-SFQ will be assessed weekly until Week 16.

WEEK 4:

INTERVIEW	• AE assessment	• Prior/concomitant therapy
PRO	• Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI, HADS	• Study-S: PSS, Scalp Itch NRS, DLQI, HADS
EXAM	• Vital signs • Photography (optional)	• Study-G: sPGA-G, sPGA • Study-S: scalp IGA, PSSI, sPGA
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
TREATMENT	• Administer study drug	• In-clinic post-dose monitoring for hypersensitivity reactions

NOTES: GPSS and PSS will be assessed daily and GenPs-SFQ will be assessed weekly until Week 16.

WEEK 16:

INTERVIEW	• AE assessment	• Prior/concomitant therapy
PRO	• Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI, HADS	• Study-S: PSS, Scalp Itch NRS, DLQI, HADS • Collect handheld ePRO device
EXAM	• Vital signs • Photography (optional)	• Study-G: sPGA-G, sPGA • Study-S: scalp IGA, PSSI, sPGA
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
TREATMENT	• Administer study drug	• In-clinic post-dose monitoring for hypersensitivity reactions

WEEK 28:

INTERVIEW	• AE assessment	• Prior/concomitant therapy
PRO	• Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI, HADS	• Study-S: PSS, Scalp Itch NRS, DLQI, HADS
EXAM	• Vital signs • Photography (optional)	• Study-G: sPGA-G, sPGA • Study-S: scalp IGA, PSSI, sPGA
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
CENTRAL LAB	• Hematology (including CBC)	• Clinical chemistry
TREATMENT	• Administer study drug	• In-clinic post-dose monitoring for hypersensitivity reactions

WEEK 40:

INTERVIEW	• AE assessment	• Prior/concomitant therapy
PRO	• Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI, HADS	• Study-S: PSS, Scalp Itch NRS, DLQI, HADS
EXAM	• Vital signs • Photography (optional)	• Study-G: sPGA-G, sPGA • Study-S: scalp IGA, PSSI, sPGA
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
TREATMENT	• Administer study drug	• In-clinic post-dose monitoring for hypersensitivity reactions

WEEK 52/Premature Discontinuation:

INTERVIEW	• AE assessment	• Prior/concomitant therapy
PRO	• Study-G: GPSS, GenPs-SFQ, PatGA-Genital, DLQI, HADS	• Study-S: PSS, Scalp Itch NRS, DLQI, HADS
EXAM	• Weight • Vital signs • Physical exam • Photography (optional)	• Study-G: sPGA-G, sPGA • Study-S: scalp IGA, PSSI, sPGA
CENTRAL LAB	• Hematology (including CBC) • Clinical chemistry	• TB test (QuantiFERON-TB Gold test [or IGRA equivalent] and/or local PPD skin test)

NOTES: Photography is not required for premature discontinuation. TB test is not required for premature discontinuation if less than 52 weeks since previous TB test.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during follow-up. The dot pattern on the upper right indicates the place of the visit/call in the overall Post-Treatment Period Activity Schedule.

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

FOLLOW-UP PHONE CALL (20 Weeks After Last Study Drug Dose):

INTERVIEW	• AE assessment	• Prior/concomitant therapy

NOTES: Does not apply to subjects who initiate commercial risankizumab or continue in the optional CTE.

2.3 Optional Continuous Treatment Extension (CTE)

This section presents a list of activities performed during the optional CTE, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall CTE.

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

WEEK 52 AND EVERY 12 WEEKS:

INTERVIEW	• Subject information and informed consent (Week 52 only) • AE assessment	• Concomitant medication
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	
TREATMENT	• Administer study drug	• In-clinic post-dose monitoring for hypersensitivity reactions

NOTES: At Week 52, these activities will be performed in addition to the Week 52 activities in Section 2.1. At Week 52, subjects will be administered open-label risankizumab to begin CTE. Subjects will be evaluated per standard of care.

CTE WITHDRAWAL:

INTERVIEW	• AE assessment	• Concomitant medication
LAB	• Urine pregnancy test (for all female subjects of childbearing potential)	

NOTES: If a subject discontinues treatment with risankizumab, the withdrawal visit should be completed and the subject will automatically discontinue CTE participation.

FOLLOW-UP PHONE CALL (20 Weeks After Last Study Drug Dose):

INTERVIEW	• AE assessment	• Concomitant medication

NOTES: Does not apply to subjects who initiate commercial risankizumab or transitions to CTTP OLE study.

3 STUDY PROCEDURES

3.1 Study Subject Information and Informed Consent

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

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

Optional photography will only be performed if the subject has voluntarily signed and dated a separate written consent form for photography that has been approved by an IRB/IEC, after the nature of the photography has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the subject does not consent to the photography, it will not impact the subject's participation in the study.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

3.2 Medical History

A complete medical and surgical history including demographics, history of hepatitis B vaccination, TB screening, tobacco, alcohol, and drug use will be taken at screening. The subject's medical and surgical history will be updated at the Study Baseline/Day 1 visit. This updated medical history will serve as the baseline for clinical assessments.

Subjects should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

3.3 Adverse Event Assessment

Please refer to Section 4.1.

3.4 Patient-Reported Outcomes

Subjects will complete the self-administered PRO instruments (when allowed per local regulatory guidelines). Subjects should be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

PRO instruments that are administered at the site should be completed at the specified study visit prior to clinical assessments, dosing, or any other procedure and prior to any discussion of adverse events or any review of laboratory findings. The subject should complete the questionnaire before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

The following PRO assessments that are required between site visits will be collected electronically from subjects in the evening using a handheld ePRO device provided to the subject at Screening:

- GPSS and PSS will be collected DAILY starting at Screening until Week 16.
- GenPs-SFQ will be collected WEEKLY starting at Screening until Week 16.

At the visits specified in Section 2.1, all PRO assessments will be collected electronically at the site using an electronic device supplied by AbbVie. The device will be programmed to allow data entry for only the visits specified in the protocol and will not allow subjects to complete more than one of the same assessments at one visit.

All data entered on the handheld and electronic tablet devices will be immediately stored to the devices themselves and automatically uploaded to a central server.

The PRO instruments are described as follows.

All Subjects

- Dermatology Life Quality Index (DLQI): The DLQI is a self-administered, 10-question questionnaire covering 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, treatment) and has a 1-week recall period. The response options range from 0 (not affected at all) to 3 (very much affected). This gives an overall range of 0 to 30 where lower scores mean better quality of life.
- Hospital Anxiety and Depression Scale (HADS): The HADs is a self-assessment scale which detects the presence and severity of anxiety and depression in the general population. It contains 14 items and is comprised of anxiety (7 items) and depression (7 items) subscales, which are scored separately and summed to give a total score. Item scores range from 0 (best) to 3 (worst) and total scores are categorized as normal (0 – 7), borderline abnormal (8 – 10) and abnormal (11 – 21). The HADs has been widely used in clinical trials in a variety of disease areas and has extensive evidence to support its acceptability, reliability and validity.

Study-G

- Genital Psoriasis Symptoms Scale (GPSS): The GPSS is a patient-administered assessment of 8 symptoms: itch, pain, discomfort, stinging, burning, redness, scaling, and cracking. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Genital area is defined as the labia majora (outer lip), labia minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (area between the penis and anus) for males. The self-reported overall severity of each of the 8 symptoms individually in the genital area is assessed on an 11-point horizontal NRS anchored at 0 (no) and 10 (worst imaginable), using a recall period of 1 day.
- Genital Psoriasis Sexual Frequency Questionnaire (GenPs-SFQ): The GenPs-SFQ is a PRO measure to evaluate the impact of genital psoriasis symptoms on sexual frequency, using a 1-week recall period. It consists of 2 items that assess the impact of genital psoriasis symptoms on the frequency of sexual activity. Each item uses a Likert scale. Respondents are asked to answer the questions based on their psoriasis symptoms in the genital area. Genital area is defined as the labia majora (outer lip), labia minora (inner lip), and perineum (area between vagina and anus) for females; penis, scrotum, and perineum (area between the penis and anus) for males. The definition of sexual activity is not limited to intercourse and includes activities such as masturbation.

  Item 1 asks how many times a patient engaged in sexual activity in the past week with response options of none/zero (2), once (1), and two or more (0). Item 2 assesses how often genital psoriasis symptoms limited the frequency of sexual activity with response options ranging from 0 (never) to 4 (always). The individual item scores of the SFQ are reported separately. No total score is calculated for SFQ. The instructions for completion are embedded within the SFQ questionnaire for patients to read before responding to items. SFQ individual item scores at Week 16 are the scores collected at Week 16 on site.
- Patient's Global Assessment of Genital Psoriasis (PatGA-Genital): The PatGA-Genital is a patient-administered, single-item scale on which patients are asked to rank, by circling a number on a 0 to 5 NRS, the severity of their genital psoriasis "today" from 0 (clear), no genital psoriasis; to 5 (severe).

Study-S

- Psoriasis Symptoms Scale (PSS): The PSS is a 4-item PRO instrument that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis, using a recall period of 1 day. The symptoms include pain, redness, itching and burning from psoriasis. Current symptom severity is assessed using a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe). Until Week 16, the weekly average score is calculated based on the 7 available daily scores from the days within each visit window that were closest to the nominal. The PSS was developed based on published evidence supporting the development of two similar, proprietary PRO instruments: the Psoriasis Symptom Inventory and the Psoriasis Symptom Diary.
- Scalp Psoriasis Itch Numeric Rating Scale (Scalp Itch NRS): The Scalp Itch NRS is a self-administered NRS that asks the patients to assess their scalp itch on a scale from 0 to 10 where 0 represents no itch and 10 represents worst imaginable itch. Scalp Itch NRS has been used in previous trials assessing the efficacy of apremilast among patients with scalp psoriasis.[1]

3.5 Efficacy Assessments

Most efficacy assessments will be recorded on paper worksheets and entered into the eCRF (sPGA-G and scalp IGA will be collected electronically). Efficacy assessments will be conducted at the study visits specified in the protocol. To minimize variability, the same assessor should evaluate the subject at each visit for the duration of the trial. A back-up assessor should be identified. The assessor must be a qualified medical professional (e.g., nurse, physician's assistant, or physician). Any assessor must have completed training for skin assessments (sPGA-G, scalp IGA, and BSA) as detailed by the sponsor, and be competent in performing such assessments. It is the responsibility of the site investigator to ensure that all assessors are qualified and trained to perform assessments and that all training is documented. If the assessor is not available, the pre-identified back-up assessor should perform such assessments.

All Subjects

- Body Surface Area (BSA) – Psoriasis: The subject's right or left hand should be selected as the measuring device. For purposes of clinical estimation, the total surface of the palm plus five digits will be assumed to be approximately equivalent to 1%. Measurement of the total area of involvement by the physician is aided by imagining if scattered plaques were moved so that they were next to each other and then estimating the total area involved.
- Static Physician Global Assessment (sPGA): This sPGA is a 5-point score ranging from 0 to 4 (where 0 = clear), based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. The assessment is considered "static" which refers to the patient's disease state at the time of the assessments, without comparison to any of the patient's previous disease states, whether at Baseline or at a previous visit.

Study-G

- Static Physician Global Assessment of Genitalia (sPGA-G): The sPGA-G is a 5-point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. The assessment is considered "static" which refers to the patient's disease state at the time of the assessments, without comparison to any of the patient's previous disease states, whether at Baseline or at a previous visit.

Study-S

- Scalp Investigator Global Assessment (scalp IGA): The scalp IGA is a measurement of overall scalp involvement by the investigator at the time of evaluation. The scalp IGA is a 5-point scale ranging from 0 (clear) to 4 (severe) incorporating an assessment of the severity of the 3 primary signs of the disease: erythema, scaling, and plaque elevation. When making the assessment of overall scalp severity, the investigator should factor in areas that have already been cleared (i.e., have scores of 0) and not just evaluate remaining lesions for severity, i.e., the severity of each sign is averaged across all areas of involvement, including cleared lesions.
- Psoriasis Scalp Severity Index (PSSI): The physician will assess the severity of scalp psoriasis using the PSSI, which consists of an assessment of erythema, induration, and desquamation on a scale from 0 (none) to 4 (very severe) and the percentage of scalp involved on a scale from 0 (< 10%

of scalp involved) to 6 (90 to 100% of scalp involved). The composite score is calculated as the sum of the scores for erythema, induration and desquamation multiplied by the score recorded for the extent of scalp area involved. The PSSI ranges from 0 to 72. A negative change from baseline indicates improvement.

3.6 Photography

Subjects at prospectively selected sites in the US will be asked to have optional photographs taken of their genitals (Study-G) or scalp (Study-S) to document disease response during the study. Photographs will be taken prior to study drug administration. Subjects must voluntarily provide consent, approved by an IRB/IEC, after the nature of the photographs has been explained and the subject has had an opportunity to ask questions. Subjects who agree to photographs are consenting to photographs at visits specified in Section 2.1.

Training and detailed instructions will be provided by the vendor selected to coordinate the photography portion of the study.

3.7 12-Lead Electrocardiogram

Resting 12-lead ECGs will be obtained singly as specified in Section 2.1.

The ECG acquired prior to dosing will serve as the baseline measurements for clinical assessment.

When an ECG is scheduled at the same time as a blood collection, the ECG will be obtained prior to the blood collection. ECGs occurring near meals will take place prior to meals.

ECGs will be acquired after the subject has been in the supine position for at least 5 minutes. Subjects will be instructed to remain completely stationary (no talking, laughing, deep breathing, sleeping, or swallowing) for approximately 10 seconds during the ECG recording. While ECGs are being acquired, subjects and staff are prohibited from having devices (e.g., cellular telephones, fans, heaters, etc.) that emit electrical interference in the room.

For subjects with a normal ECG taken within 90 days of Screening, a repeat ECG at Screening will not be required, provided all protocol-required documentation is available and nothing has changed in the subject's health status since the time of the test that warrants a repeat test.

ECG Safety Review

Each ECG will be evaluated by an appropriately trained physician (preferably a cardiologist) at the study site (the "local reader"). The local reading of the ECG will be used by the investigator for subject safety assessments, including adverse event determination and management, and decision on whether a subject is eligible for study participation.

The local reader will sign and date all the ECGs collected in this study and provide a global interpretation for each ECG using the following categories:

- Normal ECG

- Abnormal ECG – Not clinically significant (NCS)
- Abnormal ECG – Clinically significant (CS)
- Unable to evaluate

Clinically significant ECG findings noted at screening will be captured in Medical History.

All local reader evaluations of ECGs will be entered into the source documents. If the global interpretation is Abnormal (NCS or CS), the local reader will provide further information (e.g., sinus bradycardia, arrhythmia). The QT interval corrected for heart rate using QTcF will be calculated and documented for all ECGs.

All ECG source documentation will be retained at the study site. The automatic cardiograph reading (i.e., cardiograph-generated measurements and interpretations) will not be collected for analysis.

3.8 Height and Weight

Height will be measured at screening only. Body weight will be measured at scheduled visits as specified in Section 2.1. The subject will wear lightweight clothing and no shoes during weighing.

3.9 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at visits as specified in Section 2.1. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

Measurements should be assessed consistently throughout the study. Vital signs measurements determined prior to dosing on Baseline/Day 1 or specify timing will serve as baseline.

3.10 Physical Examination

A complete physical examination, including height (at Screening only) and weight, will be performed at the designated study visits as specified in Section 2.1. The physical examination performed at Baseline/Day 1 will serve as the baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as adverse events, while any finding prior to the first dose will be recorded as medical history. All findings, whether related to an AE or part of a subject's medical history, will be captured on the appropriate eCRF page.

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

3.11 Dispense Study Drug

Study drug will be administered to subjects beginning at Baseline/Day 1 and as specified in Section 2.1. All doses of risankizumab and placebo will be administered by designated and qualified study site

personnel under the direction of the investigator. Date and exact time (to the nearest minute) of study drug administration will be recorded on eCRFs. The first dose of study drug will be administered after all other Baseline procedures are completed. Study drug administration instruction for risankizumab PFS will be provided to the site.

Monitoring for Hypersensitivity Reactions

Therapeutic protein products, such as biologics, may elicit a range of acute effects, from symptomatic discomfort to sudden, fatal reactions and may encompass a wide range of clinical events, including anaphylaxis and other events that may not be directly related to antibody (Ab) responses, such as cytokine release syndrome.

Subjects should be closely monitored at the site for signs and symptoms of hypersensitivity reactions, including allergic reactions and anaphylaxis, for approximately 1 hour after all PFS dosing of study drug have been administered at each dosing visit. A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the injections.

All appropriate medical support measures (e.g., antihistamines, steroids, epinephrine, oxygen) for the treatment of suspected hypersensitivity reactions should be available for immediate use in the event that a suspected hypersensitivity reaction occurs. Subjects who manifest any new signs or symptoms during the injection should be monitored for appropriate resolution prior to leaving the site. Subjects are encouraged to report any symptoms related to a possible injection-related reaction or local injection site reaction or late phase reactions to the site any time during the study. A patient information card listing the symptoms of these reactions will be provided to the participants.

Subjects will be monitored throughout the study for signs and symptoms suggestive of hypersensitivity reactions, including allergic reactions and anaphylaxis. In the event of a suspected anaphylactic/systemic hypersensitivity reaction, in addition to the standard AE eCRF, the supplemental Hypersensitivity Reaction Signs and Symptoms eCRF should also be completed by the site. The clinical criterion for diagnosing anaphylaxis is provided in Section 9.1 for reference; symptoms of anaphylactic reactions usually occur within minutes to hours after exposure to an allergen. These are guidelines that are used to help diagnose anaphylaxis. The investigator is encouraged to report any suspected reactions.

In the event of a suspected anaphylactic reaction, blood and serum samples should also be collected as described in Section 3.12.

3.12 Clinical Laboratory Tests

The blood samples for serum chemistry tests will be collected following a minimum 8-hour fast for the Baseline/Day 1 visit (glucose, total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglycerides). If a subject is not able to fast at that visit, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation and lab requisition. Blood samples at other visits can be drawn without prior fast. The Baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

Blood draws should be performed after all questionnaires, clinical assessments, and vital sign determinations are obtained. Unscheduled clinical labs may be obtained at any time during the study if deemed appropriate per investigator's discretion.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Other Tests</th></tr>
<tr>
<td>Hematocrit
Hemoglobin
MCV
RBC count/Erythrocytes
WBC count/Leukocytes
Platelet count/Thrombocytes
Diff. Automatic (absolute count):
Neutrophils
Eosinophils
Basophils
Monocytes
Lymphocytes
Manual Differential (ONLY IF Automated Differential is abnormal):
Neutrophils, bands (Stabs)
Neutrophils, polymorphonuclear
Eosinophils
Basophils
Monocytes
Lymphocytes
<u>Coagulation:</u>
PT/INR[a]</td>
<td>Enzymes
ALT
AST
AP
GGT
CK
Only if CK is elevated:
Troponin (point-of-care) OR
Troponin (central lab)
Electrolytes
Sodium
Potassium
Chloride
Bicarbonate
Calcium
Phosphorus
Substrates
Glucose
BUN/Urea
Creatinine with eGFR (CKD-EPI)
Bilirubin total
Bilirubin direct (if total is elevated)
Bilirubin indirect (if total is elevated)
Albumin
hsCRP
Cholesterol, total[b]
LDL-C[b]
HDL-C[b]
Triglycerides[b]
FSH[c]</td>
<td>Dipstick Urinalysis
Urine nitrite
Urine protein
Urine glucose
Urine ketone
Urobilinogen
Urine bilirubin
Urine RBC/erythrocytes
Urine WBC/leukocytes
Urine pH
Urine creatinine
Urine Sediment (microscopic examination, ONLY IF urine analysis abnormal):
Urine
UACR</td>
</tr>
<tr><th>ADDITIONAL TESTING</th><th>INFECTION SCREENING [d]</th><th>PREGNANCY TESTING[e]</th></tr>
<tr>
<td>N/A</td>
<td>HBs Ag (qualitative)
HBs Ab (qualitative)
Anti-HBc total (qualitative)
HBV DNA (quantitative)
Anti-HCV (qualitative)
HCV RNA (quantitative)
HIV-1 and HIV-2 Ab (qualitative)
QuantiFERON®-TB (or IGRA equivalent) and/or PPD</td>
<td>Urine pregnancy test (local)[f]
Serum pregnancy test[g]
ANAPHYLAXIS TESTING[h]
Serum risankizumab concentration
ADA
NAb
Tryptase
Histamine</td>
</tr>
</table>

a. INR test only performed if ALT or AST > 3 × ULN (upper limit of normal).

b. Performed at Baseline/Day 1 visit (following a minimum 8-hour fast).

c. FSH testing is to be done at Screening in all women aged ≤ 55 years with no menses for 12 or more months without an alternative medical cause.

d. Performed only at Screening. Per regional requirements: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV-DNA PCR test should be performed again as noted in the Operations Manual, Section 3.12. Retesting is not necessary for subjects that have a history of HBV vaccine and are HBs Ab (+).
e. Pregnancy testing is not required for female subjects of non-childbearing potential (defined in protocol Section 5.2).
f. Urine pregnancy test will be performed at every dosing visit and must be conducted prior to study drug dosing. Negative urine pregnancy test results must be confirmed prior to study drug dosing.
g. Serum pregnancy test is conducted at Screening and at other visits only if urine pregnancy test is positive. Negative serum pregnancy test results must be confirmed prior to study drug dosing.
h. Only performed in case of a suspected anaphylactic reaction. Refer to anaphylaxis testing Section 9.1 below.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

Pregnancy Tests (Serum and Urine)

Pregnancy testing should not be performed for postmenopausal women. Determination of postmenopausal status will be made during the Screening Period based on the subject's history and confirmed by FSH, if appropriate.

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Pregnant subjects must discontinue from study drug treatment. Refer to Section 5.5 of the protocol for additional details.

Serum Pregnancy Test

A serum pregnancy test will be performed for all female subjects of childbearing potential (defined in the protocol) at Screening. The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, the subject is considered a screen failure. If the serum pregnancy test is borderline, study drug should be held and the test should be repeated ≥ 3 days later to determine eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;
- Still borderline ≥ 3 days later: If no clinical suspicion of pregnancy and there are other pathological causes of borderline results, the borderline results will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study.

Urine Pregnancy Test

A urine pregnancy test will be performed for all females of childbearing potential at the Baseline Visit prior to the first dose of study drug. Additional urine pregnancy tests for female subjects of childbearing

potential will be performed at visits indicated in Section 2.1. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements.

If the urine pregnancy test (which is performed at the site) is negative, dosing may begin or continue. If the urine pregnancy test is positive, dosing should be withheld, and a serum pregnancy test performed. Pregnant subjects must discontinue from the study.

Follicle-Stimulating Hormone

Follicle-stimulating hormone (FSH) should be tested at Screening if the female subject is ≤ 55 years of age AND has had no menses for ≥ 12 months AND has no history of permanent surgical sterilization.

Hepatitis B and C Testing

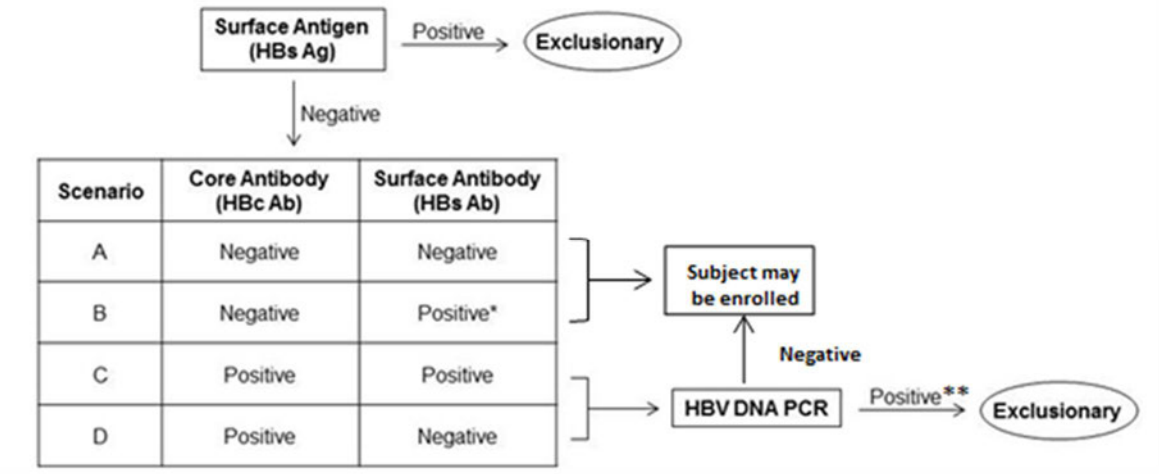
All subjects will be tested for the presence of the HBV and HCV at Screening (Figure 1). Subjects with HBs Ag positive [+] or detected sensitivity on the HBV-DNA PCR qualitative test) or hepatitis C (HCV RNA detectable in any subject with anti-HCV antibodies) will be excluded. Subjects who have been vaccinated against hepatitis B and are HBs Ab positive may be enrolled. If HBs Ag is negative but HBc Ab total is positive, HBV DNA will be quantified. If HBV DNA level is undetectable at Screening, the subject can participate in this trial.

Where mandated by local requirements, subjects with HBs Ab+ and/or HBc Ab+ and negative HBV DNA at screening should have HBV DNA PCR testing performed approximately every 12 weeks (q12w). HBV DNA PCR testing q12w is not necessary when the subject has a history of HBV vaccine and is HBs Ab+ and HBc Ab–.

Per regional requirements: for subjects with HBs Ab (+) and/or HBc Ab (+) at Screening, the HBV DNA PCR test should be performed as outlined in the Section 2.1. In cases where the recurrence of HBV-DNA is observed, the subject should be discontinued from the study drug. Retesting is not necessary for subjects that have a history of HBV vaccine and are HBs Ab (+).

If HCV antibodies are positive, HCV RNA will be quantified. If HCV RNA level is undetectable at Screening, the subject can participate in this trial.

Figure 1. Interpretation and Management of HBV Serologic Test Results



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

HIV Testing

HIV testing will be performed at Screening. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary. If a subject has a confirmed positive result, the investigator must discuss with the subject the potential implications to the subject's health and subject should receive or be referred for clinical care promptly. A subject will not be eligible for study participation if test results indicate a positive HIV infection. In case a screened subject has a confirmed positive HIV Ab test, Eligibility Criterion 13 should be selected in eCRF for documentation of screening failure.

Tuberculosis Screening

All subjects will be tested for TB by either the QuantiFERON-TB Gold Test (or IGRA equivalent) or a TB Skin Test (PPD) at the Screening visit and annually, or as specified in the study activity table.

At Screening and annually, or as specified in the study activity table, all subjects will be assessed for evidence of TB and TB risk factors. Subjects who have had a TB test performed within 90 days of the Screening Visit will not need to have the test repeated, provided all of the protocol required documentation is available at the site, and no new TB risk factors have been identified.

The QuantiFERON®-TB Gold test (or IGRA equivalent) will be supplied and analyzed by the central laboratory. (QuantiFERON-TB test is preferred over TB Skin Test.) Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

- If the **QuantiFERON-TB Gold Test (or IGRA equivalent) is NOT possible** or if both the QuantiFERON-TB Gold Test [or IGRA equivalent] and the PPD Skin Test are required per local guidelines, the PPD Skin Test will be performed according to standard clinical practice.

    - The PPD Skin Test should be read by a licensed healthcare professional between 48 and 72 hours after administration. A subject who does not return within 72 hours will need to be rescheduled for another skin test.
    - The reaction will be measured in millimeters (mm) of induration and induration ≥ 5 mm is considered a positive reaction. The absence of induration will be recorded as "0 mm," not "negative."
- If subject had a positive QuantiFERON-TB Gold (or IGRA equivalent) or PPD test at Screening, the test should not be repeated. Subjects who have had an ulcerating reaction to the TB Skin Test in the past should not be re-exposed and should not be tested by a PPD skin test.
- If the **TB screening test** (either PPD or the QuantiFERON-TB Gold test [or IGRA equivalent]) **is positive, or** if there is a **repeat indeterminate** QuantiFERON-TB Gold test (or IGRA equivalent) upon retesting, subjects may participate (or continue participation) in the study if **further work-up** (according to local practice/guidelines) establishes conclusively that the subject has **NO** evidence of active TB. If presence of **latent TB** is established, subjects should be treated (per local guidelines or by investigator judgement) with TB prophylaxis prior to receiving risankizumab or adalimumab and should be carefully monitored for any sign of TB reactivation.
- If the subject is diagnosed with **active TB**, the subject should not be randomized in the study and should not receive study drug. Subject will be considered as a **screening failure**.
- If the subject is diagnosed with **active TB** after being randomized, the subject should not receive any further study drug and follow the Week 52/Premature Discontinuation visit procedure (Section 2.1).
- If **TB (latent or active)** is diagnosed during the study, it is also necessary to report it as an AE in the source documents and eCRFs. In the case of a TB-related AE, a TB supplemental form that provides additional information will be completed by the investigator or designee.

Suspected Anaphylactic/Systemic Hypersensitivity Reaction Testing

Clinical criteria for diagnosing anaphylaxis are provided in Section 9.1. Blood tests to be conducted in the event of a suspected systemic hypersensitivity/ anaphylactic reaction:

- PK and ADA/NAb samples drawn in context of a suspected anaphylactic reaction are only collected if an anaphylactic reaction occurs while subject is at the study site.
    - A serum risankizumab, ADA, and NAb sample should be collected once within 24 hours.
- Serum tryptase: 15 minutes to 3 hours of symptom onset, and no later than 6 hours (as tryptase may remain elevated for 6 or more hours after the onset and therefore may still be informative if obtained after 3 hours).
- A follow-up tryptase level should be collected a minimum of 2 weeks after the recorded event or at the next study visit.
- Plasma histamine: 5 to 15 minutes of symptom onset, and no later than 1 hour.

Subjects will be closely monitored on site during study drug administration at all visits. A medical person qualified in the treatment of acute hypersensitivity reactions must be present during the injections. The duration of the post-dose safety surveillance is for 1 hour post-dose at all visits.

In the event that a suspected anaphylactic reaction occurs while the subject is not on site at the study clinic, please advise the treating facility to perform serum tryptase and histamine testing to help better understand and characterize the diagnosis and the Anaphylactic/Hypersensitivity Supplemental form will be completed.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible within 7 days from the scheduled visit.

3.13 Subject Withdrawal

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

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

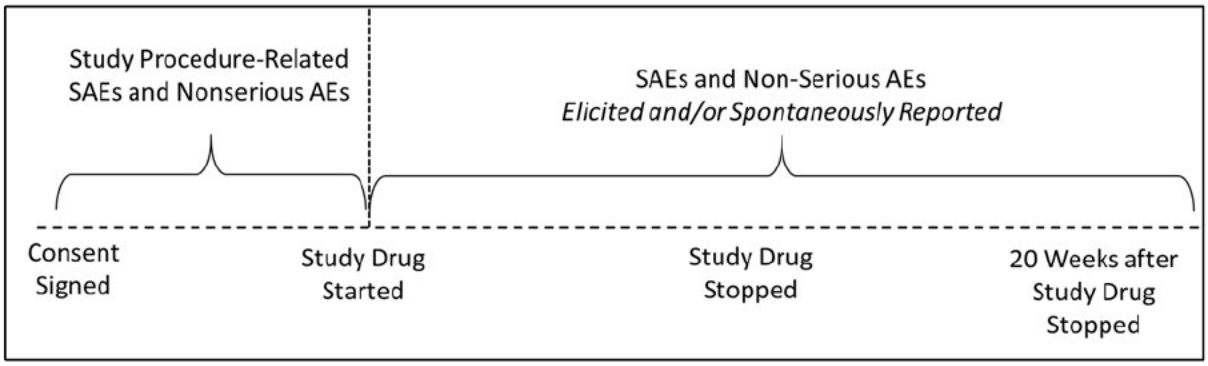
All serious and nonserious adverse events which could be related to study procedures, (e.g., infection at liver biopsy site, done during screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until the follow-up phone call (20 weeks [140 days] after the last dose of study drug), all nonserious and SAEs will be collected whether solicited or spontaneously reported by the subject.

The completion of the study for a subject is defined as one following:

- The date of the completed follow-up call (20 weeks after the last dose), as applicable
- The date of the Week 52 visit (for subjects who enter the optional CTE)

- The date of the last study visit (for subjects who prematurely discontinue and do not consent to and/or complete the follow-up call)
- The date of commercial risankizumab initiation (for subjects who initiate commercial risankizumab)

After the treatment-emergent AE window of 20 weeks (140 days) following the last dose of study drug, only spontaneously reported SAEs will be collected (nonserious AEs will not be collected).



4.2 Recording Data and Analyses of Safety Findings

An AE can result from use of the drug as stipulated in the protocol, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet criteria as specified in the protocol and/or they arere clinically significant and the investigator considers them to be AEs (as outlined in relevant sections).

Adverse events will be coded using the MedDRA. The number and percentage of subjects with TEAEs (i.e., any event that begins or worsens in severity after initiation of study drug through 20 weeks (140 days) after the last dose of study drug) will be tabulated by primary MedDRA SOC and preferred term. The tabulation of the number of subjects with treatment-emergent AEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade for the severity grade table and the most related for the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the EDC system. SAEs that occur prior to the site having access to the EDC system, or the EDC

system is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

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

For safety questions, contact the Immunology Safety Team at:

Immunology Safety Team
Email: SafetyManagement_Immunology@abbvie.com

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

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

Contact Information:

Office: [redacted]
Mobile:
Fax:
Email:

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

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for SUSAR reporting for the IMP in accordance with Directive 2001/20/EC.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

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).

SARS-CoV-2 infections should be captured as adverse events. If the event meets the criteria for a SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID -19 Supplemental Signs/ Symptoms
- COVID-19 Status Form

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

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

5.2 Treatment After End of Study

At the subject's last study visit, the investigator will discuss the appropriate subsequent treatment with the subject. If the subject and investigator determine continued therapy with risankizumab remains the best course of treatment, AbbVie will work with the investigator to evaluate a path for continued treatment in accordance with local regulations until such time when AbbVie treatment is commercially available and/or the subject has reasonable access to the treatment locally.

Eligible subjects will sign a separate consent to participate in the optional CTE. Safety assessments will be collected. Please refer to Section 2.3 and Section 7 of this Operations Manual, and Appendix D of protocol for CTE related activities.

5.3 Geo-Political Conflict in Ukraine and Surrounding Impacted Countries – Acceptable Protocol Modifications

The geo-political conflict in Ukraine and surrounding impacted regions may pose significant challenges in performing protocol-specified procedures. To ensure the safety of study participants and minimize risks to the integrity of the study, alternative methods for study assessments, activities, data collection, or study drug shipment may be implemented for impacted sites and study participants in these regions/countries, if needed. Protocol modifications employed due to the COVID-19 pandemic may be followed for study sites and participants impacted by the geo-political conflict in these regions as well.

Study Subject Information and Informed Consent

It is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional temporary verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with

local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

Study Drug Interruption or Discontinuation:

Delays in study drug dosing must be discussed with the sponsor medical contact, along with the possibility of premature discontinuation from study drug. The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Study Visits:

Study visits may be impacted and include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted, discuss the next steps with the sponsor medical contact.

Follow the instructions in Section 2 above for the COVID-19 Pandemic-Related Acceptable Protocol Modifications instructions.

Laboratory Tests, Exams, and Activities:

Subjects may have laboratory testing performed at a local laboratory, hospital, or other facility as needed. Follow the instructions in Section 3.12, Clinical Laboratory Tests, above for the COVID-19 Pandemic-Related Acceptable Protocol Modifications instructions on how to obtain local laboratory samples or if samples cannot be obtained.

6 STUDY DRUG

6.1 Treatments Administered

The study drugs risankizumab or matching placebo will be administered by a healthcare professional in the form of an SC injection at the visits listed in Section 2.1.

Risankizumab and matching placebo will be provided by AbbVie as solution for injection in PFS.

During the 16-week double-blind placebo-controlled treatment period (Period A), subjects will receive 1 injection SC of risankizumab (150 mg total dosage, for those randomized to risankizumab) or matching placebo (for those randomized to placebo) at Baseline/Day 1 and Week 4. During the 36-week open-label treatment period (Period B), subjects will receive 1 injection SC of risankizumab (150 mg total dosage) at Weeks 16, 28 and 40. Study drug administration instructions will be provided separately.

Study drug must not be dispensed without contacting the IRT system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the Treatment Period or at the Premature Discontinuation Visit, the site will contact the IRT system to provide visit date information.

6.2 Packaging and Labeling

Study drug packaged in pre-filled syringes will be provided in a double-blind fashion for the 16-week double-blind Placebo-Controlled Period (Period A). Risankizumab packaged in pre-filled syringes will be provided in open-blind fashion for the 36-week Open-Label Period (Period B) and the optional CTE.

Each kit will be labeled as required per local requirements. Each kit label will contain a unique kit number. This kit number is assigned to a subject via the IRT and encodes the appropriate study drug to be administered at the subjects corresponding study visit.

All labels must remain affixed to the study drug at all times and should never be removed for any reason. All blank spaces should be completed by site staff prior to dispensing to subject.

6.3 Storage and Disposition of Study Drug/Medical Device

Risankizumab (ABBV-066) and matching placebo kits must be kept protected from light in their original packaging, in a refrigerator between 2°C to 8°C (36°F to 46°F), within a secure limited access storage area, and in accordance with the recommended storage conditions on the label. Risankizumab and matching placebo must not be frozen at any time.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label.

All original study drug units (containing unused study drugs) will be returned to the sponsor (or designee) or destroyed on site. All destruction procedures will be according to instructions from the sponsor and according to local regulations following completion of drug accountability procedures.

Sites are responsible for maintaining the investigational study drug according to the storage conditions specified on the clinical label and monitoring for temperature excursions with the use of a calibrated continuous temperature monitoring device (for example, chart recorders and/or acceptable calibrated min/max thermometers) or continuous monitoring systems. Specific guidance on appropriate temperature monitoring and temperature excursions reporting requirements will be provided separately.

6.4 Method of Assigning Subjects to Treatment Groups

This study includes a 16-week randomized double-blind Placebo-Controlled Period during which subjects will receive risankizumab (150 mg SC) or matching placebo, followed by a 36-week Open-Label Period and an optional CTE Period during which subjects will receive risankizumab (150 mg SC). All eligible subjects will receive injections at all specified timepoints, which will consist of either active drug or matching placebo.

At the screening visit, all subjects will be assigned a unique subject number using the IRT. Subjects who meet the criteria for both Study-G and Study-S will first be randomized to either Study-G or Study-S with equal probability and then will be randomized to receive either risankizumab or placebo in a 1:1 ratio.

Randomization within Study-G and within Study-S will be stratified by weight (≤ 100 kg vs. >100 kg) and number of prior biologic therapies for psoriasis (0 vs. ≥ 1).

For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system.

Contact information and user guidelines for IRT use will be provided to each site.

6.5 Selection and Timing of Dose for Each Subject

Administration of study drug will be performed after all other visit procedures are completed (see Section 2.1), with the exception of post-dose monitoring for hypersensitivity reactions. Study site staff will administer 1 injection SC of double-blind study drug, either risankizumab (150 mg) or matching placebo at Baseline/Day 1 and Week 4. Study site staff will administer 1 injection SC of open-label risankizumab (150 mg) at Weeks 16, 28, and 40 (see Section 2.1).

7 Optional Continuous Treatment Extension (CTE)

Prior to the last study visit (Week 52), the investigator will discuss the appropriate subsequent treatment with the subject. If the subject and investigator determine continued therapy with risankizumab remains the best course of treatment, AbbVie will work with the investigator to evaluate a path for continued treatment in accordance with local regulations until such time when AbbVie treatment is commercially available and/or the subject has reasonable access to the treatment locally.

Eligible subjects will sign a separate consent to participate in optional CTE. Safety assessments will be collected (Section 2.3 and Appendix D of protocol).

Study drug will be provided as 150 mg (1 × 150 mg PFS) during CTE. Subjects who participate in the optional CTE will receive 1 injection SC of open-label risankizumab (150 mg) at Week 52 and every 12 weeks thereafter until the subject withdraws, risankizumab is commercially available, and/or the subject has reasonable access to the treatment locally or transitions to a separate CTTP OLE study.

8 References

1. Van Voorhees AS, Stein Gold L, Lebwohl M, et al. Efficacy and safety of apremilast in patients with moderate to severe plaque psoriasis of the scalp: Results of a phase 3b, multicenter, randomized, placebo-controlled, double-blind study. J Am Acad Dermatol. 2020;83(1):96-103.

9 Appendices

9.1 CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis[1] is highly likely when any one of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

   AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline.

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

Serious Systemic Hypersensitivity Reaction: A drug hypersensitivity reaction is an objectively reproducible clinical sign or symptom, or constellation of signs or symptoms, caused by exposure to a drug at a dose tolerated by normal individuals. A systemic hypersensitivity reaction is a hypersensitivity reaction that does not only occur at the local site of study drug administration (e.g., not an injection site reaction). A serious systemic hypersensitivity reaction is a systemic hypersensitivity reaction that fulfills criteria for a SAE.

In the event of an anaphylactic reaction, blood samples will be drawn per Section 3.12 after the onset of the reaction. This will include: histamine and tryptase. A blood sample for drug (serum risankizumab concentration), ADA, and NAb samples will be collected by venipuncture along with 1 hour blood samples for above assessments. The time that each blood sample (drug and ADA/NAb) is collected will

be recorded to the nearest minute. Separate instructions for the collection, handling, storage, and shipping of these labs will be provided outside of the study protocol.

1. Sampson HA, Muñoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

Document Approval

Study M23702 - A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis - Operations Manual for Protocol Version 2-0 - 07Jun2023

Version: 2.0 **Date:** 07-Jun-2023 **Company ID:** 20230607-0900f9f6862d7e5c-2.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	07-Jun-2023 17:57 UTC	Approver - Statistics
	07-Jun-2023 17:13 UTC	Approver

Document Approval

Study M23702 - A Phase 4 Multicenter, Randomized, Double-Blind Study of Risankizumab for the Treatment of Adult Subjects with Moderate to Severe Genital Psoriasis or Moderate to Severe Scalp Psoriasis - Protocol Version 2-0 - EU CT 2023-504154-35-00 - 07Jun2023

Version: 2.0 **Date:** 07-Jun-2023 **Company ID:** 20230607-0900f9f6862d7e5e-2.0-en

Signed by:	Date:	Meaning of Signature:
[redacted]	07-Jun-2023 17:57 UTC	Approver - Statistics
	07-Jun-2023 17:13 UTC	Approver