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Protocol for Study M15-999

Psoriasis: Phase 3 New Formulation Efficacy Study (1311.26)

VERSION:	4.0	DATE:	08 January 2020
SPONSOR:	AbbVie Inc.* 1 North Waukegan Road [redacted] North Chicago, IL 60064 USA	NUMBER OF SITES:	Approximately 45 sites
ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab	EUDRACT:	Not applicable

FULL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Risankizumab Using a New Formulation for the Treatment of Adult Subjects with Moderate to Severe Plaque Psoriasis

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

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1 SYNOPSIS

Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Risankizumab Using a New Formulation for the Treatment of Adult Subjects with Moderate to Severe Plaque Psoriasis	
Background and Rationale:	This study is being conducted to provide support for bridging of safety and efficacy of the 150 mg/mL formulation (1 × 150 mg injection) and the 90 mg/mL formulation (2 × 75 mg injections) that was used in the Phase 3 trials in psoriasis.
Objective(s) and Endpoint(s):	The primary objective of this study is to evaluate the efficacy, safety, and tolerability of risankizumab (150 mg/mL) administered by pre-filled syringe (PFS) for the treatment of adult patients with moderate to severe plaque psoriasis. Co-Primary Endpoints: • Proportion of subjects achieving PASI 90 (defined as at least 90% improvement from baseline in PASI) at Week 16 • Proportion of subjects achieving sPGA clear or almost clear at Week 16 Key Secondary Endpoints: The following ranked secondary endpoints will be tested between risankizumab and placebo in a hierarchical order only if the null hypotheses for the primary endpoints have been rejected. 1. Proportion of subjects achieving PASI 100 (defined as 100% improvement from baseline in PASI) at Week 16 2. Proportion of subjects achieving sPGA of clear at Week 16
Investigator(s):	Investigator information on file at AbbVie.
Study Site(s):	Approximately 45 sites in the United States
Study Population and Number of Subjects to be Enrolled:	Approximately 150 subjects with moderate to severe plaque psoriasis
Investigational Plan:	This is a Phase 3, randomized, double-blind, placebo-controlled study. Subjects will be randomized 2:1 to risankizumab 150 mg or placebo. The study includes a 30-day screening period with study visits at Week 0, 4, 16, and 28 with a subsequent follow up telephone call at approximately 20 weeks (140 days) after the last dose of study drug (Week 36). Study drug dosing will consist of 3 self-administered doses given subcutaneously on Weeks 0, 4, and 16. Subjects will be instructed at Week 0 (pre-injection) by the site staff on how to self-inject via the PFS. The Week 0 and Week 16 usability assessments will take place in the context of an observed assessment under the supervision of one site staff member. Site staff will assess potential use-related hazards with a predefined possible hazards checklist. Dosing on Week 4 will be self-administered at home. Efficacy assessments will be performed at each study visit (Weeks 0, 4, 16, and 28).

Key Eligibility Criteria:	Adult male or female subjects with stable moderate to severe plaque psoriasis, defined as ≥ 10% body surface area (BSA) psoriasis involvement, sPGA score of ≥ 3, and PASI ≥ 12 at Screening and baseline visit.
Study Drug and Duration of Treatment:	Subjects randomized to risankizumab: 150 mg (1 × 150 mg PFS) subcutaneous (SC) at Weeks 0, 4, and 16. Subject randomized to placebo: placebo injections at Weeks 0, 4, and 16.
Date of Protocol Synopsis:	08 January 2020

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2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Risankizumab is a fully humanized mAb of the immunoglobin G1 subclass directed towards interleukin (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.

Positive results were observed from 4 pivotal Phase 3 clinical trials that evaluated risankizumab compared with ustekinumab, placebo, and adalimumab for the treatment of patients with moderate to severe plaque psoriasis. Results from these pivotal studies demonstrated that risankizumab is highly effective for the treatment of psoriasis, meeting co-primary endpoints of achieving at least a 90% improvement in the Psoriasis Area and Severity Index (PASI 90) and static physician global assessment (sPGA) score of clear or almost clear (0 or 1) versus comparator or placebo at Week 16 across all 4 studies.[1]

In the pivotal Phase 3 clinical trials, the risankizumab 150-mg dose was administered with a 90-mg/mL formulation via 2 subcutaneous (SC) 75-mg injections delivered with a pre-filled syringe (PFS). To deliver a more patient-friendly experience, a new formulation was developed at 150 mg/mL that will enable delivery of the 150 mg dose with one SC injection. This study will evaluate the new 150-mg single injection formulation of risankizumab versus placebo using the same dosing regimen and delivery method (PFS) of risankizumab and same co-primary endpoints used in the Phase 3 pivotal trials.

Clinical Hypothesis

The primary null hypothesis of this study is that risankizumab is not different from placebo with respect to either achieving PASI 90 or achieving sPGA of clear or almost clear at Week 16.

2.2 Benefits and Risks to Subjects

In Phase 1 and Phase 2 studies of risankizumab in patients with psoriasis, the majority of subjects receiving risankizumab achieved 90% improvement of their disease, and risankizumab was well tolerated. As with many immune modulating agents, risankizumab may impair immune function resulting in a risk of infection. This will be monitored by collection of all adverse events (AEs) during the treatment and observation periods. In addition, subjects with active infection will not be included in the study.

Subjects with a positive QuantiFERON®-test or a positive Purified Protein Derivative (PPD) skin test for tuberculosis (TB) must fulfill entry criteria as specified in Section 5.1 of this protocol. Interleukin-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[2,3] There have been no cases of active tuberculosis, including no reactivation of tuberculosis in subjects diagnosed with latent TB, across the entire risankizumab development program. Across the Phase 3 psoriasis clinical studies, of the 72 subjects with latent TB who were concurrently treated with risankizumab and appropriate TB prophylaxis during the study, none developed active TB during a mean follow-up of 61 weeks on risankizumab. Of the 33 subjects in Study M15-992 with a

positive test for latent TB and who did not receive prophylaxis during the study, none developed active TB during the mean follow-up of 77 weeks on risankizumab.

Thus, low risk subjects with positive QuantiFERON testing do not need to be treated with anti-tuberculosis therapy prior to receiving risankizumab, but should be carefully monitored for any sign of TB reactivation. Absence of TB reactivation, despite not receiving anti-tuberculosis prophylaxis, will provide important information in humans as to whether TB testing is required prior to treatment with risankizumab.[4]

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. Preclinical data have moreover demonstrated beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models. However, there is not enough clinical information at this time to rule out a risk of cancer with risankizumab, but this risk is considered small.

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

Increases in major adverse cardiovascular events (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. While the likelihood of increased MACE is small, all suspected cardiovascular events (serious or nonserious) observed in this study will be adjudicated by an independent adjudication committee. An independent Cardiovascular Adjudication Committee will adjudicate all observed cardio- and cerebro-vascular events and will remain blinded to treatment allocation (Section 6.2).

Injection-site reactions to biologic therapies may be characterized by redness, swelling, or induration at the injection site. Manifestations of anaphylaxis may include pruritus, hypotension, swollen lips and tongue, abdominal pain, and respiratory distress. Both local and systemic hypersensitivity reactions and anaphylaxis are readily detectable, transient in nature, and manageable with standard medical treatment. Subjects will be closely monitored on site during study drug administration at Weeks 0 and 16. The duration of the post-drug-administration safety surveillance is 2 hours post-first dose and 1 hour postdose at Week 16. Subjects will be given instructions regarding management of signs and symptoms of anaphylaxis to be followed during home dosing at Week 4. An independent Anaphylaxis Adjudication Committee (AAC) will adjudicate suspected anaphylactic reactions. The AAC will remain blinded to treatment allocation (Section 6.3).

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development. 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.[1]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objective

The objective of this study is to evaluate the efficacy and safety of the 150 mg/mL formulation of risankizumab in a PFS compared with placebo for the treatment of adult subjects with moderate to severe plaque psoriasis.

3.2 Primary Endpoint

The co-primary endpoints of this study are:

1. Proportion of subjects achieving PASI 90 (defined as at least 90% improvement from baseline in PASI) at Week 16
2. Proportion of subjects achieving sPGA of clear or almost clear at Week 16.

3.3 Secondary Endpoints

Key Secondary Endpoints:

The following ranked secondary endpoints will be tested between risankizumab and placebo in a hierarchical order only if the null hypotheses for the primary endpoints have been rejected:

1. Proportion of subjects achieving PASI 100 (defined as 100% improvement from baseline in PASI) at Week 16
2. Proportion of subjects achieving sPGA of clear at Week 16.

3.4 Additional Endpoints

All primary and key secondary endpoints will be analyzed at all other visits collected. In addition, the following endpoints will be analyzed in all visits collected.

- Proportion of subjects achieving PASI 50/75
- Change and percent change from baseline in PASI

The following usability endpoints will also be summarized, for each treatment arm, at all visits collected.

- Proportion of subjects with an observer rating of successful subject self-administration, defined as any subjects who successfully completed the sequence of 3 critical steps in the Instructions for Use (IFU) without errors to administer study drug
- Proportion of subjects who experienced no potential hazards as measured by an observer
- Subject rating of acceptability using the Self-Injection Assessment Questionnaire (SIAQ)

3.5 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry) as measures of safety and tolerability.

3.6 Pharmacokinetic Endpoints

Serum risankizumab concentrations and anti-drug antibodies (ADA), and neutralizing antibodies (nAb) will be determined at the visits indicated in the Study Activities Table (Appendix D). Serum risankizumab concentrations will be summarized at Week 16, using descriptive statistics. ADA titers will be tabulated for each subject by regimen at the respective study visits. The number and percentage of subjects with ADA and NAb by regimen will be calculated.

3.7 Biomarker Research

Optional blood samples for exploratory biomarker research will be collected as described in the Study Activities Table (Appendix D). The objective of biomarker research is to analyze samples that will help understand psoriasis or related conditions and the subject's response to risankizumab. Prognostic, surrogate, predictive and pharmacodynamics biomarkers signatures may be investigated. Samples for different applications, potentially including but not limited to pharmacogenetic, epigenetic, transcriptomic, proteomic, metabolomic, metagenomic, phenotypic, functional and targeted investigations will be collected at various time points. Assessments may include but may not be limited to nucleic acids, proteins, metabolites, lipids, or peripheral blood mononuclear cells (PBMC). AbbVie (or people or companies working with AbbVie) will store the biomarker exploratory biomarker samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on risankizumab (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion.

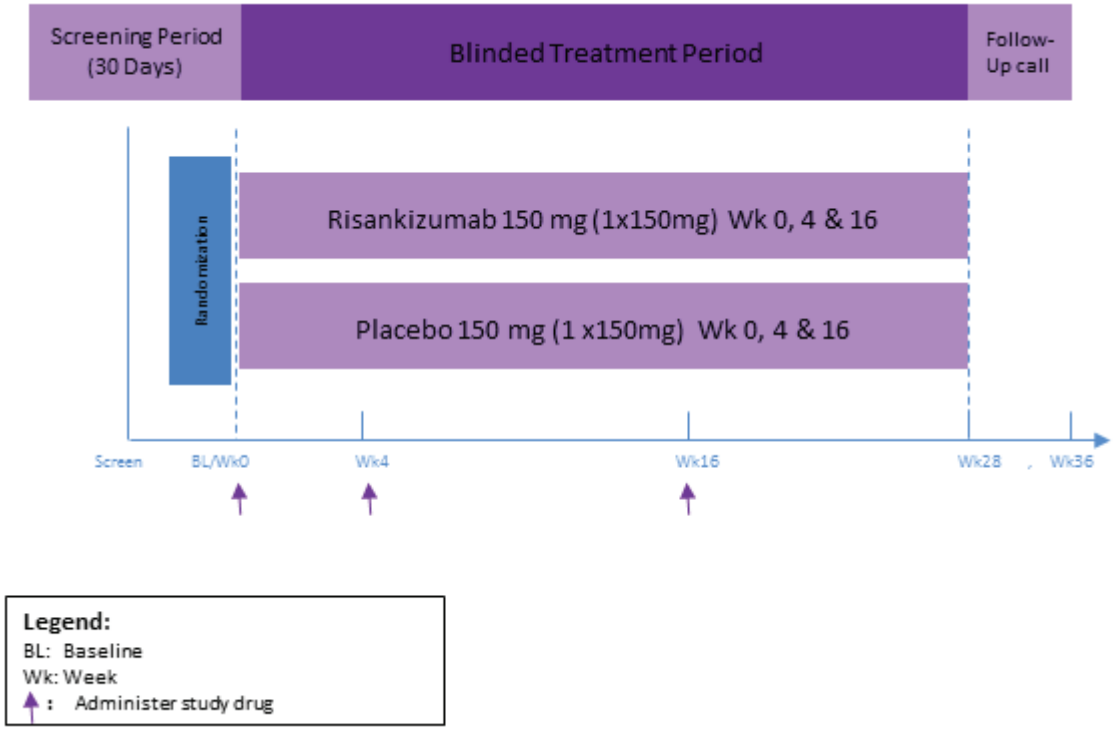
4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, parallel group study that will evaluate the safety and efficacy of risankizumab 150 mg/mL formulation in PFS in patients with moderate to severe plaque psoriasis. The study includes a 30-day screening period, a 28-week treatment period with study visits at Weeks 0, 4, 16 and 28, and a subsequent follow up telephone call at approximately 20 weeks after the last dose of study drug. Study drug dosing will consist of 3 self-administered doses given subcutaneously on Weeks 0, 4, and 16. Dosing on Week 4 will be self-administered at home. Efficacy and safety will be assessed throughout at the Visits described in Study Activities Table (Appendix D).

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic for Protocol M15-999



If an exclusionary laboratory result is obtained at the initial Screening Visit, one re-test of that particular test is allowed without repeating all other laboratory tests within the 30 day screening window.

Subjects who initially do not meet all eligibility criteria for the study may be permitted to repeat the Screening Visit one time following re-consent. The subject must meet all eligibility criteria on the repeat Screening Visit in order to qualify for the study. The repeat screening procedure is:

- A repeat of all screening procedures is needed at this repeat Screening Visit with these exceptions:
  - If the subject had a complete initial screening evaluation, including the assessment of an Interferon-Gamma Release Assay (IGRA; QuantiFERON Tuberculosis [TB] Gold In Tube test) or a PPD test (or equivalent), and electrocardiogram (ECG), these tests will not be required to be repeated at the repeat Screening Visit.
- There is no minimum period of time a subject must wait prior to the repeat Screening Visit.

Subjects will be instructed at Week 0 (pre-injection) by the site staff on how to self-inject via the PFS. Self-injections will be administered into one of the following body regions, changing the injection site if possible at each timepoint: right thigh, left thigh, right abdominal area, left abdominal area.

At Week 0 (after training) and Week 16, subjects will be instructed by site staff to refer to the IFU and proceed with self-injection. At the Week 4 Visit, subjects will be sent home with one PFS to be self-administered within 24 hours of the Week 4 Visit with instructions from the site staff to use the IFU.

The Week 0 and Week 16 usability assessments will take place in the context of an observed assessment under the supervision of one site staff member. Each assessment is to be conducted on a 1:1 basis. The observer (site staff member) will measure and evaluate the subject's usability of the PFS using the self-injection assessment checklist as they observe the injections at Week 0 and Week 16. Site staff will also assess potential hazards with a predefined potential use hazards checklist for self-injections at Week 0 and Week 16. During the self-injection, if a subject is not acting in a safe or reasonable manner, the observing site staff member is required to intervene. Use errors, which could pose a risk to the health or well-being of a subject, require the observing staff member to ask the subject to pause, to point out the use error, and to decide whether to terminate the self-injection. If the observing site staff judges the self-injection can continue, they should correct the subject's usage of the product and notify the subject to recommence at the same point. These errors will be documented from the list of potential use hazards. Any risk of a health and safety incident could result in termination of the self-injection at the discretion of the observing site staff member.

Subject-derived usability assessment will measure acceptability of the PFS using the SIAQ. Subjects will fill out the SIAQ PRE module immediately before the first self-injection at Week 0 and the POST module 20 to 40 minutes following self-injections at Week 0, Week 4, and Week 16. These modules are to be completed by subjects while alone in a quiet environment. The subject's self-rated assessment of each item of the SIAQ, will be transformed during analysis to scores ranging from 0 (worst experience) to 10 (best experience).

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 measurements in this study are standard for assessing disease activity in subjects with plaque psoriasis. All clinical and laboratory procedures in this study are standard and generally accepted.

The SIAQ evaluates patients' experiences with self-injection and enables assessment of their success in giving self-injections and the likelihood of them adhering to a self-injection regimen.[5] It has been validated in patients with rheumatoid arthritis and measured in patients with psoriasis and psoriatic arthritis.[6-8]

Suitability of Subject Population

Subjects who have moderate to severe plaque psoriasis, defined as a PASI score ≥ 12, body surface area (BSA) involvement ≥ 10%, and sPGA ≥ 3 who are candidates for systemic therapy are eligible for this

study. Criteria such as laboratory values (minimums and maximums) and subject history (absence of chronic infections such as human immunodeficiency virus [HIV], hepatitis B or C, and other exclusions) are specified to ensure subject safety and to allow adequate evaluation of the study drug. The study population selected reflects a standard population for moderate to severe psoriasis trials with new treatment intervention.

Selection of Doses in the Study

The risankizumab dosing regimen selected for the current study (i.e., 150 mg SC at Weeks 0, 4, and 16) is the same as used in the risankizumab pivotal Phase 3 studies in subjects with moderate to severe chronic plaque psoriasis. Risankizumab has been found to be safe and well tolerated with no dose limiting safety findings following single- or multiple-dose administration at doses up to 360 mg SC or 1800 mg intravenously in Phase 1 to 3 clinical studies.[1]

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

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

Consent

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

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old.
- 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase < 2 × upper limit of normal (ULN);
  - Serum alanine transaminase < 2 × ULN;
  - Serum direct bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to a confirmed diagnosis of Gilbert syndrome;
  - Total white blood cell count > 3,000/µL;
  - Absolute neutrophil count > 1,500/µL;
  - Platelet count > 100,000/µL;
  - Hemoglobin > 8 g/dL.
- 4. Are willing or able to comply with procedures required in this protocol including self-administration of study drug.

Disease Activity

- 5. Diagnosis of chronic plaque psoriasis for at least 6 months before the baseline visit.
- 6. Subject meets the following disease activity criteria:
  - Stable moderate to severe chronic plaque psoriasis, defined as ≥ 10% BSA psoriasis involvement, sPGA score of ≥ 3, and PASI ≥ 12 at Screening and baseline visit;
  - Candidate for systemic therapy as assessed by the investigator;

Subject History

- 7. No history of:
  - Erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis;
  - Active skin disease other than psoriasis that could interfere with the assessment of psoriasis;
  - Chronic infections including human immunodeficiency virus, viral hepatitis (hepatitis B, hepatitis C), and/or active TB. Subjects with a positive QuantiFERON®-TB/purified protein derivative (tuberculin) test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB. If presence of latent TB is established, subjects are not required to be treated with prophylactic anti-TB therapy prior to or during the study, if the subject is considered low risk for reactivation per investigator judgment.
  - Active systemic infection during the last 2 weeks prior to baseline visit (exception: common cold), as assessed by the investigator.
- 8. No history of any documented 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.
- 9. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 10. No history of underlying medical diseases or problems including but not limited to the following:
  - Subject has been a previous recipient of a solid organ transplant;
  - Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than psoriasis, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and electrocardiogram), or laboratory value at the screening visit outside the given range that, in the opinion of the investigator, is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data;
- 11. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.

- 12. No major surgery performed within 12 weeks prior to randomization or planned to be performed during the conduct of the trial (e.g., hip replacement, aneurysm removal, stomach ligation) as assessed by the Investigator.

Contraception

- 13. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline and following visits (as outlined in the Study Activity Table of this protocol) prior to the first dose of study drug.
- 14. Female subjects must be postmenopausal OR permanently surgically sterile OR for a woman of child bearing potential be practicing at least one protocol-specified method of birth control (Section 5.2) that is effective from the baseline visit through at least 140 days (20 weeks) after the last dose of study drug
- 15. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or for approximately 140 days (20 weeks) after the last dose of study drug.
- 16. Additional local requirements may apply.

Concomitant Medications

- 17. No previous exposure to risankizumab.
- 18. No use of any restricted medication as specified in the prohibited medications/therapy section or any drug considered likely to interfere with the safe conduct of the study.
- 19. 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 is currently enrolled in another clinical study.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

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

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

- Females who have not experienced menarche (at least one menstrual period)

- Females of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 140 days 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).

If required per local guidelines, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence)

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

5.3 Prohibited Medications and Therapy

In addition to the medications listed in the eligibility criteria, the following concomitant psoriasis treatments are prohibited within the specified timeframe prior to baseline visit and throughout the study.

1. Any systemic biologic to treat psoriasis:
   - Adalimumab, infliximab or biosimilar versions within 12 weeks;
   - Etanercept or biosimilar versions within 6 weeks;
   - Ixekizumab, brodalumab, secukinumab or other IL-17 inhibitors within 16 weeks;
   - Ustekinumab, efalizumab, guselkumab, tildrakizumab, mirikizumab, or other IL-23 inhibitors within 24 weeks.

2. Systemic non-biologic therapy for psoriasis, including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, apremilast, and fumaric acid derivatives within 4 weeks.
3. Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments within 4 weeks.
4. Topical psoriasis treatments, including but not limited to corticosteroids, anthralin, calcipotriene, 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 D3 analogues) within 2 weeks.
    - Exception: Subjects are allowed to use bland (containing no psoriasis treatment) emollients and shampoos and/or low potency topical corticosteroids (US Class 6 - 7) on the palms, soles, face, inframammary area, and groin only.
5. Treatment with an experimental non-biologic for psoriasis within 4 weeks or 5 half-lives of the drug (whichever is longer).
6. Treatment with an experimental biologic for psoriasis within 12 weeks or 5 half-lives of the drug (whichever is longer).
7. Receipt of any live vaccine within 6 weeks or is expected to need live vaccination during study participation, including at least 20 weeks after the last dose of study drug.

Live or attenuated vaccines are NOT allowed during the study and for 140 days after the last dose of study drug. Examples of such vaccines include but are not limited to the following:

- Live attenuated influenza
- Herpes zoster (i.e., Zostavax®)
- Rotavirus
- Varicella (chicken pox)
- Measles-mumps-rubella or measles mumps rubella varicella
- Oral polio vaccine
- Smallpox
- Yellow fever
- Bacille Calmette-Guérin
- Oral typhoid

Vaccines that are inactivated, toxoid, or biosynthetic may be administered at any time without restrictions. Examples of common vaccines that meet these criteria include but are not limited to: injectable influenza vaccine, pneumococcal, pertussis (Tdap), and Shingrix®.

5.4 Prior and Concomitant Therapy

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation are permissible. All concomitant medications should be carefully evaluated by the investigator, and the AbbVie clinical monitor should be contacted when there are questions regarding concomitant medications.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 4 weeks 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.

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:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director (TA MD) (as applicable).
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD, after consultation with the Investigator.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk as determined by the AbbVie TA MD.
- Subject develops active TB at any time during the study.
- The subject becomes pregnant while on study drug.
- Subject is diagnosed with a malignancy. Exception: localized non-melanoma skin cancer or carcinoma in-situ of the cervix, where discontinuation is at the discretion of the Investigator.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk

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

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (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, a 20-week (140 days) follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse event (SAE) have been resolved.

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

5.7 Study Drug

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

Table 1. Description of Study Drug and Placebo

Study Drug	Dosage Form	Strength	Route of Administration
Risankizumab (ABBV-066)	Solution for injection in PFS	150 mg/1.0 mL	SC injection
Placebo for Risankizumab	Solution for injection in PFS	Not applicable	SC injection

PFS = pre-filled syringe; SC = subcutaneous

Blinded risankizumab or matching placebo will be packaged in quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Risankizumab or matching placebo kits will be kept protected from light in their original packaging, in a refrigerator between 2°C to 8°C (36°F to 46°F), and within a secure limited access storage area, and in accordance with the recommended storage conditions on the label. Risankizumab or matching placebo must not be frozen at any time. At the Week 4 visit, subjects will be provided with a cooler bag and ice pack to maintain adequate storage temperature of the study drug kit.

Upon receipt, study drug should be stored as specified on the label 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 interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit.

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

5.8 Randomization/Drug Assignment

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

Subjects will be randomized in a 2:1 ratio to risankizumab 150 mg or placebo. Stratification is not planned for this study.

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 placebo PFS provided for the study will be identical in appearance.

In the event of a medical emergency in which the investigator believes that knowledge of study drug treatment is required, reasonable efforts must be made to contact the AbbVie emergency contact prior to breaking the blind, as long as it does not compromise subject safety. However, if an urgent therapeutic intervention is necessary which warrants breaking the blind prior to contacting the AbbVie emergency contact, the investigator can directly access the IRT system to break the blind without AbbVie agreement. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the investigator is responsible for notifying independent ethics committee (IEC)/independent review board (IRB), regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

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

Product Complaint

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

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

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

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

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

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

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.

Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All adverse events reported from the time of study drug administration until 30 days or 5 half-lives after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected unexpected serious adverse reactions (SUSAR) reporting for the Investigational Medicinal Product in accordance with global and local requirements.

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

If AEs in any of the following areas of safety interest are reported during the study, then the corresponding supplemental report must be completed (Table 2).

Table 2. Adverse Events that Require Supplemental Reports

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

AE = Adverse event; Cardiac = Cardiovascular; eCRF = electronic case report form; SAE = Serious adverse event; TB = tuberculosis

Adverse Event Severity and Relationship to Study Drug

AEs must be graded to the 5 criteria as described in the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5,[9] which can be accessed at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

If no specific criteria per CTCAE V. 5.0 guidelines are available for the reported event, the event should be graded per the investigator's judgment:

- Grade 1 (Mild); asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 (Moderate); minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
- Grade 3 (Severe); medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

- Grade 4 (Severe); Life-threatening consequences; urgent intervention indicated.
- Grade 5 (Severe); Death related to AE.

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day 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

An independent adjudication committee 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 Adjudication Committee Charter. Dedicated eCRFs will be used as outlined in Table 2.

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

6.3 Anaphylaxis Adjudication Committee

While no concerns with 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 eCRF will be used to collect information pertinent to the events (Table 2). In addition, the site may be contacted for additional source documentation.

If a suspected systemic hypersensitivity reaction occurs at the investigative site, subjects should be tested for tryptase and histamine levels. 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.

6.4 Product Complaint

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

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

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The primary analysis for all primary and secondary efficacy endpoints will occur after all ongoing subjects complete the Week 16 Visit. This will be the only and final analysis for the primary and secondary efficacy endpoints at Week 16.

The statistical analysis will be described and fully documented in the Statistical Analysis Plan (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 intent-to-treat (ITT) Population includes all randomized subjects. The ITT Population will be used for all efficacy analyses. Subjects will be analyzed according to treatment as randomized.

The Safety Analysis Population consists of all subjects who received at least 1 dose of study drug. For the safety analysis, subjects will be analyzed according to the first dose of study drug (risankizumab or placebo) that the subject received.

7.3 Statistical Analyses for Efficacy

Analysis of the primary and secondary efficacy endpoints will be conducted on the ITT Population based on treatment as randomized.

Overall type-I error will be controlled by testing the co-primary endpoints, followed by the ranked secondary endpoints, in a hierarchical order as described in Section 3.2 and Section 3.3.

Comparison of the primary and secondary efficacy endpoints will be made between the risankizumab and the placebo treatment groups using the Chi-square test.

Non-Responder Imputation will be used for categorical endpoints. Mixed-effect Model Repeat Measurements will be used for continuous endpoints.

Usability endpoints will be analyzed by as-observed cases.

Additional details on the primary and other efficacy analyses are provided in the SAP.

Sample Size Estimation

This study is designed to enroll approximately 150 subjects, randomized in a 2:1 ratio to risankizumab or placebo. Assuming the response rates at Week 16 to be 74% for the risankizumab arm and 3% for the placebo arm for PASI 90, and 85% for the risankizumab arm and 7% for the placebo arm for sPGA of clear or almost clear, the study will provide more than 95% power for each of the two co-primary efficacy endpoints (an overall power of more than 90%).

7.4 Statistical Analyses for Safety

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

7.5 Analyses of PK and Immunogenicity

Serum risankizumab concentrations will be summarized at Week 16 using descriptive statistics. For immunogenicity assessment, the number and percentage of subjects with ADA and NAb by regimen will be calculated. In addition, ADA titers will be tabulated for each subject by regimen at the respective study visits.

8 ETHICS

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

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

8.2 Ethical Conduct of the Study

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

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

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

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last's subject's last visit.

12 REFERENCES

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

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAC	anaphylaxis adjudication committee
ADA	antidrug antibody
AE	Adverse event
BSA	body surface area
ECG	electrocardiogram
eCRF	electronic case report form
GCP	good clinical practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IFU	Instructions for Use
IL	interleukin
IRB	Institutional review board
IRT	Interactive response technology
ITT	intent-to-treat
mAb	monoclonal antibody
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
NAb	neutralizing antibody
PASI	Psoriasis Area Severity Index
PBMC	peripheral blood mononuclear cell
PFS	pre-filled syringe
PK	Pharmacokinetic(s)
PPD	purified protein derivative
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	subcutaneous
SIAQ	Self-Injection Assessment Questionnaire
sPGA	static physician global assessment
SUSAR	Suspected unexpected serious adverse reactions
TA MD	Therapeutic Area Medical Director

TB	tuberculosis
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M15-999: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of Risankizumab Using a New Formulation for the Treatment of Adult Subjects with Moderate to Severe Plaque Psoriasis

Protocol Date: 08 January 2020

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

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

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Immunology Development
		Immunology Development
		Clinical Program Development
		Data and Statistical Sciences
		Clinical Pharmacology
		Data and Statistical Sciences
		Medical Writing (Protocol Author)

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities the subject encounters. The individual activities are described in detail in the **Operations Manual** (Appendix F).

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Table 3. Study Activity Schedule

Activity	Screening	Baseline/Week 0	Week 4	Week 16	Week 28/PD	Week 36 Follow Up Call
	Day –30 to Day –1	Day 1	Day 28	Day 112	Day 196	Day 252
INTERVIEWS & QUESTIONNAIRES						
Informed consent	P					
Eligibility criteria	P	P				
Medical/surgical history	P	P				
Demographics	P					
Alcohol and nicotine use	P					
Psoriasis and psoriatic arthritis history	P					
Prior/concomitant therapy	P	P	P	P	P	P
Adverse event assessment	P	P	P	P	P	P
LOCAL LABS & EXAMS						
12-lead ECG	✓					
Physical examination	✓	✓		✓	✓	
Height (screening only) and weight	✓			✓	✓	
Vital signs	✓	✓	✓	✓	✓	
Self-injection assessment (SIAQ) predose		✓				
SIAQ 20 to 40 minutes postdose		✓	✓	✓		

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Activity	Screening	Baseline/Week 0	Week 4	Week 16	Week 28/PD	Week 36 Follow Up Call
	Day –30 to Day –1	Day 1	Day 28	Day 112	Day 196	Day 252
Observer-rated assessments: - Usability assessment - Use hazard assessments		✓		✓		
PASI, sPGA	✓	✓	✓	✓	✓	
BSA	✓	✓				
PPD skin test for TB (if required)	✓					
Urine pregnancy test (females of child-bearing potential only)		✓	✓	✓	✓	
CENTRAL LABS						
Serum pregnancy/ follicle-stimulating hormone test (females of child-bearing potential only)	P					
Total cholesterol, HDL-C, LDL-C, triglycerides		P			P	
TB screening	P					
Chemistry and hematology	P	P	P	P	P	
HIV, Hepatitis B and C	P					
Urinalysis	P	P				
Blood samples for risankizumab PK assay				P		
Blood sample for risankizumab ADA/nAb assay		P	P	P		
Optional RNA biomarker blood samples		P	P		P	
Optional PBMC blood samples		P			P	

Activity	Screening	Baseline/Week 0	Week 4	Week 16	Week 28/PD	Week 36 Follow Up Call
	Day –30 to Day –1	Day 1	Day 28	Day 112	Day 196	Day 252
℞ TREATMENT						
Randomization/drug assignment		✓				
Dispense study drug		✓	✓	✓		
Training subject on self-administration		✓				
Subject to self-administer study drug in office		✓		✓		
Subject to self-administer study drug at home			✓			

ADA = antidrug antibody; BSA = body surface area; ECG = electrocardiogram; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; NAb = neutralizing antibody; PASI = Psoriasis Area Severity Index; PBMC = peripheral blood mononuclear cell; PK = Pharmacokinetic(s); PPD = purified protein derivative (tuberculin); RNA = ribonucleic acid; SIAQ = Self-Injection Assessment Questionnaire; sPGA = static physician global assessment; TB = tuberculosis

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	27 November 2018
Version 2.0	07 January 2019
Version 3.0	11 March 2019

The purpose of this amendment was to:

- Update ranking of Secondary Endpoints
- Add additional detail around controlling for type-I error
- Update Sponsor/emergency medical contact
- Update protocol signatories

APPENDIX F. OPERATIONS MANUAL