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Protocol for Study M19-164

Psoriasis: Risankizumab for Adult Subjects with Moderate to Severe Plaque Psoriasis Following Suboptimal Response to Secukinumab or Ixekizumab

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FULL TITLE: A Phase 3b, multicenter, interventional, open-label study of adult subjects with moderate to severe plaque psoriasis who have a suboptimal response to secukinumab or ixekizumab and are switched to risankizumab.

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

SPONSOR/ EMERGENCY MEDICAL CONTACT:*

Sponsor contact for all non-emergency issues:
[redacted] PhD
Scientific Director Dermatology
Global Medical Affairs
AbbVie
Mainzer Strasse 81
65189 Wiesbaden, Germany

Cell: [redacted]
EMAIL: [redacted]

Sponsor emergency medical contact:
[redacted] MD
Global TA Lead, Global Medical Affairs (GMA)
GMA Biotherapeutics Immunology
AbbVie
Montehiedra Office Center
9615 Los Romeros Avenue, Suite 600
San Juan, Puerto Rico 00926-7038

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

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

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1 SYNOPSIS

Title: A Phase 3b, multicenter, interventional, open-label study of adult subjects with moderate to severe plaque psoriasis who have a suboptimal response to secukinumab or ixekizumab and are switched to risankizumab	
Background and Rationale:	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. While the majority of mild psoriasis subjects are managed with topical therapies, those with moderate or severe and/or refractory disease usually require phototherapy and/or systemic therapy. Risankizumab is approved for use in moderate to severe chronic plaque psoriasis in the United States (US), the European Union (EU), Japan, Canada, Brazil, and Switzerland, with additional global reviews of marketing applications ongoing. Clinical studies are ongoing evaluating risankizumab for use in the treatment of Crohn's disease, ulcerative colitis, psoriatic arthritis, hidradenitis suppurativa, and atopic dermatitis. Risankizumab is a humanized monoclonal antibody (mAb) of the immunoglobin (Ig) G1 subclass directed towards the p19 subunit of IL-23. Risankizumab binds with high affinity to human IL-23. Today there are multiple treatments with different modes of action available to treat plaque psoriasis. The risankizumab clinical program assessed the efficacy versus placebo and adalimumab and ustekinumab up to 1 year. Risankizumab showed high levels of sustained clearance in these clinical trials. A head-to head randomized controlled trial is ongoing to compare risankizumab versus secukinumab up to 1 year. Ixekizumab is another approved IL-17A inhibitor. No head-to-head data are currently available. Secukinumab and ixekizumab are anti-IL-17A antibodies. Secukinumab was approved by the United States Food and Drug Administration (FDA) for the treatment of psoriasis in 2015 and from the European Medicines Agency (EMA) for the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis in 2015. Ixekizumab was approved by the United States Food and Drug Administration (FDA) and from EMA for the treatment of psoriasis in 2016. Important evidence is lacking on the efficacy and safety of subjects with psoriasis who have suboptimal response on secukinumab or ixekizumab switching to risankizumab and the impact this switch has on subject's quality of life and treatment satisfaction. This study aims to evaluate whether those suboptimal responders on secukinumab or ixekizumab benefit significantly from a switch to risankizumab with regards to skin symptoms, as well as quality of life and psoriasis symptoms.
Objective and Endpoints:	The objective of this study is to evaluate the efficacy and safety of switching to risankizumab for subjects with moderate to severe plaque psoriasis who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a suboptimal

	response. Suboptimal response is defined as a static Physician's Global Assessment (sPGA) 2 or 3, and a Body Surface Area (BSA) 3% - < 10% after at least 6 months treatment with secukinumab or ixekizumab. The primary endpoint is the proportion of subjects achieving sPGA 0/1 at Week 16. The secondary endpoints are: • The proportion of subjects achieving a static Physician Global Assessment clear response (sPGA 0) at Week 16; • The proportion of subjects achieving a Dermatology Life Quality Index (DLQI) 0 or 1 at Week 16; • The proportion of subjects achieving a Psoriasis Symptoms Scale (PSS) 0 at Week 16; • The proportion of subjects achieving a sPGA 0/1 at Week 52; • The proportion of subjects achieving a sPGA 0 at Week 52; • The proportion of subjects achieving a DLQI 0/1 at Week 52; • The proportion of subjects achieving a PSS 0 at Week 52; • Time to achieve sPGA 0/1; • Time to achieve sPGA 0.
Investigator(s):	Multi-center
Study Site(s):	United States, Germany, Italy, Spain, United Kingdom, Israel, Australia, and Taiwan.
Study Population and Number of Subjects to be Enrolled:	Adult subjects with moderate to severe plaque psoriasis who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a sub-optimal response. Suboptimal response is defined as a sPGA 2 or 3 and a BSA 3% - < 10% after at least 6 months treatment with secukinumab or ixekizumab. Approximately 250 subjects are expected to be enrolled.
Investigational Plan:	This is a Phase 3b, global, interventional, multicenter, open-label, single-arm study examining the effect of risankizumab 150 mg administered at Week 0, Week 4, and then every 12 weeks (q12w) thereafter in adult subjects with moderate to severe plaque psoriasis who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a sub-optimal response. The study duration will be up to 64 weeks. The study comprises a 30-day Screening Period, a 52-week open-label study period, and a 20-week follow-up period (after Week 40). The 52-week open label period consists of an initial phase (Weeks 0 - 16) and a maintenance phase (Weeks 16 - 52). The follow-up period consists of a follow-up phone call 20 weeks after the last injection of study drug (at Week 40).
Key Eligibility Criteria:	Subject must be ≥ 18 years old with a previous diagnosis of moderate to severe chronic plaque psoriasis for which they are currently being treated with secukinumab or ixekizumab according to the respective label. Subjects will have 3% - < 10% BSA psoriasis involvement, sPGA

	score of 2 or 3 at Screening and Baseline Visit; and must be eligible for continued biologic therapy as assessed by the investigator.
Study Drug and Duration of Treatment:	Participants will receive 2 injections of risankizumab 75 mg (150 mg total dosage) subcutaneously at Weeks 0 and 4, and then q12w until the last dose at Week 40.
Date of Protocol Synopsis:	27 January 2021

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] It is increasingly recognized that 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] While the majority of mild psoriasis patients are managed with topical therapies, those with moderate or severe and/or refractory disease usually require phototherapy and/or systemic therapy.

Oral systemic agents provide modest efficacy; therefore, patients are increasingly being treated with biologic agents, such as Tumor Necrosis Factor (TNF)-alpha inhibitors (etanercept or adalimumab), the interleukin (IL)-12/23 inhibitor (ustekinumab),[4] and IL-17A inhibitors (secukinumab and ixekizumab). Ustekinumab, a monoclonal antibody (mAb) targeting the common p40 subunit of IL-12 and IL-23, was approved for the treatment of psoriasis and psoriatic arthritis (PsA) in 2009, and for Crohn's disease in 2016.

Secukinumab and ixekizumab are anti-IL-17A antibodies and have been approved by the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of psoriasis in 2015 and 2016, respectively. In addition, other recently approved systemic agents for the treatment of psoriasis include an IL-17RA inhibitor (brodalumab), IL-23p19 inhibitors, guselkumab and tildrakizumab. Mirikizumab, another IL-23 inhibitor, is still under investigation.

While the clinical efficacy of ustekinumab indicates a role for both IL-12 and IL-23 in the pathogenesis of psoriasis,[5] more recent data suggest that IL-23 is disproportionately involved in the maintenance of chronic psoriasis.[6] IL-23 is thought to be involved in the pathophysiology of psoriasis via induction and maintenance of Th17 type cells, and other IL-23 responsive cells. This is supported by recent clinical data indicating that monoclonal antibodies that block IL-17A (the cytokine produced by Th17 cells), IL-17RA, and direct blockade of IL-23 with IL-23p19 inhibitors, have high efficacy in psoriasis.[5,7-9]

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.[5,7-9]

Risankizumab is approved for use in moderate to severe chronic plaque psoriasis in the United States (US), the European Union (EU), Japan, Canada, Brazil, and Switzerland, with additional global reviews of marketing applications ongoing. Clinical studies are ongoing evaluating risankizumab for use in the treatment of Crohn's disease, ulcerative colitis, PsA, hidradenitis suppurativa, and atopic dermatitis.

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

Today there are multiple treatments with different modes of action available to treat plaque psoriasis efficiently. The risankizumab clinical program assessed the efficacy versus placebo and other commonly used biological therapies such as adalimumab and ustekinumab up to 1 year. Risankizumab showed high levels of sustained clearance in these clinical trials. A head-to head randomized controlled trial (RCT) is ongoing to compare risankizumab versus secukinumab up to 1 year. Ixekizumab is another approved IL-17A inhibitor. No head-to-head data are currently available.

Important evidence is lacking on the efficacy and safety of patients with suboptimal response on secukinumab or ixekizumab switching to risankizumab and the impact this switch has on patient's quality of life and treatment satisfaction.

This study aims to evaluate whether those suboptimal responders on secukinumab or ixekizumab benefit significantly from a switch to risankizumab with regards to skin symptoms, as well as quality of life and psoriasis symptoms.

Clinical Hypothesis

Risankizumab will significantly improve skin symptoms and quality of life in subjects with moderate-to-severe plaque psoriasis who had a suboptimal response to secukinumab or ixekizumab.

2.2 Benefits and Risks to Subjects

Risankizumab is a monoclonal antibody antagonist specific for IL-23, which has been implicated in the pathophysiology of immune-mediated inflammatory diseases. Non-clinical studies have shown that risankizumab has no inhibitory effects on IL-12, the inhibition of which has been associated with increased risk of serious infections.[10,11] Selective IL-23 inhibition may not increase risk of serious infection, including mycobacterial infections.[12] Despite the availability of various psoriasis therapies, many subjects still do not respond adequately to these treatments, or gradually lose response over time.

In Phase 1 and Phase 2 studies of risankizumab in subjects with psoriasis, the majority of subjects receiving risankizumab achieved 90% improvement of their disease and risankizumab was well tolerated. Recently, positive top-line results were observed from 3 pivotal Phase 3 clinical trials evaluating risankizumab compared to ustekinumab, placebo, or adalimumab, for the treatment of subjects with moderate to severe plaque psoriasis.[13-15] After 16 weeks of treatment, all 3 studies met their co-primary endpoints of at least a 90% improvement in the Psoriasis Area Severity Index (PASI 90) and a static physician global assessment (sPGA) score of clear or almost clear (sPGA 0 or 1) for risankizumab (150 mg) treatment versus ustekinumab, placebo and adalimumab.[13-15] The safety profile was consistent with that observed in Phase 2 clinical trials, with no important identified risks for risankizumab. 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 clinically important active infection will not be included in the study.

In the Phase 3 clinical trial program for risankizumab, up to 57% of subjects had prior exposure to biologics including IL-17 inhibitors. Consistent PASI 90 responses were observed regardless of prior psoriasis treatment, including those who were bio-naïve or who reported prior biologic exposure to IL-17 inhibitors at Week 16 (74 - 77%) and Week 52 (78 - 81%).[16] Even in subjects who reported failing prior biologics (including those with primary or secondary non-response), risankizumab treatment resulted in high levels of PASI 90 response. In terms of safety, the Phase 3 clinical trials ranged from 30% prior biologic exposure in UltIMMa –1 and –2 to 57% in IMMhance and there were no differences observed in the safety profile across the trials. Furthermore, no additional safety concerns were identified in the 270 subjects who switched from adalimumab to risankizumab without a washout period in the IMMvent study.

This study is required to learn more about the potential treatment effect of risankizumab in adult subjects with moderate to severe plaque psoriasis who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a sub-optimal response.

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 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®-TB (or interferon gamma release assay [IGRA] equivalent)/TB skin test result for TB must fulfill entry criteria as specified in Section 5.1 of this protocol. IL-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models.[17,18] Thus, subjects with positive QuantiFERON®-TB Gold testing (or IGRA equivalent)/TB skin test who have latent TB (defined by local guidelines) are not required to be treated (unless recommended by local guidelines or by investigator judgement) with anti-TB therapy prior to receiving risankizumab but should be carefully monitored for any sign of TB reactivation.

Published literature indicates that inhibition of IL-23 is unlikely to increase the risk for cancer. Expression of IL-23 is increased in human tumors.[19-21] Moreover, preclinical data have demonstrated a beneficial effect of IL-23 p19 inhibition in animal models, both for pre-existing and tumor-induction models.[22] While there is not enough clinical information at this time to rule out a risk of cancer with risankizumab, this risk is considered small.

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

Increases in major adverse cardiovascular (MACE) events, including myocardial infarction, cerebrovascular accident, and cardiovascular death, were initially reported 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 or cerebrovascular events (serious or non-serious) observed in this study will be adjudicated by an independent Cardiovascular Adjudication Committee (CAC). The committee will remain blinded to treatment allocation (Section 6.2).

Local reactions to subcutaneously (SC) administered biologic therapies are usually limited to redness, swelling, or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard

medical treatment. Subjects will be closely monitored during study drug administration. An independent Anaphylaxis Adjudication Committee (AAC) will adjudicate observed systemic hypersensitivity and anaphylactic events. The AAC will remain blinded to treatment allocation (Section 6.3).

There are no important identified risks for risankizumab.[23]

In conclusion, the benefit-risk profile of risankizumab is considered appropriate for this stage of clinical development.[15] 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.[23]

Given that eligible subjects for inclusion are those who have been on either secukinumab or ixekizumab treatment for at least 6 months and are experiencing a sub-optimal response, physicians in routine practice would switch those patients to another biologic to improve skin symptoms and patient's quality of life. Current international guidelines for the treatment of moderate to severe psoriasis adopted "skin clearance" as a new treatment goal, as newer biologic treatments are able to provide this clearance to a majority of patients, which directly links to the improvement of patient's quality of life and workability.[24-26]

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

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective of this study is to evaluate the efficacy and safety of switching to risankizumab in subjects with moderate to severe plaque psoriasis, who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a sub-optimal response. Suboptimal response is defined as a sPGA 2 or 3, and a Body Surface Area (BSA) 3% - < 10% after at least 6 months treatment with secukinumab or ixekizumab.

3.2 Primary Endpoint

The primary endpoint is the proportion of subjects achieving sPGA 0/1 at Week 16.

3.3 Secondary Endpoints

The secondary endpoints are:

- The proportion of subjects achieving a sPGA clear response (sPGA 0) at Week 16;
- The proportion of subjects achieving a Dermatology Life Quality Index (DLQI) 0 or 1 at Week 16;

- The proportion of subjects achieving a Psoriasis Symptoms Scale (PSS) 0 at Week 16;
- The proportion of subjects achieving a sPGA 0/1 at Week 52;
- The proportion of subjects achieving a sPGA 0 at Week 52;
- The proportion of subjects achieving a DLQI 0/1 at Week 52;
- The proportion of subjects achieving a PSS 0 at Week 52;
- Time to achieve sPGA 0/1;
- Time to achieve sPGA 0;

3.4 Exploratory Endpoints

- The change from baseline in DLQI by visit;
- Treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication Version 9 (TSQM-9) at Baseline (Week 0) and at each visit;
- The proportion of subjects achieving absolute Psoriasis Area Severity Index (PASI) by visit (e.g., PASI ≤ 1, ≤ 3);
- The change from baseline in PASI by visit;
- The proportion of subjects achieving BSA ≤ 1%, ≤ 3%, by visit;
- The change from baseline in BSA by visit;
- The change from baseline in BSA (%) × sPGA by visit;
- The proportion of subjects achieving sPGA 0/1 at Week 16 and maintained sPGA 0/1 response at Week 52;

3.5 Safety Parameters

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiograms (ECG), and clinical laboratory testing (hematology, chemistry and urinalysis) as a measure of safety and tolerability for the entire study duration.

3.6 Biomarker Research

For subjects who consent, optional samples (whole blood, serum, plasma and tissue) will be collected at specific visits as listed in the Optional Biomarker Research Sample Activity Schedule (Appendix E) to evaluate known and or novel disease related or drug related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The objective of research is to analyze samples for biomarkers that will help to understand psoriasis, related conditions, response to treatment with risankizumab or similar compounds. Research on samples collected in Germany will be limited to psoriasis and risankizumab. Research may also include changes in epigenetics, gene expression, and

proteomics that may associate with psoriasis, related conditions, or the subject's response to treatment. This research is exploratory in nature and the results may not be included with the clinical study report.

Blood Samples

Blood samples will be collected for genetic, transcriptomic and proteomic testing as per the Optional Biomarker Research Sample Activity Table (Appendix E) and as described in the laboratory manual.

Skin Biopsy and Skin Tapes

Lesional skin punch biopsies and tape strip samples should be collected at the Baseline (Week 0) and Week 16 visits.

Skin punch biopsy and tape strip samples will be obtained for investigations including, but not limited to epigenetics, transcriptomics, proteomics, immunohistochemistry (IHC), and targeted investigations.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a Phase 3b, global, interventional, multicenter, open-label, single-arm study examining the effect of risankizumab 150 mg administered at Week 0, Week 4, and then every 12 weeks (q12w) thereafter for 52 weeks in adult subjects with moderate to severe plaque psoriasis who have been treated with labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a sub-optimal response. The subject population must be on the labeled secukinumab or ixekizumab for at least 6 months and are switched to risankizumab at Baseline (Week 0) (within ± 1 week of next scheduled dose for secukinumab or ixekizumab). Suboptimal response is defined as a sPGA 2 or 3 and a BSA 3% - < 10%.

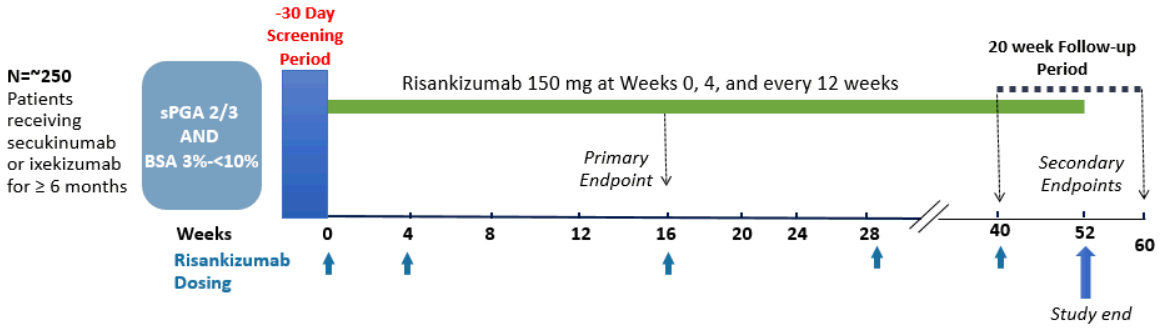
The study is designed to enroll 250 subjects.

Eligible subjects will receive 2 injections of active risankizumab 75 mg (150 mg total dosage) SC at Weeks 0 and 4, and then q12w until the last dose at Week 40.

The study duration will be up to 64 weeks. The study comprises a 30-day Screening Period, a 52-week open-label study period, and a 20-week follow-up period (after Week 40). The 52-week open label period consists of an initial phase (Weeks 0 – 16) and a maintenance phase (Weeks 16 – 52). The follow-up period consists of a follow-up phone call 20 weeks after the last injection of study drug (at Week 40).

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

Figure 1. Study Schema



BSA = body surface area; sPGA = Static Physician Global Assessment

4.2 Discussion of Study Design

Choice of Control Group

There is no control group for this open-label study. The study design is consistent with current standards investigating the efficacy and safety of a new treatment in psoriasis. As subjects have experienced a suboptimal psoriasis response for 6 months or longer, the single-arm design was chosen in order to prevent subjects from remaining on sub-optimal treatment by switching to risankizumab, which provides an opportunity to benefit subject's skin symptoms and quality of life outcomes. This reflects routine clinical practice, where patients are switched to another biologic without any wash-out period.

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 moderate to severe plaque psoriasis. All clinical and laboratory procedures in this study are standard and generally accepted. All patient-reported outcomes (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 a previous diagnosis of moderate to severe plaque psoriasis and have to be eligible for biologic therapy prior to receiving secukinumab. To qualify for this study, subjects have been treated with a labeled dose of secukinumab or ixekizumab for at least 6 months and are experiencing a sub-optimal response at time of Screening and Baseline visits, defined by a sPGA of 2 or 3 and a BSA of 3% - < 10% at Baseline visit.

Selection of Doses in the Study

The risankizumab dose of 150 mg SC selected for this study is the same as the approved labeled dose in the treatment of moderate to severe plaque psoriasis tested in global Phase 3 studies in subjects with

moderate to severe plaque psoriasis. The risankizumab 150 mg SC dose has been shown to be efficacious with an acceptable safety profile and considered appropriate for the treatment of subjects with 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.

- 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.
- 2. Employees of the sponsor and/or study sites and their family members may not be enrolled in this study.

Demographic and Laboratory Assessments

- 3. Adult male or female, at least 18 years old (subjects must also meet the legal age of majority per local law).
- 4. Laboratory values meeting the following criteria within the screening period prior to the first dose of study drug:
  - Serum aspartate transaminase (AST) < 2 × upper limit of normal (ULN);
  - Serum alanine transaminase (ALT) < 2 × ULN;
  - Serum total bilirubin ≤ 2.0 mg/dL; except for subjects with isolated elevation of indirect bilirubin relating to Gilbert syndrome;
  - Total white blood cell (WBC) count > 3,000/µL;
  - Absolute neutrophil count (ANC) > 1,500/µL;
  - Platelet count > 100,000/µL;
  - Hemoglobin > 10.0 g/dL (100 g/L).

Subject History

- 5. 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 electrocardiogram (ECG) performed during the Screening period;
- 6. Subject must not have a history of erythrodermic psoriasis, generalized or localized pustular psoriasis, medication-induced or medication-exacerbated psoriasis, or new onset guttate psoriasis;

- 7. Subject must not have a history of active skin disease other than plaque psoriasis that could interfere with the assessment of plaque psoriasis;
- 8. Subject must not have a history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 6 months;
- 9. 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;
- 10. 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);
- 11. No known active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, they should undergo molecular (e.g., polymerase chain reaction [PCR]) testing to rule out SARS-CoV-2 infection. In addition, if based on the answers to the SARS-CoV-2 Infection Risk Assessment Tool the site considers the subject currently at risk for developing SARS-CoV-2 infection, then the subject should either be tested or advised to come back for study screening after 14 days. Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:
  - At least 14 days since first PCR test result have passed in asymptomatic patients or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.
- 12. Subject must not have evidence of:
  - **Hepatitis B (HBV) or hepatitis C (HCV) infection**, defined as:
    - HBV: Hepatitis B surface antigen (HBs Ag) positive (+) test or detected sensitivity on the HBV deoxyribonucleic acid (DNA) PCR qualitative test for subjects who are hepatitis B core antibody (HBc Ab) positive (+) (and for hepatitis B surface antibody [HBs Ab] positive [+] subjects where mandated by local requirements);
    - HCV: HCV ribonucleic acid (RNA) detectable in any subject with anti-HCV antibody (HCV Ab);
  - **Human immunodeficiency virus (HIV)**, defined as confirmed positive anti-HIV antibody (HIV Ab) test. Note: In case a screened subject has a confirmed positive HIV Ab test, eligibility criterion 5 should be selected in electronic case report form (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 (Week 0) Visit as assessed by the investigator.
- 13. 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 which 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 (NMSC) or localized carcinoma in situ of the cervix.

14. Subject must not have a concurrent clinically significant medical condition other than the indication being studied or any other reason that the investigator determines would **interfere with the subject's participation** in this study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the study.

Disease Activity

15. Subject must have been previously diagnosed moderate to severe chronic plaque psoriasis prior to initiation of secukinumab or ixekizumab treatment;
16. Subject must have been on labeled secukinumab or ixekizumab treatment for at least 6 months and are experiencing a sub-optimal response at time of Screening and Baseline (Week 0) visits; treated with 300 mg secukinumab by SC injection at Weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks for at least 6 months total treatment or treated with 160 mg ixekizumab at Week 0, followed by 80 mg at Weeks 2, 4, 6, 8, 10, and 12, then maintenance dosing of 80 mg every 4 weeks;
17. Subject must have 3% - < 10% BSA psoriasis involvement, sPGA score of 2 or 3 at Screening and Baseline (Week 0) Visits;
18. Subject must be eligible for continued biologic therapy as assessed by the investigator.

Contraception

19. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening Visit and **a negative urine pregnancy test** at Baseline (Week 0) prior to the first dose of study drug is required;
20. Female subjects of childbearing potential must practice at least 1 protocol-specified **method of birth control**, that is effective from Study Day 0 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;
21. 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 (Prior Medication Restrictions)

22. Subject must not have prior exposure to risankizumab or any IL-23 inhibitors (guselkumab, tildrakizumab, mirikizumab);
23. Subject must not be currently using any approved psoriasis therapy other than secukinumab or ixekizumab for at least 6 months;

- 24. Subject must not be using 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) for at least 2 weeks prior to baseline;
- 25. Subject must not have received **any live viral or bacterial vaccine** within 6 weeks prior to the first dose of study drug or expect the need for live vaccine administration 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;
- 26. 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.

5.2 Contraception Recommendations

Contraception@Abbvie.com

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

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

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

- Females, of Childbearing Potential

  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study drug. Females must commit to one of the following methods of birth control:

    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline (Week 0).
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline (Week 0).
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).

- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized 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

During the study, no other biologic treatment other than risankizumab is allowed.

Therapies including but not limited to the following biologic therapies are prohibited medications during the study:

1. Any other approved biologic therapy to treat moderate to severe plaque psoriasis, other than risankizumab:
   - Adalimumab, infliximab, certolizumab pegol and biosimilar versions;
   - Etanercept and biosimilar versions;
   - Secukinumab, ixekizumab, brodalumab, and other IL-17 inhibitors;
   - Ustekinumab, efalizumab, guselkumab, tildrakizumab, mirikizumab, and other IL-23 inhibitors.
2. Systemic (including oral) non-biologic therapy to treat psoriasis or possibly benefit psoriasis, including but not limited to cyclosporine, corticosteroids, methotrexate, oral retinoids, apremilast, and fumaric acid derivatives.
3. Phototherapy treatment, laser therapy, tanning booth, or extended sun exposure that could affect disease severity or interfere with disease assessments.
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).
5. Treatment with an experimental biologic or non-biologic drug for psoriasis.
6. Live attenuated vaccines are not permitted during study participation and including up to 140 days (20 weeks or as guided by the local risankizumab label [if approved], whichever is longer) after the last dose of study drug. Examples of live attenuated vaccines include, but are not limited to, the following:

- Bacille Calmette-Guérin (BCG)
- Zoster vaccine live (Zostavax)
- Measles-mumps-rubella or measles mumps rubella varicella
- Monovalent live attenuated influenza A (intranasal)
- Oral polio vaccine
- Rotavirus
- Seasonal trivalent live attenuated influenza (intranasal)
- Smallpox
- Oral typhoid vaccine
- Varicella (chicken pox)
- Yellow fever

Treatment with any investigational drug within the past 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.

Washout Period of Biologic Therapies

Subjects must have discontinued biologic therapies prior to the first dose of study drug as specified in the washout procedures (Protocol Section 5.1 Concomitant Medications [Prior Medication Restrictions]). At a minimum of 6 months prior to screening, no other biologics other than secukinumab or ixekizumab are allowed. For all other biologic therapies, the required washout period is at least five times the mean terminal elimination half-life of the medication prior to the first dose of study drug.

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 electronic case report form (eCRF).

A detailed history of all prior biologic use will be obtained in the electronic data capture (EDC) system.

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.[23]

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

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.

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

- 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 AbbVie TA MD.
- Subject is non-compliant with TB prophylaxis (if applicable) or develops active TB at any time during the study.
- Malignancy, except for localized NMSC 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.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial.
- Post-Baseline occurrence of one or more of the following hepatic test abnormalities (confirmed on a second separate sample):
  - ALT or AST > 8 × ULN;
  - ALT or AST > 5 × ULN for more than 2 weeks;
  - ALT or AST > 3 × ULN and Total Bilirubin > 2 × ULN or international normalized ratio [INR] > 1.5;
  - ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

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 "planned per protocol," to ensure all acceptable mitigation steps have been explored.

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

5.6 Follow-Up for Subject Withdrawal from Study

Discontinuation of Study Drug and Continuation of Study Participation

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, 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.

Premature Discontinuation of Study (Withdrawal of Informed Consent)

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit (PD 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 after the last dose of study drug may be completed to ensure all treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs) have been resolved.

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

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

5.7 Study Drug

Study site staff will administer risankizumab 150 mg SC [2 × 75 mg pre-filled syringe] (Table 1).

AbbVie will not supply drug other than risankizumab.

Risankizumab will be packaged in quantities sufficient to accommodate study design. Risankizumab will be provided as two prefilled syringes per carton 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 interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to administering to subjects. Study drug will only be used for the conduct of this study. Instructions for drug administration will be provided by AbbVie.

Table 1. Identity of Investigational Product

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Risankizumab (ABBV-066)	Pre-filled syringe	75 mg per syringe	SC	Boehringer-Ingelheim Pharma GmbH & Co. KG

SC = subcutaneously

Interruption/Discontinuation of Study Drug Due to COVID-19

Delays in study drug dosing due to a subject with COVID-19 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.

5.8 Randomization/Drug Assignment

There is no randomization in this open-label study. All subjects will be administered risankizumab 150 mg.

All subjects will be assigned a unique identification number by the IRT at the screening visit. For subjects who do not meet the study eligibility criteria, the site personnel must register the subject as a screen failure in both IRT and electronic Case Report Form (eCRF) systems.

Rescreening

- Subjects that initially screen fail for the study may be permitted to re-screen once/one time following re-consent; the screening number assigned by the IRT at the initial screening visit should be used.
- There is no minimum period of time a subject must wait to re-screen for the study.
- A repeat of all screening procedures is needed with the possible exceptions noted below:
  - If the subject had a complete initial Screening visit including the assessment of a PPD test (or equivalent), or QuantiFERON-TB Gold test, and ECG, these tests will not be required to be repeated for the rescreening visit, provided the conditions noted in Section 5.1 are met and no more than 90 days have passed since the original screening visit.

- If there is an exclusionary laboratory result during screening, a re-test of that particular value is allowed without repeating all other lab tests provided no more than 30 days have passed since the original screening visit.
- The subject must meet all inclusion and none of the exclusion criteria at the time of re-screening to qualify for the study.
- As appropriate, sites are encouraged to contact the AbbVie TA MD to confirm if subjects should or should not be re-screened.

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

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (CRO) (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 of the Operations Manual [Appendix G] 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 140 days (20 weeks) after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

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

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

Areas of Safety Interest

Infections, especially opportunistic infections, are a theoretical risk with immunomodulators. Subjects will be screened and monitored throughout the study for Areas of Safety Interest (ASI). Screening procedures are outlined in the Activity Schedule (Appendix D).

In consideration of the ASI, the following supplemental report form(s) must be completed if AEs in any of the following areas are reported during the study (Table 2).

Table 2. Areas of Safety Interest

Adverse Event	Supplemental Report
Cardiac events **Myocardial infarction or unstable angina** **Cerebral vascular accident** **Cardiovascular death**	• Cardiovascular History and CV Risk Factors eCRF • Cardiovascular (Cardiac) AE eCRF • Myocardial Infarction and Unstable Angina AE eCRF • Heart Failure AE eCRF • Cerebral Vascular Accident and Transient Ischemic Attack AE eCRF • Combination Thrombotic Event AE eCRF • Arrhythmia AE eCRF
Discontinuation or interruption of study drug due to a hepatic-related AE **Hepatic-related SAE**	• Hepatic AE eCRF
Suspected anaphylactic/systemic hypersensitivity reactions	• Hypersensitivity Reaction Signs and Symptoms eCRF
TB Subjects 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

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

Adverse Event Severity and Relationship to Study Drug

Adverse events must be graded to the 5 criteria described in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[27]

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 (CAC)

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 Cardiovascular Adjudication Committee (CAC) Charter. Dedicated eCRFs will be used as outlined in Table 2.

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

6.3 Anaphylaxis Adjudication Committee

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 Anaphylaxis Adjudication Committee (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, 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.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The objectives of the statistical analyses are to evaluate the efficacy and safety of subjects with moderate to severe plaque psoriasis, who have been treated with labeled doses of secukinumab or ixekizumab for at least 6 months and are experiencing a sub-optimal response at time of Screening and Baseline visits and are switched to risankizumab at Baseline (Week 0).

For ease of description, Period A refers to Weeks 0 - 16 and Period B refers to the rest of the study.

The Primary Analysis for all efficacy endpoints pertaining to Period A will be conducted after all continuing subjects completed Week 16 and all data pertaining to Period A are cleaned and when a database lock will occur to enable the analysis. This is the one and final efficacy analysis for Period A. The results will be included in an interim clinical study report to support the efficacy and safety evaluation of the initial 16 weeks of treatment.

The Primary Analysis for all efficacy endpoints in Period B will be conducted at the study completion.

The statistical analyses will be described and fully documented in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to the database lock for the Primary Analysis for Period A. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Population

The Intent-to-Treat (ITT) Population, which is defined as all subjects who have at least 1 dose of study drug in Study M19-164, will be used for the efficacy analyses. The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug in Study M19-164 and will be used for all safety analyses. In this study, the Safety Analysis Set is the same as the ITT Population.

7.3 Statistical Analyses for Efficacy

Primary Analysis

For all efficacy endpoints, the analysis will be conducted in the ITT Population. No statistical tests will be performed considering single-arm design.

The last non-missing observation collected on or before the date of the first dose of study drug injection will be used as Baseline for safety and efficacy analyses. Descriptive statistics will be reported at baseline, primary time point of Week 16 and at study end of Week 52 in overall population and clinically important subgroups. Categorical endpoints will be summarized by frequencies, percentages, and associated 95% confidence intervals (CIs). Continuous endpoints will be summarized by means, standard deviations as well model based least square means, standard errors, and the 95% CIs after accounting for relevant baseline characteristics. Stratified analysis by prior use of secukinumab or ixekizumab will be considered.

Missing data will be handled by non-responder imputation incorporating multiple imputation for missing data due to COVID-19 (NRI-C) for categorical endpoints and mixed effect model repeat measurements (MMRM) for continuous endpoints. As-observed analysis will also be performed to handle missing data as sensitivity analysis for the primary and secondary endpoints.

Non-Responder Imputation incorporating multiple imputation to handle missing data due to COVID-19 (NRI-C): Missing data due to a COVID-19 infection or logistical restrictions related to the COVID-19 pandemic will be handled through multiple imputation (MI). Missing data at a scheduled assessment visit due to reasons other than the COVID-19 pandemic will be handled by NRI for that visit.

Details on the efficacy analyses are provided in the SAP.

Sample Size Estimation

There is no published literature or clinical trial data to accurately estimate the primary endpoint of sPGA 0/1 response rate at Week 16 for this study population – suboptimal response of subjects treated with secukinumab or ixekizumab. The assumption for risankizumab sPGA 0/1 response rate at Week 16 is expected to be between [redacted] based on the subjects who self-reported as prior IL-17 failure in Phase 3 trials ULTIMMA 1 & 2 and IMMhance.

The statistical precision measured by half-width of 95% confidence interval (CI) is the main criteria for sample size determination. By examining it over varying sample size, a choice of 250 subjects is associated with a half-width of no more than [redacted] across all possible response rates (Figure 2).

A total of 250 subjects will be enrolled in this study. From historical data of enrollment of the psoriasis studies conducted by AbbVie, the projected screen failure (SF) rate is [redacted]. Thus, [redacted] subjects will be needed to be screened to enroll 250 subjects.

7.4 Statistical Analyses for Safety

The safety analyses will be carried out using the Safety Analysis Set. Safety will be assessed by AEs, physical examination, laboratory assessments, and vital signs. Analysis details will be specified in the SAP.

Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs are defined as those that began or worsened in severity after the first dose of study drug and within 140 days (20 weeks) after the last dose of study drug. The number and percentage of subjects experiencing TEAEs will be tabulated using the MedDRA system organ class (SOC) and preferred term (PT), 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 Area of Safety Interest (ASI) will be provided as well. Pre-treatment AEs will be summarized separately.

For selected laboratory and vital signs, mean change from baseline and percentage of subjects with evaluations meeting criteria for pre-defined Potentially Clinically Significant (PCS) values will be summarized.

7.5 Interim Analysis

The interim analysis for all efficacy and safety data of Period A (Week 0 – 16) will be conducted after 50% of all continuing subjects completed Week 16 visit and when an interim database lock will occur to enable the analysis. The goal is to preliminarily assess response rates and potentially enable a potential earlier scientific communication.

8 ETHICS

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

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

8.2 Ethical Conduct of the Study

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

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods of assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), and study visit schedule modification. Refer to the Operations Manual in Appendix G for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

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

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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 investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug, and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last contact, which will be a follow-up phone call 20 weeks after the last dose.

12 REFERENCES

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AAC	Anaphylaxis Adjudication Committee
Ab	Antibody
AE	Adverse event
Ag	Antigen
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASI	Areas of special interest
AST	Aspartate aminotransferase
ATEMS	AbbVie Temperature Excursion Management System
BCG	Bacille Calmette-Guérin
BSA	Body surface area
BUN	Blood urea nitrogen
CAC	Cardiovascular Adjudication Committee
CI	Confidence interval
CK	Creatine kinase
COVID-19	Coronavirus Disease - 2019
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European medicines agency
EMEA	Evaluation of Medicinal Products
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
GGT	Gamma-glutamyl transferase

HB	Hepatitis B
HBc Ab	Hepatitis B core antibody
HBs Ab	Hepatitis B surface antibody
HBs Ag	Hepatitis B surface antigen
HBV	Hepatitis B virus
HBV Ab	Hepatitis B virus antibody
HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HIV Ab	Human immunodeficiency virus antibody
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
Ig	Immunoglobulin
IGRA	Interferon gamma release assay
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational medicinal product
INR	International normalized ratio
IRB	Institutional review board
IRT	Interactive response technology
ITT	Intent-to-treat
IU	International unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
LDL-C	Low density lipoprotein cholesterol
mAb	Monoclonal antibody
MACE	Major adverse cardiac event
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed effect model repeat measurements
NCI	National cancer institute

NMSC	Non-melanoma skin cancer
NRI	Non-responder imputation
NRI-C	Non-responder imputation incorporating multiple imputation for missing data due to COVID-19
PASI	Psoriasis Area Severity Index
PCR	Polymerase chain reaction
PCS	Potentially clinically significant
PD	Premature discontinuation
PD visit	Premature Discontinuation visit
PPD	Purified protein derivative (tuberculin)
PRO	Patient-reported outcome
PsA	Psoriatic arthritis
PSS	Psoriasis Symptoms Scale
PT	Preferred term
q12w	Every 12 weeks
RBC	Red blood cell
RCT	Randomized controlled trial
RNA	Ribonucleic acid
RSI	Reference Safety Information
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneously
SOC	System organ class
sPGA	Static Physician Global Assessment
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
TSQM-9	Treatment Satisfaction Questionnaire for Medication Version 9
ULN	Upper limit of normal
UACR	Urine albumin-to-creatinine ratio
US	United States
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-164: A Phase 3b, multicenter, interventional, open-label study of adult subjects with moderate to severe plaque psoriasis who have a suboptimal response to secukinumab or ixekizumab and are switched to risankizumab

Protocol Date: 27 January 2021

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]	Therapeutic Area Lead	Global Medical Affairs
[redacted]	Scientific Director	Global Medical Affairs
[redacted]	Program Lead	Clinical Program Development
[redacted]	Director	Data and Statistical Sciences Biometrics
[redacted]	Senior Medical Writer	Medical Writing

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the Screening and subsequent study visits. The individual activities and allowed modifications due to COVID 19 are described in detail in the Operations Manual (Appendix G).

Study Activities Table

Activity	Screening	Baseline (Week 0)	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52/ Premature Discontinuation[a]	20 Weeks Follow-up Call[b]
	Day –30 to Day –1	Day 0	Day 28	Day 56	Day 112	Day 196	Day 280	Day 364	140 days after last dose
Visit Window			± 3 Days			± 7 Days			
INTERVIEWS & QUESTIONNAIRES									
Informed consent[c]	✓								
Demographics	✓								
Eligibility criteria	✓	✓							
Medical/surgical history[d]	✓								
Alcohol and nicotine use	✓								
Latent TB risk factor questionnaire	✓								
SARS-CoV-2 Infection Risk Assessment Tool or comparable tool	✓								
Psoriasis therapy history	✓								
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient-reported outcomes questionnaires (DLQI, PSS, TSQM-9)[e]		✓	✓	✓	✓	✓	✓	✓	
LOCAL LABS & EXAMS									
Height (screening only),[f] weight, waist circumference	✓				✓			✓	
Vital signs[g]	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination[h] C = Complete; T = Targeted	C	C	T	T	C	T	T	C	
12-lead ECG[i]	✓							✓	
Adverse event assessment[j]	✓	✓	✓	✓	✓	✓	✓	✓	✓

Activity	Screening	Baseline (Week 0)	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52/ Premature Discontinuation[a]	20 Weeks Follow-up Call[b]
	Day –30 to Day –1	Day 0	Day 28	Day 56	Day 112	Day 196	Day 280	Day 364	140 days after last dose
Visit Window			± 3 Days			± 7 Days			
Efficacy assessor assessments (PASI, sPGA, BSA)	✓	✓	✓	✓	✓	✓	✓	✓	
Urine pregnancy test[k]		✓	✓	✓	✓	✓	✓	✓	
CENTRAL LABS									
Hepatitis B and C screening, urinalysis[l]	✓								
HIV (if required)[m]	✓								
FSH[n]/serum pregnancy test[o]	✓								
QuantiFERON-TB Gold test (and/or local PPD skin test)[p]	✓								
Clinical chemistry, hematology	✓	✓			✓			✓	
Total cholesterol, HDL-C, LDL-C, triglycerides[q]		✓			✓			✓	
TREATMENT									
Administer risankinumab[r]		✓	✓		✓	✓	✓		

a. Subjects that prematurely discontinue from the study (withdrawal of informed consent), will have a premature discontinuation (PD) visit within 2 weeks after the decision to discontinue.

b. For those subjects who prematurely discontinue from the study, a follow up call will occur approximately 20 weeks after the last dose of study medication regardless if they are switching to risankizumab commercial product (Skyrisi®). The follow-up phone call will be to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

c. Obtain informed consent prior to performing any study related procedures.

d. Note hepatitis B vaccination status in medical history.

e. All PROs will be completed prior to any study procedure and prior to study drug administration.

f. Height will be measured at Screening Visit only (with shoes off).

g. Blood pressure, pulse rate, body temperature, and respiratory rate should be performed before blood draws are performed. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

h. A complete (full) physical exam is required at the visits indicated. A symptom-directed (targeted) physical exam may be performed when necessary (e.g., to evaluate a reported adverse event).

i. The ECG should be performed prior to blood collection. 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.

j. At Screening visit until prior to the first dose of study drug, serious AEs and protocol-related non-serious AEs that occur after a subject signs the informed consent have to be collected. From the time of first study drug administration until 140 days (20 weeks) following discontinuation of study treatment has elapsed, all AEs and SAEs will be collected, whether solicited or spontaneously reported by the subject. If appropriate, a targeted physical exam should be performed. If an anaphylactic reaction is suspected, a serum tryptase and a plasma histamine sample will be drawn.

k. For all female subjects of childbearing potential, collect urine for pregnancy test at Baseline and all subsequent visits when the female subjects will receive study drug. More frequent pregnancy tests will be performed throughout the study if required per local/country requirements. If urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold study drug dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from study drug treatment. Refer to Section 6.1 Complaints and Adverse Events for additional details.

l. A urine dipstick macroscopic urinalysis will be completed by the central laboratory. A microscopic analysis will be performed in the event the dipstick results show leukocytes, nitrite, protein, ketones, or blood greater than negative or glucose greater than normal.

m. HIV testing will be performed at Screening Visit. 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. AbbVie will not receive results from the testing and will not be made aware of any positive result.

n. 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.

o. For all women of childbearing potential, collect serum for pregnancy test at Screening. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test comes back borderline, a repeat test is necessary (pregnancy is an exclusion criterion). If still borderline ≥ 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study.

p. TB testing will be performed at Screening Visit. Refer to Tuberculosis Testing section of the Operations Manual for further information.

q. Lipid testing required at Baseline (Week 0), Week 16, and Week 52. A minimum 8-hour fast is requested. If a subject is not able to fast when necessary, due to unforeseen circumstances, the non-fasting status will be recorded in study source documentation and lab requisition.

r. Study drug will be administered at the study site by authorized site personnel (e.g., study nurse) after all study procedures have been completed.

Note: Visit window is ± 3 days for the visits Week 4 up to Week 16, and ± 7 days thereafter. Any of the procedures may be performed at an unscheduled visit at the discretion of the Investigator.

APPENDIX E. OPTIONAL BIOMARKER RESEARCH SAMPLE ACTIVITY TABLE

Activity	Screening	Baseline	Week 4	Week 8	Week 16	Week 28	Week 40	Week 52/ Premature Discontinuation	20 Weeks Follow-up Call
	Day –30 to Day –1	Day 0	Day 28	Day 56	Day 112	Day 196	Day 280	Day 364	140 days after last dose
Visit Window			± 3 Days			± 7 Days			
Whole blood – genetic (DNA)[a]		✓[b]	✓		✓			✓	
Whole blood – transcriptomic (RNA)[a]		✓[b]	✓		✓			✓	
Whole blood – proteomic (plasma)[a]		✓[b]	✓		✓			✓	
Whole blood – proteomic (serum)[a]		✓[b]	✓		✓			✓	
Biopsy – Skin Punch and Tape Strip[a]		✓[b]			✓				

a. Collections to be performed only if subject provides consent.

b. Pre-dose collection.

APPENDIX F. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	07 August 2019
Administrative Change 1	21 August 2020

The purpose of this version is to update the Sponsor emergency medical contact information based on Administrative Change 1, incorporate necessary protocol modifications due to the COVID-19 pandemic, and to modify the eligibility criteria as follows:

- Title page – changed number of sites from 50 to 70.

  Rationale: *Mitigation to enrollment issues.*

- Section 2.2 – included information on the re-evaluation of the benefit and risk to subjects participating in the study. There is no anticipated additional risk to subjects.

  Rationale: *To account for the emerging COVID-19 pandemic.*

- Section 2.2 – removed language that no active TB cases have been observed.

  Rationale: *To reflect current safety database.*

- Section 5.1 – removed psoriatic arthritis exclusion criterion.

  Rationale: *Given the additional approval of secukinumab and ixekizumab for PsA and the significant PsA and PsO patient overlap, the removal of PsA as an exclusion criterion will result in a more practical and relevant translation of the study outcomes into real life clinical settings.*

- Section 5.1 – added criterion to exclude active SARS-CoV-2 infection.

  Rationale: *To account for the emerging COVID-19 pandemic.*

- Section 5.3 – revised item #2 to clarify systemic (including oral) non-biologic therapy to treat psoriasis or possibly benefit psoriasis in prohibited medications and therapy.

  Rationale: *For clarification.*

- Section 5.5 – added instructions to refer to Operations Manual for necessary changes to activities or procedures.

  Rationale: *To account for the emerging COVID-19 pandemic and ensure consistency between the study protocol and Operations Manual.*

- Section 5.7 – provided instructions in the event of temporary study drug interruption/halt due to COVID-19.

  Rationale: *To account for the emerging COVID-19 pandemic.*

- Section 5.9 – clarified that protocol deviations may include modifications due to COVID-19.

  Rationale: *To account for the emerging COVID-19 pandemic.*

- Section 7.3 – added NRI-C to incorporate handling of missing data due to COVID-19.

  Rationale: *To account for the emerging COVID-19 pandemic.*

- Section 7.3 – added as-observed analysis to incorporate handling of missing data as sensitivity analysis for the primary and secondary endpoints.

  Rationale: *To assess robustness of findings and potential impact of missing data handling.*

- Section 8.2 – noted that AbbVie will modify the study protocol as necessary due to the pandemic, referring to the Operations Manual in Appendix G for additional details. Investigators must also notify AbbVie if any urgent safety measures are taken.

  Rationale: *To account for the emerging COVID-19 pandemic and ensure consistency between the study protocol and Operations Manual.*

- Section 9 – noted that remote monitoring may be employed as needed.

  Rationale: *To account for the emerging COVID-19 pandemic.*

- Appendix D – added reference to Operations Manual for allowed modification.

  Rationale: *To account for the emerging COVID-19 pandemic and ensure consistency between the study protocol and Operations Manual.*

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

  Rationale: *To account for the emerging COVID-19 pandemic and ensure consistency between the study protocol and Operations Manual.*

APPENDIX G. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M19-164

Psoriasis: Risankizumab for Adult Subjects with Moderate to Severe Plaque Psoriasis Following Suboptimal Response to Secukinumab or Ixekizumab

SPONSOR:	AbbVie Inc.	ABBVIE INVESTIGATIONAL PRODUCT:	Risankizumab, ABBV-066

FULL TITLE: A Phase 3b, multicenter, interventional, open-label study of adult subjects with moderate to severe plaque psoriasis who have a suboptimal response to secukinumab or ixekizumab and are switched to risankizumab.

1 CONTACTS

Sponsor/ Non-Emergency Contact	[redacted] PhD Scientific Director Dermatology Global Medical Affairs AbbVie Mainzer Strasse 81 65189 Wiesbaden, Germany	Cell: [redacted] EMAIL: [redacted]
Sponsor/ Emergency Medical Contact	[redacted] MD Global TA Lead, Global Medical Affairs (GMA) GMA Biotherapeutics Immunology AbbVie Montehiedra Office Center 9615 Los Romeros Avenue, Suite 600 San Juan, Puerto Rico 00926-7038 **EMERGENCY 24-hour Number:** **+1 (973) 784-6402**	Mobile: [redacted] Email: [redacted]
Safety Concerns	Immunology Safety Team Dept. R48S, Bldg. AP51-3 1 North Waukegan Road North Chicago, IL 60064, USA	CTPS Safety Line: (833) 942-2226 (Toll free) Email: GPRD_SafetyManagement_Immunology@abbvie.com
Serious Adverse Event Reporting outside of RAVE	Email: PPDINDPharmacovigilance@abbvie.com	Fax: +1 (847) 938-0660
Protocol Deviations	[redacted] Study Project Manager I 1 North Waukegan Road North Chicago, IL 60064	Office: [redacted] Email: [redacted]
Certified Clinical Lab	Covance Central Laboratory Services SA 8211 Scicor Drive Indianapolis, IN 46214, USA	Phone: +1 (866) 762-6209 (Toll free) +1 (317) 271-1200 (Local calls) Fax: +1 (317) 616-2362 For country specific toll-free numbers, please refer to Covance Lab Manual.

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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.

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	• Informed consent • Demographics • Eligibility criteria • Medical/surgical history • Alcohol and nicotine use	• Latent tuberculosis (TB) risk factor questionnaire • Psoriasis therapy history • Prior/concomitant therapy • SARS-CoV-2 Infection Risk Assessment Tool
EXAM	• Height (with shoes off) • Weight • Waist circumference • Vital signs • Physical exam (complete) • 12-lead electrocardiogram (ECG)	• Adverse event (AE) assessment • Psoriasis Area Severity Index (PASI) • Static Physician's Global Assessment (sPGA) • Body Surface Area (BSA)
CENTRAL LAB	• Human Immunodeficiency Virus (HIV) (if required) • Clinical chemistry • Hematology • Follicle-stimulating hormone (FSH)/serum pregnancy test	• Hepatitis B and C screening • Urinalysis • QuantiFERON-TB Gold test (and/or local PPD skin test)

BASELINE (WEEK 0):

INTERVIEW	• Eligibility criteria	• Prior/concomitant therapy
PRO	• Dermatology Life Quality Index (DLQI) • Psoriasis Symptom Scale (PSS)	• Treatment Satisfaction Questionnaire for Medication (TSQM-9)
EXAM	• Vital signs • Physical exam (complete) • AE assessment	• PASI • sPGA • BSA
LAB	• Urine pregnancy test	
CENTRAL LAB	• Clinical chemistry • Hematology • Total cholesterol • High-density lipoprotein cholesterol (HDL-C) • Low-density lipoprotein cholesterol (LDL-C) • Triglycerides	• Optional Biomarker Whole Blood Samples: DNA/RNA/serum/plasma • Optional Biomarker Biopsy Samples: skin punch and skin tape
TREATMENT	• Administer risankizumab	

WEEK 4:

INTERVIEW	• Prior/concomitant therapy	
PRO	• DLQI • PSS	• TSQM-9
EXAM	• Vital signs • Physical exam (targeted) • AE assessment	• PASI • sPGA • BSA
LAB	• Urine pregnancy test • Optional Biomarker Whole Blood Samples: DNA/RNA/serum/plasma	
TREATMENT	• Administer risankizumab	

WEEK 8:

INTERVIEW	• Prior/concomitant therapy	
PRO	• DLQI • PSS	• TSQM-9
EXAM	• Vital signs • Physical exam (targeted) • AE assessment	• PASI • sPGA • BSA
LAB	• Urine pregnancy test	

WEEK 16:

INTERVIEW	• Prior/concomitant therapy	
PRO	• DLQI • PSS	• TSQM-9
EXAM	• Weight • Waist circumference • Vital signs • Physical exam (complete)	• AE assessment • PASI • sPGA • BSA
LAB	• Urine pregnancy test	
CENTRAL LAB	• Clinical chemistry • Hematology • Total cholesterol • HDL-C • LDL-C • Triglycerides	• Optional Biomarker Whole Blood Samples: DNA/RNA/serum/plasma • Optional Biomarker Biopsy Samples: skin punch and skin tape
TREATMENT	• Administer risankizumab	

WEEK 28:

INTERVIEW	• Prior/concomitant therapy	
PRO	• DLQI • PSS	• TSQM-9
EXAM	• Vital signs • Physical exam (targeted) • AE assessment	• PASI • sPGA • BSA
LAB	• Urine pregnancy test	
TREATMENT	• Administer risankizumab	

WEEK 40:

INTERVIEW	• Prior/concomitant therapy	
PRO	• DLQI • PSS	• TSQM-9
EXAM	• Vital signs • Physical exam (targeted) • AE assessment	• PASI • sPGA • BSA
LAB	• Urine pregnancy test	
TREATMENT	• Administer risankizumab	

WEEK 52/Premature Discontinuation:

INTERVIEW	• Prior/concomitant therapy	
PRO	• DLQI • PSS	• TSQM-9
EXAM	• Weight • Waist circumference • Vital signs • Physical exam (complete) • 12-lead ECG	• AE assessment • PASI • sPGA • BSA
LAB	• Urine pregnancy test	
CENTRAL LAB	• Clinical chemistry • Hematology • Total cholesterol • HDL-C • LDL-C • Triglycerides	• Optional Biomarker Whole Blood Samples: DNA/RNA/serum/plasma

2.2 Individual Post-Treatment Period Visit Activities

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

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

POST-TREATMENT 20 WEEKS FOLLOW-UP CALL:

INTERVIEW	• Prior/concomitant therapy
EXAM	• AE assessment

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study,

the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

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

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.

3.2 Medical History

A complete medical and surgical history including history of hepatitis B vaccination, tuberculosis (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 (Week 0) visit. This updated medical history will serve as the baseline for clinical Drug and Alcohol Screen.

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 4.2.

3.4 Subject Questionnaires

Subjects will complete the self-administered patient-reported outcome (PRO) instrument (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.

The subject should complete the questionnaires before site personnel perform any clinical assessments and before any interaction with site personnel has occurred to avoid biasing the subject's response.

PROs will be completed prior to any clinical assessments and treatment administration following the schedule of activities outlined in the protocol.

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, and bother with psoriasis treatment) (Appendix 8.1). 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.

Psoriasis Symptoms Scale (PSS)

The PSS is a 4-item patient-reported outcome (PRO) instrument that assesses the severity of psoriasis symptoms in patients with moderate to severe psoriasis (Appendix 8.2). The symptoms included are: pain, redness, itching and burning from psoriasis. Current symptom severity is assessed as a daily diary, using a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe). 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.

Treatment Satisfaction Questionnaire for Medication Version 9 (TSQM-9)

The abbreviated 9-item TSQM (TSQM-9) assesses patient's satisfaction with medication through 9 items representing 3 domains: Effectiveness (3 items), Convenience (3 items), and Global Satisfaction scale (3 items), scored by dimension ranging from 0 to 100, with higher scores indicating higher satisfaction (Appendix 8.3).

The TSQM-9 is a validated 9-item questionnaire designed as a general measure of treatment satisfaction with medication. The recall period is the last 2 to 3 weeks, or since the last medication use.

A score can be obtained for each domain by summing of the corresponding items transformed on a 0 – 100 scale (0 = complete dissatisfaction, 100 = maximum satisfaction). Higher values indicate higher satisfaction, better perceived effectiveness, lower burden associated to side-effects, and better convenience.

3.5 Efficacy Assessments

Efficacy assessments will be recorded on paper worksheets and entered into the electronic case report form (eCRF) and 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 (PASI, BSA, and sPGA) as detailed by 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.

Psoriasis Assessments

Psoriasis Area Severity Index (PASI)

The PASI is a measure of psoriasis severity. Four anatomic sites – head, upper extremities, trunk, and lower extremities – are assessed for erythema, induration and desquamation using a 5-point scale (Appendix 8.4). Based on the extent of lesions in a given anatomic site, the area affected is assigned a numerical value. Since the head, upper extremities, trunk and lower extremities correspond to approximately 10, 20, 30 and 40% of body surface area, respectively; the PASI score is calculated using the formula:

PASI = 0.1(Eh + Ih + Dh)Ah + 0.2(Eu + Iu + Du)Au + 0.3(Et + It + Dt)At + 0.4(El + Il + Dl)Al

Where *E, I, D*, and A denote erythema, induration, desquamation, and area, respectively, and *h, u, t*, and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI scores range from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest possible degree.

Typically scores of 3 or less represent mild disease, scores over 3 and up and including 15 represent moderate disease and scores over 15 are considered to be associated with severe disease.

Static Physician Global Assessment (sPGA)

This sPGA 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 (Appendix 8.5).

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.

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 (Appendix 8.6).

3.6 Biomarker Research Sampling

For subjects who consent, optional samples (whole blood, serum, plasma, and tissue) will be collected for biomarker research. Please refer to Section 2.1 for the schedule of biomarker research sample collections. All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store the samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on risankizumab (or drugs of this class) or psoriasis and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

Whole Blood

The whole blood sample will be collected for genetic, transcriptomic and proteomic analysis. Baseline (Week 0) samples will be collected at pre-dose. Week 4, Week 16, and Week 52/Premature Discontinuation samples will be collected at any time during the visit.

Skin Punch Biopsy Samples

Skin biopsies should be between 4.5 and 5 millimeters. Suitable sites for skin biopsy will include any cutaneous surface except the head and neck, genitals, hands, feet, elbows, lower leg or knees. Skin biopsies should be 5 millimeters (not less than 4.5 mm). Skin punch biopsy samples will be taken from lesional skin. As described in the laboratory manual, a baseline 5 mm lesional biopsy should be taken from the most involved, chronic active erythematous, scaly lesion. The subsequent biopsy samples should be obtained from the same area and location as the baseline lesional sample (> 5 mm but not further than 1 cm from the baseline biopsy site).

If the lesion has cleared, collect the sample close to the previous biopsies scar (> 5 mm but not further than 1 cm from the biopsy scar). Do not biopsy the previous biopsy scar. Baseline (Week 0) samples will be collected at pre-dose. Week 16 samples will be collected at any time during the visit.

Skin Tape Biopsy Samples

Skin tape strip samples will be taken from adjacent sites used for skin punch biopsies. Patches will be applied to the skin briefly and then removed. Each sample will consist of 4 patches applied to the same exact area in succession. Skin tape strip samples should be taken from the same lesional area for each visit. Skin tape strip samples should be taken prior to skin punch biopsies. Baseline (Week 0) samples will be collected at pre-dose. Week 16 samples will be collected at any time during the visit.

3.7 12-Lead Electrocardiogram

A 12-lead ECG will be performed at the designated study visits, as specified in Section 2.1.

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. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

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

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected but will be retained in subject's source records.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

3.8 Height, Weight, and Body Circumference

Height will be measured at screening only, without shoes. Body weight and waist circumference should be measured at scheduled visits as specified in Section 2.1. The subject will wear lightweight clothing and no shoes during weighing. If the screening weight is missed, it should be done at the Baseline (Week 0) visit prior to the first dose. Waist circumference should also be measured at Screening; however, if missed, it can be recorded at the Baseline (Week 0) visit.

3.9 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse 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. Clinically significant abnormalities in vital signs will also be reported as an AE or SAE.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed.

3.10 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2.1. The physical examination performed on Baseline (Week 0) 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. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

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

3.11 Study Drug Administration

Study drug will be administered to subjects beginning at Baseline (Week 0) and as specified in Section 2.1. All subcutaneous (SC) doses of risankizumab will be administered by designated or 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 (Week 0) procedures are completed. Injection site locations include lower abdomen, thigh, or outer upper arm. Study drug administration instruction for risankizumab pre-filled syringes (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., diphenhydramine, 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 reactions 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 Appendix 8.7 for reference; symptoms of anaphylactic reaction usually occur within 24 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

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests (Table 1). 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.

The blood samples for serum chemistry tests will be collected following a minimum 8-hour fast for Baseline (Week 0), Week 16, and Week 52 visits. If a subject is not able to fast at those visits, 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.

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

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

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

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory and sent to the following certified laboratory addresses:

Covance Central Laboratory Services SA
8211 Scicor Drive
Indianapolis, IN 46214

Table 1. Clinical Laboratory Tests

Clinical Laboratory Tests		
HEMATOLOGY	**CLINICAL CHEMISTRY**	**URINALYSIS**
Hematocrit Hemoglobin Mean corpuscular volume (MCV) Red blood cell (RBC) count/ Erythrocytes White blood cell (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> International normalized ratio (INR)[a]	**Enzymes** Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT/γ-GT) Creatine kinase (CK) **Only if** CK is elevated: Troponin (point-of-care) OR Troponin (central lab) **Electrolytes** Sodium Potassium Chloride Bicarbonate Calcium Phosphorus **Substrates** Glucose[b] Blood urea nitrogen (BUN) Creatinine 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]	**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 is abnormal):** **Urine** Urine albumin-to-creatinine ratio (UACR)

Clinical Laboratory Tests		
ADDITIONAL TESTING	**INFECTION SCREENING**	**PREGNANCY TESTING[e]**
N/A	Hepatitis B surface antigen (HBs Ag) (qualitative)[d] Hepatitis B surface antibody (HBs Ab) (qualitative)[d] Anti-Hepatitis B core (HBc) total (qualitative)[d] HBV DNA (quantitative)[d] Anti-HCV (qualitative)[d] HCV RNA (quantitative)[d] HIV-1 and HIV-2 Ab (qualitative)[d] QuantiFERON®-TB (or Interferon gamma release assay [IGRA] equivalent) and/or purified protein derivative (PPD)	Urine pregnancy test (local)[f] Serum pregnancy test[g] **ANAPHYLAXIS TESTING[h]** Tryptase Histamine

Ab = antibody; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; DNA = deoxyribonucleic acid; FSH = follicle-stimulating hormone; GGT/ γ-GT = gamma-glutamyl transferase; HBc = hepatitis B core; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL-C = high density lipoprotein cholesterol; HIV = human immunodeficiency virus; hsCRP = high-sensitivity c-reactive protein; IGRA = interferon gamma release assay; INR = international normalized ratio; LDL-C = low density lipoprotein cholesterol; MCV = mean corpuscular volume; PCR = polymerase chain reaction; PPD = purified protein derivative; RBC = red blood cell; RNA = ribonucleic acid; TB = tuberculosis; UACR = urine albumin-to-creatinine ratio; ULN = upper limit of normal; WBC = white blood cell

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

b. Performed at Baseline (Week 0), Week 16, and Week 52 visits (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 2.1. 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 visit from Baseline (Week 0) through Week 52/Premature Discontinuation 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 3.12 below.

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at the Screening visit. 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 6.1 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, it should be repeated 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. 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 hepatitis B virus (HBV) and hepatitis C virus (HCV) at Screening (Figure 1). Subjects with hepatitis B (hepatitis B surface antigen [HBs Ag] positive [+] or detected sensitivity on the HBV DNA polymerase chain reaction [PCR] qualitative test) or hepatitis C (HCV RNA detectable in any subject with anti-HCV antibodies) will be excluded. Subjects who have been

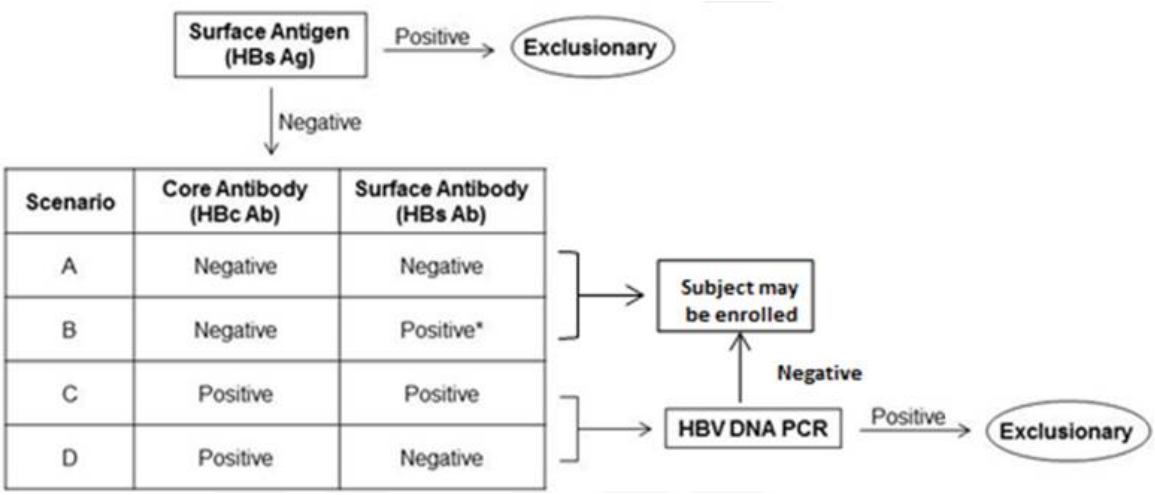
vaccinated against hepatitis B and are HBs Ab positive may be enrolled. If HBs Ag is negative but Hepatitis B core antibodies (HBc Ab) total is positive, HBV DNA will be quantified. If HBV DNA level is undetectable at Screening, the subject can participate in this trial.

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 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 Operation Manual 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



DNA = deoxyribonucleic acid; HBc Ab = hepatitis B core antibody; HBs Ab = hepatitis B surface antibody; HBs Ag = hepatitis B surface antigen; HBV = hepatitis B virus; PCR = polymerase chain reaction

* 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.

Human Immunodeficiency Virus (HIV) Testing

Human immunodeficiency virus 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. AbbVie will not receive results from the testing and will not be made aware of any positive result. In case a screened subject

has a confirmed positive HIV Ab test, eligibility criterion 5 should be selected in eCRF for documentation of screening failure.

Tuberculosis Testing

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, as specified in the study activity table.

At Screening, 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 assay test 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 in the study if **further work-up** (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active TB. If the 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 (i.e., no risk factors identified using the TB risk assessment questionnaire or defined by local guidelines or investigator judgment) for 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 Premature Discontinuation Visit procedure.

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 Appendix 8.7. Blood tests to be conducted in the event of a suspected anaphylactic reaction are:

- 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 Baseline (Week 0), Week 4, Week 16, Week 28, and Week 40. 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 to help better understand and characterize the diagnosis.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If logistical 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 with 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.

3.13 Subject Withdrawal from Study

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

3.14 Out of Window Visits Due to COVID-19 Pandemic

If a visit can be performed onsite out of window (OOW), consult with the sponsor to determine if the OOW visit is permitted.

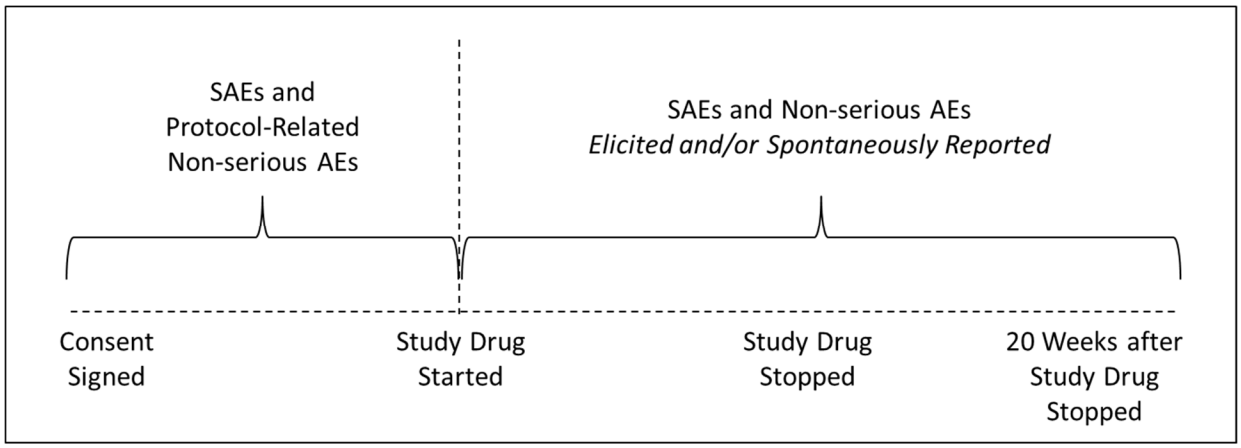
Regardless of whether an onsite OOW visit can occur, a phone call from the site to the enrolled subject should be conducted as close to the date of the study visit as possible to query for any AEs and to review concomitant medications.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All serious adverse events (SAEs) as well as protocol-related non-serious AEs (e.g., bruising related to blood draw) 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 20 weeks (140 days) after discontinuation of study treatment, all AEs and SAEs will be collected, whether solicited or spontaneously reported by the subject.

Figure 2. Safety Assessment



AEs = adverse events; SAEs = serious adverse events

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're clinically significant and the investigator considers them to be AEs (as outlined in relevant sections).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (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 System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with TEAEs 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 electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE 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 to: +1 (847) 938-0660

For safety concerns, contact the Immunology Safety Team at:

Immunology Safety Team
Dept. R48S, Bldg. AP51-3
1 North Waukegan Road
North Chicago, Illinois 60064
CTPS Safety Line: 1 (833) 942-2226 (Toll free)
Email: GPRD_SafetyManagement_Immunology@abbvie.com

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **MD**
Global TA Lead, Global Medical Affairs (GMA)
GMA Biotherapeutics
Immunology
AbbVie
Montehiedra Office Center
9615 Los Romeros Avenue, Suite 600
San Juan, Puerto Rico 00926-7038

Contact Information:

Mobile: [redacted]
Email: [redacted]

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

HOTLINE: +1 (973) 784-6402

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

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).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (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 non-serious events):

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

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor before reintroducing study drug.

4.4 Reporting Product Complaints

Product Complaints concerning the investigational product and/or device must be reported to the sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. 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 adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

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

6 STUDY DRUG

6.1 Treatments Administered

The study drug (risankizumab) will be administered by a healthcare professional in the form of a SC injection at the visits listed in Section 2.1.

Risankizumab will be provided by AbbVie as solution for injection in pre-filled syringe.

Study site staff will administer 2 injections of risankizumab 75 mg (150 mg total dosage) SC at Weeks 0 and 4, and then every 12 weeks (q12w) until the last dose at Week 40.

Study drug must not be dispensed without contacting the interactive response technology (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 Early Termination Visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

6.2 Packaging and Labeling

Study drug packaged in pre-filled syringe will be provided in an open-label fashion and administered at each dosing visit.

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.

Storage and Disposition of Study Drug

Risankizumab 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 must not be frozen at any time.

The refrigerator temperature must be recorded each business day. Malfunctions or any temperature excursion must be reported to the sponsor immediately upon notice. Study drug should be quarantined and not dispensed until AbbVie or AbbVie Temperature Excursion Management System (ATEMS) deems the drug as acceptable.

All clinical supplies must be stored and locked in a secure place until they are dispensed for subject use, are destroyed at the site or are returned to AbbVie or a local destruction depot. Investigational products are for investigational use only and are to be used only within the context of this study.

6.3 Method of Assigning Subjects to Treatment Groups

This is a non-randomized, open-label, single arm study. All eligible subjects will receive risankizumab 150 mg total dosage through last dose at Week 40.

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

6.4 Selection and Timing of Dose for Each Subject

Subjects will receive 2 injections of active risankizumab (150 mg total dosage) SC at Weeks 0, 4 and every 12 weeks (q12w) thereafter until the last dose at Week 40.

7 References

1. Robinson A, Kardos M, Kimball AB. Physician Global Assessment (PGA) and Psoriasis Area and Severity Index (PASI): why do both? A systematic analysis of randomized controlled trials of biologic agents for moderate to severe plaque psoriasis. J Am Acad Dermatol. 2012;66(3):369-75.

2. Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.

3. Sampson HA, Munoz-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.

8 Appendices

8.1 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

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

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

Please check you have answered EVERY question. Thank you.

8.2 PSORIASIS SYMPTOM SCALE (PSS)

Listed below are a set of problems that people with psoriasis have said are important. For each question, click on the circle that best describes the severity of your symptoms during the past 24 hours.

Please answer every question.

1. How severe was your pain from your psoriasis during the past 24 hours?
    - None
    - Mild
    - Moderate
    - Severe
    - Very severe
1. How severe was the redness from your psoriasis during the past 24 hours?
    - None
    - Mild
    - Moderate
    - Severe
    - Very severe
2. How severe was your itching from your psoriasis during the past 24 hours?
    - None
    - Mild
    - Moderate
    - Severe
    - Very severe
3. How severe was your burning from your psoriasis during the past 24 hours?
    - None
    - Mild
    - Moderate
    - Severe
    - Very severe

8.3 TREATMENT SATISFACTION QUESTIONNAIRE FOR MEDICATION VERSION 9 (TSQM-9)

TSQM-9

Abbreviated Treatment Satisfaction Questionnaire for Medication

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness and convenience of the medication *over the last two to three weeks, or since you last used it.* For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

4. How easy or difficult is it to use the medication in its current form?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

5. How easy or difficult is it to plan when you will use the medication each time?

☐1 Extremely Difficult
☐2 Very Difficult
☐3 Difficult
☐4 Somewhat Easy
☐5 Easy
☐6 Very Easy
☐7 Extremely Easy

6. How convenient or inconvenient is it to take the medication as instructed?

☐1 Extremely Inconvenient
☐2 Very Inconvenient
☐3 Inconvenient
☐4 Somewhat Convenient
☐5 Convenient
☐6 Very Convenient
☐7 Extremely Convenient

7. Overall, how confident are you that taking this medication is a good thing for you?

☐1 Not at All Confident
☐2 A Little Confident
☐3 Somewhat Confident
☐4 Very Confident
☐5 Extremely Confident

8. How certain are you that the good things about your medication outweigh the bad things?

☐1 Not at All Certain
☐2 A Little Certain
☐3 Somewhat Certain
☐4 Very Certain
☐5 Extremely Certain

2

9. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐1 Extremely Dissatisfied
☐2 Very Dissatisfied
☐3 Dissatisfied
☐4 Somewhat Satisfied
☐5 Satisfied
☐6 Very Satisfied
☐7 Extremely Satisfied

8.4 PSORIASIS AREA AND SEVERITY INDEX (PASI)

The PASI is an established measure of clinical efficacy for psoriasis medications.[1]

The PASI is a tool that provides a numeric scoring for subjects overall psoriasis disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, induration, and desquamation over four body regions.

The endpoints used are based on the percent reduction from baseline, generally summarized as a dichotomous outcome based on achieving over an X% reduction (or PASI X), where X is 50, 75, 90 and 100.

To calculate the PASI, the four main body areas are assessed: **head (h), trunk (t), upper extremities (u) and lower extremities (l)**. These correspond to 10, 30, 20 and 40% of the total body area respectively.

The area affected by psoriasis within these four areas site is estimated as a percentage of the total area of that anatomic site and assigned a numerical value according to the degree of psoriatic involvement as follows:

- 0 = no involvement
- 1 = < 10%
- 2 = 10% to < 30%
- 3 = 30% to < 50%
- 4 = 50% to < 70%
- 5 = 70% to < 90%
- 6 = 90% to 100%

The **signs of severity, erythema (E), induration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0 – 4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u and l and represents a composite score for each area. The signs of severity, **erythema (E), induration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0 to 4:

- 0 = No symptoms
- 1 = Slight
- 2 = Moderate
- 3 = Marked
- 4 = Very marked

	Erythema[a]	Desquamation	Induration
0 = none	No redness	No scaling	No elevation over normal skin
1 = slight	Faint redness	Fine scale partially covering lesions	Slight but definite elevation, typically edges indistinct or sloped
2 = moderate	Red coloration	Fine to coarse scale covering most of all of the lesions	Moderate elevation with rough or sloped edges
3 = marked	Very or bright red coloration	Coarse, non-tenacious scale predominates covering most or all of the lesions	Marked elevation typically with hard or sharp edges
4 = very marked	Extreme red coloration; dusky to deep red coloration	Coarse, thick, tenacious scale over most or all lesions; rough surface	Very marked elevation typically with hard sharp edges

a. Do not include residual hyperpigmentation or hypopigmentation as erythema.

Assignments for the following body regions are as follows:

- Neck: include with the head
- Buttocks: include with the lower extremities
- Axillae: include with the trunk
- Genitals: include with the trunk
- The inguinal canal separates the trunk and legs anteriorly

The PASI for each body region is obtained by multiplying the sum of the severity scores by the area score, then multiplying the result by the constant weighted value assigned to that body region. Since the head, upper extremities, trunk, and lower extremities correspond to approximately 10%, 20%, 30%, and 40% of BSA, respectively, the PASI is calculated according to the following formula:

$$PASI = 0.1(E_h + I_h + D_h)A_h + 0.3(E_t + I_t + D_t)A_t + 0.2(E_u + I_u + D_u)A_u + 0.4(E_l + I_l + D_l)A_l$$

where E, I, D, and A denote erythema, induration, desquamation, and area, respectively, and *h, u, t,* and *l* denote head, upper extremities, trunk, and lower extremities, respectively. PASI ranges from 0.0 to 72.0 with the highest score representing complete erythroderma of the severest degree.

Typically scores of 3 or less represent mild disease, scores over 3 and up and including 15 represent moderate disease and scores over 15 are considered to be associated with severe disease.

Note: Fredriksson 1978.[2]

8.5 STATIC PHYSICIAN GLOBAL ASSESSMENT

This Static Physician Global Assessment (sPGA) 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.

A lower score indicates less body coverage, with 0 being clear and 1 being almost clear. The efficacy assessor scores the erythema, induration and scaling of all psoriatic lesions from 0 – 4 based on the following descriptors:

Erythema

0 Normal (post-inflammatory hyper/hypopigmentation may be present)

1 Faint, diffuse pink or slight red coloration

2 Mild (light red coloration)

3 Definite red coloration (Dull to bright red)

4 Bright to Deep red coloration of lesions

Induration (Plaque Elevation)

0 None

1 Just detectable (possible slight elevation above normal skin)

2 Mild thickening (slight but definite elevation, typically edges are indistinct or sloped)

3 Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges)

4 Severe thickening with hard edges (marked elevation typically with hard or sharp edges)

Scaling

0 No scaling

1 Minimal focal scaling (surface dryness with some desquamation)

2 Predominately fine scaling (fine scale partially or mostly covering lesions)

3 Moderate scaling (coarser scale covering most or all of the lesions)

4 Severe/coarse scaling covering almost all or all lesions (coarse, nontenacious scale predominates)

Scoring

A composite score is generated from the above data and the final sPGA is determined from this composite score as follows:

Clear	0 = 0 for all three
Almost clear	1 = mean > 0, < 1.5
Mild	2 = mean ≥ 1.5, < 2.5
Moderate	3 = mean ≥ 2.5, < 3.5
Severe	4 = mean ≥ 3.5

8.6 BODY SURFACE AREA (BSA)

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.

8.7 CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis[3] 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 blood pressure (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.

PEF = peak expiratory flow; BP = blood pressure

* 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 hypersensitivity reaction is a clinical sign or symptom, or constellation of signs or symptoms, caused by an inappropriate and excessive immunologic reaction to study drug administration. A systemic hypersensitivity reaction is a hypersensitivity reaction that does not 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 serious adverse event.

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